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PAPER I

MD and DNB psychiatry, theory revision

Foundations of Psychiatry

The brain and its chemistry, how minds develop and differ, how we measure them, and how we reason from evidence. Seven complete sets of notes, in one book.

Dr. Wilfred D'souza · Dr. Niharika Reddy

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Dr. Niharika Reddy and Dr. Wilfred D'souza, Consultant Psychiatrists. Runwal Forests Clinic, Kanjurmarg West, Mumbai, and online.

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WEAVE SPRINT · PAPER I

Foundations of Psychiatry

THE WEAVE SPRINT SERIES

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WRITTEN BY

Dr. Wilfred D'souza and Dr. Niharika Reddy

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First compiled 2026. Free to read, share and print for study.

The clinical content is written for doctors and doctors in training. It is a study and revision aid, not a substitute for current guidelines or clinical judgement. Verify doses and thresholds against the current references and your local protocols before any clinical use.

For every resident who has ever sat up the night before,
afraid it will not be enough.

ACKNOWLEDGEMENT

A word of thanks

I want to begin by thanking something I cannot quite name. Call it whatever you like. I have never been certain what to call it, and I have stopped needing to be. There is a part of this work that does not feel like mine. The line that arrives before I have thought of it, the connection I did not plan, the steadiness on a morning I had no reason to be steady. I only hold the pen. Something moves through the holding, and I have learned to thank it without asking it for a name.

Someone once asked me why I give all of this away. Why hand out the notes I sat up making, to the very people sitting the same exam beside me. It is a fair question. If I had kept them, I would probably have scored a few marks more than the next person, and I might have been thought of as the better student. I have turned that over honestly, and I have decided it is a small thing to want. What I get instead, by putting the work in your hands, is the chance to take a little of the fear out of a great many nights. That trade is not close. Easing that fear is not a detour on the way to becoming a good psychiatrist. It is the thing itself. I did not come here to be the best student in the room. I came here to be a good psychiatrist.

And to Niharika, who reads everything first and knows when to be honest and when to wait; and to the residents who study from these pages and write back with the corrections and the questions: thank you. The book is better for you, and so am I.

Dr. Wilfred D'souza

Foreword

This is the first paper of the written examination, gathered into one book. It is the paper that asks what psychiatry is built on: the brain and its chemistry, how minds develop and differ, how we measure them, and how we reason from evidence. The clinical disorders come later, in the papers that follow. Nothing here is a symptom list yet. It is the ground the rest of the discipline stands on.

The notes were written to be understood, not just revised. Each chapter is a full account of its subject, from the mechanism up to the point the exam tests, so that you can read to learn the first time and read to recall every time after. Where a fact is worth holding exactly, it is marked. Where a mistake is easy to make, it is named before you make it. The colour code on the next pages tells your eye what kind of fact it is looking at before your mind has to decide, and after a few pages it stops being a key you consult and becomes a sense you carry.

Read it in order if you are meeting the material, or open it anywhere if you are returning to it. The contents at the front and the index at the back both jump to the page you want. However you use it, the hope held in these pages is plain: that one ordered, trustworthy place to study from makes the work a little lighter, and that you walk into the hall steadier than you would have otherwise.

HOW TO USE THIS BOOK

The colour memory code

Every note in this volume speaks one visual language, so once you learn it in the first chapter you read the rest without thinking about it.

Concept and rule	The core idea and the principle that follows from it. When a line is petrol, it is the thing to understand, and the thing worth being able to state.
Key number	A figure to hold exactly: a dose, a threshold, a prevalence, a cut-off. Amber means memorise this number, not just the shape of it.
Trap	The mistake the exam is waiting for. When a line is coral, it is warning you off an error that looks right until it costs you the mark.

Hold this is the single line from a topic you must carry out of it. **Good to remember** gathers, for each named thing, what it is, when it matters, and the one number or formula worth keeping. Both help a tired brain find the centre of a dense page fast.

The contents at the front is clickable, and so is the index at the back: every entry jumps to its page. Read to learn once, and to recall as often as you need.

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PART I

Functional Neuroanatomy & Neurophysiology

How the brain is wired for emotion, memory and arousal, and the physiology the exam builds on top of it.

01 Functional neuroanatomy

02 Neurophysiology

03 Apply and consolidate

Functional Neuroanatomy & Neurophysiology

Three sections · 23 topics · one complete notes document

The cortex is not a uniform sheet and the brainstem is not a cable. Both are sets of functionally specialised territories whose *connections*, not just their locations, decide behaviour. **Read circuits, not spots.** Almost every long-essay in this territory rewards the candidate who draws the loop that is interrupted rather than the one who lists gyri. This chapter builds the anatomy first, then the physiology that runs on it, in the order the brain actually uses: where things are, how they signal, what breaks, and how we treat what breaks.

HOW TO USE THESE NOTES

Every figure declares one clinical axis and codes it in colour and shape, with a small legend. The colours are consistent throughout: **petrol** marks structure and the executive or relay role, **coral** marks danger, pathology or the salience or limbic stream, and **marigold** highlights the reward, drive or facilitatory element. Learn the key once and every diagram reads faster.

Functional neuroanatomy

1 · Orientation: the brain as a map you can read

Before the detail, the frame. This material is built in the order the brain is actually interrogated at the bedside and in the viva: first *where* things sit (the lobes and the deep grey structures), then *how* they signal (neurotransmission and plasticity), then *what breaks* when a part fails (the lobe and localisation syndromes), and finally *how the failure is read and managed* (localise-by-sign, then the vignettes). Hold that arc and every topic below has a place to land. The single organising idea, repeated throughout, is to **read circuits, not spots**: the examinable insight is almost always the loop that is interrupted, not the gyrus that is missing.

THE MAP, IN ONE SCHEMA

Three coordinates locate almost every structure and syndrome in these notes. **Long axis:** cortex (lobes, executive and sensory maps), then the deep grey relay and drive hubs (basal ganglia, thalamus, hypothalamus, limbic ring), then the brainstem (arousal and the monoamine nuclei of origin). **Left to right:** the dominant hemisphere carries language and calculation, the non-dominant carries space and body schema. **Front to back:** anterior cortex acts (motor, executive), posterior cortex perceives (somatosensory, auditory, visual). Place a structure on those three axes and its function, and the deficit its lesion produces, follow.

Cortex

The four lobes and their association networks: the actor and perceiver, and the source of the lobe syndromes.

Deep grey

Basal ganglia (movement gating), thalamus (the relay gate to cortex), hypothalamus (the drive and endocrine hub), limbic ring (emotion and memory).

Brainstem
The reticular activating system (arousal) and the discrete monoamine nuclei that seed the ascending modulatory pathways.

The physiology on top
Neurotransmission, plasticity (long-term potentiation), sleep, the EEG readout, and the evoked potentials that test the circuits, all covered in the second half of these notes.

The consolidation block at the end pays this schema back as a single master mnemonic and a whole-chapter synthesis map to redraw from memory. Seed it now: the spine to build toward is *lobes feed the limbic loop, the basal-ganglia gate opens and closes, the monoamine nuclei run the modulators, and the EEG reads it all out.*

TRAP Listing gyri instead of the interrupted loop. A candidate who names the disconnected circuit outscores one who catalogues anatomy; **read circuits, not spots.**

HOLD THIS
Three axes place almost every structure and its lesion. Long axis (cortex, deep grey, brainstem), left-to-right (dominant language, non-dominant space), front-to-back (anterior acts, posterior perceives).

2 · The four cerebral lobes and lobe syndromes

The cerebral cortex is parcelled into four lobes, and almost every classical neurobehavioural syndrome the exam tests is a lobe lesion in disguise. The macro-map matters because localisation is the spine of the neurology-in-psychiatry viva: given a cluster of deficits, you should be able to name the lobe, the hemisphere, and the eponymous syndrome in one breath. This topic builds the four lobes as a single coherent map, then closes with the bedside tests that localise each one.

Two anatomical landmarks define the map. The **central sulcus** (of Rolando) separates the frontal lobe in front from the parietal lobe behind, dividing the motor strip (precentral gyrus) from the sensory strip (postcentral gyrus). The **lateral sulcus** (Sylvian fissure) separates the temporal lobe below from the frontal and parietal lobes above (Javed 2023). The parieto-occipital sulcus and the calcarine sulcus mark the occipital territory. A single point on this map, the temporo-parieto-occipital junction around the angular gyrus, generates a disproportionate share of exam syndromes.

2.1 Orientation: the four lobes, the defining sulci, and hemispheric dominance

The cerebrum is two hemispheres, each an outer cortex (grey matter) over inner white matter, folded into gyri and sulci so a large brain fits a small vault. Each hemisphere carries four lobes: **frontal** (executive, motor, expressive language), **parietal** (somatosensory integration, spatial attention), **temporal** (auditory, receptive language, memory, the ventral visual stream), and **occipital** (vision). The frontal lobe is the largest, accounting for roughly a third of the neocortex (Javed 2023).

Dominant versus non-dominant hemisphere. The **dominant hemisphere** is the language hemisphere, left in about 95% of people, including the large majority of left-handers (El-Baba 2023). The clinical rule the exam wants: *dominant* lobe lesions produce language and calculation deficits (aphasias, Gerstmann syndrome), while *non-dominant* lesions produce spatial, attentional and body-schema deficits (neglect, anosognosia, dressing and constructional apraxia). Fix that dichotomy first and the parietal and temporal syndromes fall out of it.

95%	~1/3
LEFT-HEMISPHERE LANGUAGE DOMINANCE	OF NEOCORTEX IS FRONTAL LOBE

RULE **Dominant equals language and calculation; non-dominant equals space and body schema.** Set the hemisphere first and the lobe syndrome follows.

PEARL

Two sulci, two dichotomies. The central sulcus splits motor (front) from sensory (back); the Sylvian fissure drops the temporal lobe below the frontoparietal cortex. Then dominant = language and calculation, non-dominant = space and body schema. Almost every lobe syndrome in the paper is a coordinate on this grid.

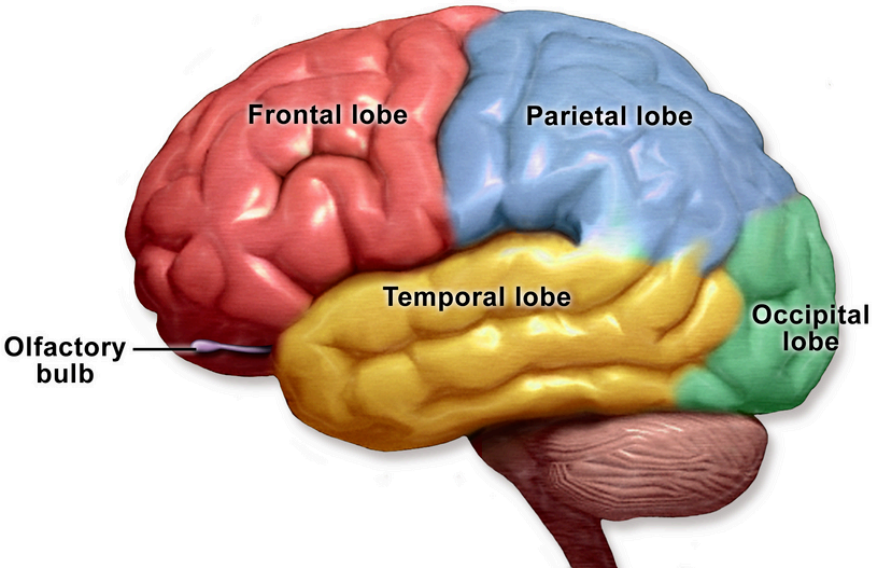


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Fig 1.1 The four cerebral lobes on the lateral surface. The central sulcus (of Rolando) separates the frontal lobe from the parietal; the lateral (Sylvian) fissure drops the temporal lobe below the frontoparietal cortex; the parieto-occipital and calcarine sulci mark the occipital territory.

2.2 Frontal lobe beyond prefrontal: motor cortex, eye fields, Broca area, micturition and release reflexes

The frontal lobe lies anterior to the central sulcus and divides into a motor tier and a prefrontal tier. Working back to front along the motor tier:

Primary motor cortex (M1, precentral gyrus, Brodmann area 4)

Origin of the corticospinal and corticobulbar tracts, holding the inverted motor **homunculus** (face near the Sylvian fissure, leg draped over the medial convexity into the interhemispheric fissure). A lesion gives contralateral weakness, initially flaccid hemiplegia, often maturing into spastic hemiparesis if premotor and supplementary areas survive (Chayer 2001).

Premotor cortex and supplementary motor area (SMA) (Brodmann area 6)

Plan and sequence movement (writing, fastening buttons). SMA lesions impair motor initiation and sequencing; damage to hand-associated premotor cortex contributes to agraphia.

Frontal eye fields (FEF, Brodmann area 8)

Generate voluntary (saccadic) contralateral gaze. A destructive FEF lesion drives conjugate gaze *towards* the side of the lesion (the eyes look at the lesion); an irritative frontal seizure drives the eyes *away* from the focus (El-Baba 2023).

Broca area (dominant inferior frontal gyrus, Brodmann areas 44 and 45)

Motor programming of speech. A dominant-hemisphere lesion produces **expressive (Broca, non-fluent) aphasia**: effortful, agrammatic, telegraphic output with relatively preserved comprehension and impaired repetition. Naming, phonemic fluency and figural fluency are degraded.

Micturition centre. The medial frontal cortex houses the cortical micturition centre; medial frontal or parasagittal lesions (for example a falx meningioma or an anterior cerebral artery infarct affecting both medial surfaces) release the bladder, producing urinary incontinence with indifference (Javed 2023).

Frontal-release (primitive) reflexes. Frontal lobe damage disinhibits developmentally primitive reflexes: *grasp, palmomental, snout, rooting, glabellar (Myerson) and sucking* reflexes re-emerge. They are non-specific but, taken together, point to frontal or diffuse frontal-subcortical dysfunction, and are a bread-and-butter bedside sign.

The three prefrontal syndromes, one line each. *Dorsolateral*: the dysexecutive syndrome (poor planning, set-shifting, working memory, perseveration). *Orbitofrontal*: the disinhibited syndrome (impulsivity, socially inappropriate behaviour, emotional lability, the Phineas Gage phenotype). *Medial frontal / anterior cingulate*: the apathetic-abulic syndrome (reduced drive, akinetic mutism at the extreme). These three are detailed on the Prefrontal cortex topic of these notes; do not duplicate here.

> **COMMON TRAP**
>
> Frontal eye field gaze direction. A structural (destructive) FEF lesion: the eyes deviate *toward* the lesion and away from the hemiparesis. A seizure (irritative focus): the eyes deviate *away* from the focus. The rule "a destructive lesion looks at the lesion" resolves the classic MCQ.

2.3 Parietal lobe: somatosensory cortex, and the dominant versus non-dominant split

The anterior parietal lobe holds the **primary somatosensory cortex (S1)** in the postcentral gyrus (Brodmann areas 3, 1, 2), receiving thalamic input for touch, proprioception, vibration, pressure, pain and temperature, and carrying its own inverted sensory homunculus. The posterior parietal cortex (superior and inferior parietal lobules) integrates that input for spatial

awareness, and here the dominant versus non-dominant dichotomy is at its sharpest (Javed 2023).

Dominant (usually left) parietal. Lesions of the dominant inferior parietal lobule, especially the angular gyrus, produce **Gerstmann syndrome**, a tetrad of *agraphia* (impaired writing), *acalculia* (patients understand numbers but cannot compute), *finger agnosia* (inability to identify or distinguish the fingers), and *left-right disorientation* (Altabakhi 2023). The full tetrad is rare; partial forms are common, and a developmental variant occurs in children. Dominant parietal lesions also cause **ideomotor apraxia** (failure to perform a learned gesture on command with intact strength and comprehension) and, because the territory abuts Wernicke area and the arcuate fasciculus, overlap into receptive-language and repetition deficits.

Non-dominant (usually right) parietal. Lesions here strike spatial attention and body schema. **Hemispatial neglect** is the signature: the patient ignores the left side of space, shaving only the right face or drawing a clock with all numbers crowded to the right. **Anosognosia** (denial of the deficit, classically of a left hemiplegia) may accompany it. *Dressing apraxia* and *constructional apraxia* (inability to organise garments onto the body, or to copy or draw a figure) round out the picture (Javed 2023).

Optic radiation, superior fibres. The superior fibres of the optic radiation sweep through the parietal lobe. A parietal lesion therefore clips the *lower* quadrant of the contralateral field, a contralateral homonymous inferior quadrantanopia ("pie on the floor").

> **CLINICAL ANCHOR**
>
> A right MCA stroke patient eats only the food on the right half of the plate, denies the weak left arm is his, and cannot copy a simple cube. That is non-dominant parietal: neglect plus anosognosia plus constructional apraxia. Swap to the left hemisphere and the same territory instead gives Gerstmann's tetrad and an aphasia. See the Stroke, TBI, delirium & focal brain syndromes notes for the clinical lobe-syndrome workup.

2.4 Temporal lobe (non-limbic): auditory cortex, Wernicke area, the ventral "what" stream and Kluver-Bucy

The superior temporal gyrus carries the **primary auditory cortex** (Heschl gyrus, Brodmann area 41), tonotopically organised, with the secondary auditory belt (area 42) and area 22 wrapped around it. Because auditory input is bilaterally represented, unilateral lesions rarely cause deafness (Zilles 2012).

Wernicke area (dominant posterior superior temporal gyrus, Brodmann area 22). A dominant-hemisphere lesion produces **receptive (Wernicke, fluent) aphasia**: fluent, well-articulated but empty speech ("word salad"), with impaired comprehension and impaired repetition. The contrast with Broca aphasia (non-fluent, comprehension preserved) is a guaranteed exam pairing (Javed 2023).

Ventral "what" stream. The inferotemporal cortex (fusiform and inferior temporal gyri, Brodmann areas 20, 37) is the object-recognition pathway. Lesions produce **visual agnosia**

(seeing an object but not recognising it) and, with fusiform "face area" damage, **prosopagnosia** (inability to recognise familiar faces). Bilateral inferior occipitotemporal damage can produce acquired *achromatopsia*.

Kluver-Bucy syndrome. *Bilateral* anterior temporal (amygdalar) damage, classically from herpes simplex encephalitis, temporal lobectomy or head injury, produces the pentad of *hyperorality* (examining objects by mouth), *hypersexuality*, *placidity* (blunted fear and rage, tameness), *hypermetamorphosis* (compulsive attention to and touching of every visual stimulus), and *visual agnosia / psychic blindness*. The bilaterality is the point: a unilateral lesion will not do it (Lanska 2018).

CLASSIC TRAP Calling a unilateral temporal lesion Kluver-Bucy; the syndrome requires **bilateral** anterior-temporal (amygdalar) destruction.

Optic radiation, inferior fibres (Meyer loop). The inferior fibres of the optic radiation loop forward through the temporal lobe, so a temporal lesion clips the *upper* contralateral quadrant, the contralateral homonymous superior quadrantanopia, the classic **"pie in the sky"** defect.

Temporal-lobe epilepsy, behaviour in brief. The mesial temporal lobe is the commonest epileptogenic zone; seizures give déjà vu, olfactory or gustatory hallucinations and affective auras, and a chronic interictal behavioural profile (the Geschwind constellation: hyperreligiosity, hypergraphia, viscosity, altered sexuality) is described. The limbic and memory detail sits on the limbic-system topic; only the neocortical temporal functions belong here.

MNEMONIC

PLACID HH

Kluver-Bucy: **P**lacidity, **L**oss of fear, **A**gnosia (visual / psychic blindness), **C**onstant examining (hypermetamorphosis), **I**nspection by mouth (hyperorality), **D**ietary change (hyperphagia), plus **H**ypersexuality and the requirement it be bilateral (both **H**emispheres). Miss the bilaterality and you miss the diagnosis.

2.5 Occipital lobe: primary visual cortex, hemianopia, cortical blindness, Anton and Balint syndromes

The occipital pole holds the **primary visual cortex (V1, striate cortex, Brodmann area 17)** along the banks of the calcarine sulcus, with the visual association cortex (areas 18, 19) anterior to it. V1 is **retinotopic**: the macula maps to the occipital pole and the peripheral field maps anteriorly, and the upper visual field projects below the calcarine sulcus while the lower field projects above (Rehman 2023).

Homonymous hemianopia with macular sparing. A unilateral occipital (posterior cerebral artery) lesion produces a contralateral homonymous hemianopia. The macular representation at the occipital pole is often spared, classically attributed to its dual blood supply (PCA and MCA collaterals), so central vision is preserved, a much-loved MCQ detail.

Cortical blindness. *Bilateral* occipital damage (typically bilateral PCA infarction, or watershed injury after cardiac surgery or hypotension) abolishes all vision including light perception, with normal pupillary light reflexes and a normal fundus, because the lesion is retro-geniculate.

Anton syndrome (Anton-Babinski). Cortical blindness in which the patient *denies* being blind, a **visual anosognosia**, and confabulates a visual scene, bumping into furniture while insisting they can see. It is understood as a disconnection of the damaged visual cortex from the language and monitoring systems (Das 2023).

Balint syndrome. *Bilateral* parieto-occipital (dorsal "where" stream) damage, classically from watershed infarction or posterior cortical atrophy, producing a triad: *simultanagnosia* (inability to perceive more than one object, or a whole scene, at a time), *optic ataxia* (inaccurate visually guided reaching, missing an object while looking at it), and *oculomotor apraxia* (inability to voluntarily direct gaze to a target). Note the "where" stream contrast with the temporal "what" stream of 2.4 (Javed 2023).

Achromatopsia and akinetopsia, in brief. Damage to the ventral occipitotemporal colour area (V4) gives acquired cerebral *achromatopsia* (loss of colour vision despite intact acuity); damage to area V5/MT gives *akinetopsia* (motion blindness, seeing the world as a series of frozen frames).

> **COMMON TRAP**
>
> Balint versus Anton, both bilateral posterior. Anton = bilateral *occipital*, cortical blindness with denial. Balint = bilateral *parieto-occipital*, vision present but the triad of simultanagnosia, optic ataxia and oculomotor apraxia. Anton denies not seeing; Balint sees but cannot assemble or reach.

2.6 Lobe function tests at the bedside, and the localiser summary

Each lobe has a small battery that localises it in minutes, the practical payoff of the whole topic. **Frontal:** phonemic *verbal fluency* (words beginning with F, A or S in one minute), the *Luria three-step* sequence (fist-edge-palm) for motor sequencing, *go/no-go* for response inhibition, and the *Wisconsin Card Sorting Test* for set-shifting and perseveration. **Parietal:** *two-point discrimination* and *graphaesthesia* (number written on the palm) for cortical sensation, *stereognosis* (object identification by touch) for tactile integration, and *line bisection* (or clock drawing) for neglect. **Temporal:** confrontation *naming*, *comprehension* of spoken commands, and *verbal memory* (word-list or story recall). **Occipital:** *confrontation visual fields* and *visual naming* of pictured objects. The table below is the localiser you should be able to reproduce in the viva.

LOBE	KEY FUNCTION	SIGNATURE LESION SYNDROME	BEDSIDE TEST
Frontal	Motor output, executive control, expressive language	**Dysexecutive / disinhibited syndrome; Broca aphasia (dominant)**	Verbal fluency, Luria three-step, go/no-go, Wisconsin Card Sort
Parietal (dominant)	Somatosensory integration, calculation, praxis	**Gerstmann syndrome; ideomotor apraxia**	Graphaesthesia, calculation, finger identification, two-point discrimination
Parietal (non-dominant)	Spatial attention, body schema	**Hemispatial neglect, anosognosia, dressing / constructional apraxia**	Line bisection, clock drawing, stereognosis
Temporal	Audition, receptive language, object recognition, memory	**Wernicke aphasia (dominant); Kluver-Bucy (bilateral)**	Naming, comprehension, verbal memory
Occipital	Primary vision	**Homonymous hemianopia; cortical blindness / Anton; Balint**	Confrontation fields, visual naming

Table: bedside localiser mapping each cerebral lobe to its key function, signature lesion syndrome and confirmatory bedside test.

HOLD THIS

Broca is non-fluent with preserved comprehension; Wernicke is fluent with impaired comprehension. Both impair repetition, and both localise to the dominant hemisphere.

CLINICAL ANCHOR

The deep clinical home for these syndromes, the full history, examination sequence, imaging correlation and differential, is the Stroke, TBI, delirium & focal brain syndromes notes; see the Stroke, TBI, delirium & focal brain syndromes notes for the clinical lobe-syndrome workup. This topic gives you the map and the localiser so the the Stroke, TBI, delirium & focal brain syndromes notes workup has somewhere to land.

3 · The limbic system

The limbic system is the brain's apparatus for **emotion, motivation and the laying down of declarative memory**. It is not a single structure but a ring of cortex and subcortical nuclei wrapped around the brainstem and diencephalon (Broca's *grand lobe limbique*, the bordering lobe). For the exam, hold three jobs and the structures that serve each: a **memory engine** (hippocampus and the Papez circuit), an **emotional salience detector** (amygdala), and a **reward and drive hub** (nucleus accumbens, septal nuclei, hypothalamic links).

Core structures

Hippocampal formation (hippocampus proper, dentate gyrus, subiculum) · amygdala · parahippocampal and entorhinal cortex · cingulate gyrus · fornix · mammillary bodies · anterior thalamic nucleus · septal nuclei · nucleus accumbens. The hypothalamus and orbitofrontal cortex are functionally limbic.

The Papez circuit is the closed loop that carries the emotional and mnemonic signal: hippocampus, then fornix to the mammillary bodies, then the mammillothalamic tract to the anterior thalamic nucleus, then to the cingulate gyrus, then the cingulum back to the entorhinal cortex and into the hippocampus again. Papez (1937)[4] proposed it as the substrate of emotional experience; we now read it primarily as a memory and contextual-emotion loop. The broader *limbic system*, including the amygdala and its emotional functions, is MacLean's (1949) later elaboration, not part of Papez's original ring, a distinction examiners reward. Its clinical relevance is that a lesion anywhere on the ring (classically the mammillary bodies in thiamine deficiency) produces amnesia.

RULE **Broca named the lobe, Papez gave the circuit, MacLean added the amygdala and the name.** Knowing who added the amygdala is a one-mark discriminator.

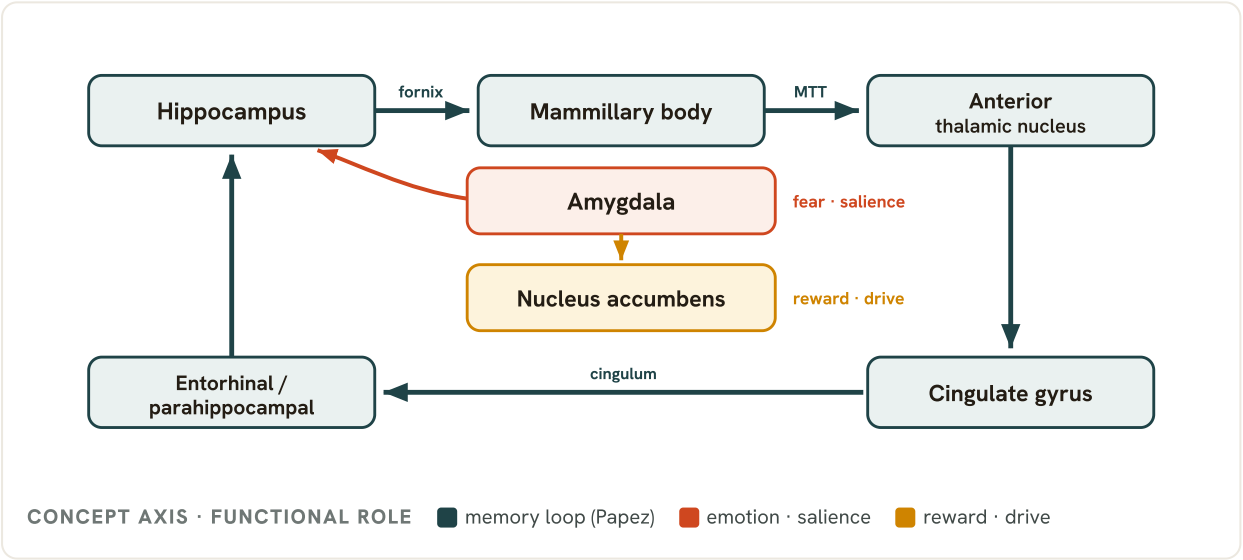


Fig 1.2 The Papez circuit drawn as a closed ring (petrol): hippocampus to fornix to mammillary body to anterior thalamus to cingulate to entorhinal and back. The amygdala (coral) tags emotional salience onto encoding and feeds the accumbens (marigold) reward hub. MTT, mammillothalamic tract.

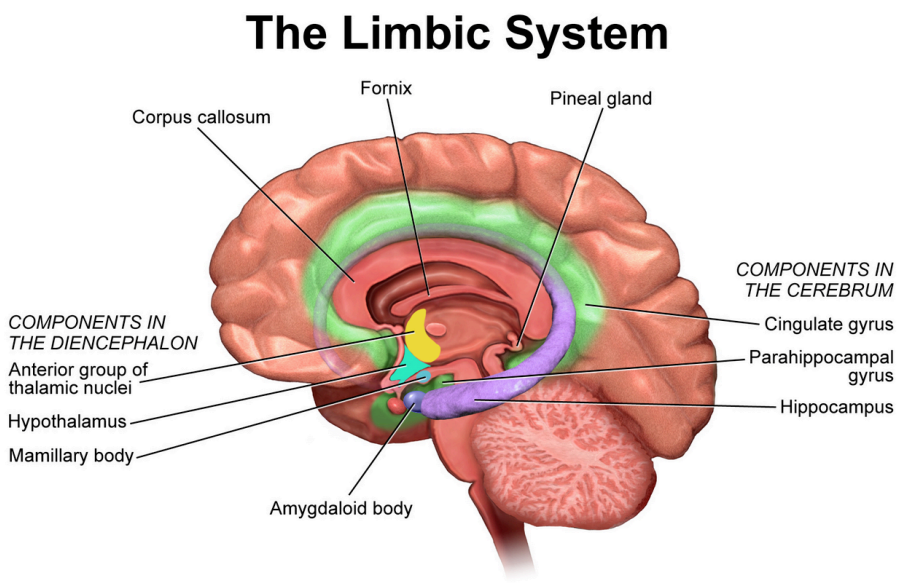


Image: BruceBlaus (Blausen Medical), CC BY 3.0, via Wikimedia Commons

Fig 1.3 The same structures in situ. Trace the Papez loop of Fig 1.2 across real anatomy: the cingulate gyrus and fornix carry the loop, the amygdala sits at the temporal pole tagging salience, and the hippocampus curls beneath it encoding new memory.

Functions by structure. The **hippocampus** consolidates new declarative (explicit) memory and supports spatial navigation; it does not store old memories, which is why bilateral damage spares remote recall. The **amygdala** attaches emotional valence, drives fear conditioning and the autonomic and endocrine fear response, and modulates how strongly the hippocampus encodes an event (emotional events are remembered better). The **cingulate** contributes to attention, conflict and the affective colouring of pain. The **nucleus accumbens** is the ventral striatal node where dopaminergic reward signalling meets limbic input, central to motivation and addiction.

HOLD THIS

The hippocampus consolidates new declarative memory but does not store the old. This is why bilateral hippocampal damage blocks new learning yet spares remote recall.

Role in psychiatric disorders

This is the part the 25-mark questions actually want.

- **Schizophrenia.** Reduced hippocampal volume is one of the most replicated structural findings; medial temporal and entorhinal changes underlie memory and contextual deficits. Amygdala dysfunction contributes to aberrant emotional salience.
- **Depression.** Smaller hippocampal volume (greater with longer untreated illness), amygdala hyperreactivity to negative stimuli, and altered cingulate (subgenual ACC) activity. The hippocampal neurogenesis and neurotrophic story links here (see topic 18).
- **PTSD.** Amygdala hyperresponsiveness with deficient ventromedial prefrontal top-down control, and reduced hippocampal volume associated with impaired contextual fear extinction.

- **Anxiety disorders.** Amygdala-centred threat circuitry overactivity.
- **Addiction.** Nucleus accumbens and the dopaminergic reward pathway are the substrate of craving and compulsive use.
- **Amnestic syndromes.** Bilateral hippocampal or Papez-ring lesions (e.g. mammillary bodies in Wernicke-Korsakoff) cause anterograde amnesia.

TRAP Pinning every limbic disorder on one structure. Map it to the node: amygdala for PTSD and anxiety, hippocampus for depression, **accumbens for addiction**.

MNEMONIC

Papez: "HF-MAT-CE-H"

Walk the loop as one phrase: **H**ippocampus to **F**ornix to **MA**mmillary body to **T**halamus (anterior) to **C**ingulate to **E**ntorhinal back to **H**ippocampus. Limbic structures: **"The Naked Hippo Found All Memories"** (Thalamus-anterior, Nucleus accumbens, Hippocampus, Fornix, Amygdala, Mammillary bodies).

Scoville & Milner (1957) LANDMARK · PATIENT H.M.

Design. Case series after bilateral medial-temporal resection for intractable epilepsy; the celebrated patient H.M. (Henry Molaison) was the epileptic case. **Finding.** Dense anterograde amnesia for new declarative memory with preserved intellect, remote memory and motor skills. **Why it matters.** First proof that the medial temporal lobe is the gateway for new declarative encoding, not the store. The clean dissociation of *intact* procedural learning (mirror-tracing despite no memory of practising) came from Milner's later work (1962) and Corkin's follow-up, not the 1957 paper itself. The anchor of topic 18.

INDIA CONTEXT

The commonest reversible amnestic syndrome in Indian practice is **alcohol-related Wernicke-Korsakoff** (a Papez-ring lesion at the mammillary bodies), not degenerative disease. The NMHS 2015-16 (Gururaj et al.) put alcohol-use disorders at roughly 4.6% current prevalence. Treat the confused heavy drinker as Wernicke and give parenteral thiamine before any glucose.

3.1 Definition, boundaries and the three competing models

The phrase *limbic system* is a moving target, and examiners love that history because it forces you to separate three overlapping ideas. In 1878 **Paul Broca** described a ring of cortex curving around the corpus callosum and brainstem and named it the **grand lobe limbique** (from Latin *limbus*, a border or hem), a purely anatomical observation about a bordering lobe. He made no claim about emotion. **James Papez** (1937) then proposed a specific closed circuit as the mechanism of emotional *experience* (detailed in Fig 1.2 and in subtopic 1.5). **Paul MacLean** (1949) coined the term **limbic system** proper and folded the amygdala and septum into Papez's ring, later embedding it in his *triune brain* scheme (reptilian basal ganglia, palaeomammalian

limbic system, neomammalian neocortex). The triune model is now regarded as an oversimplified evolutionary just-so story, but the term it produced has stuck.

MODEL	AUTHOR, YEAR	CORE CLAIM	WHAT IT DOES NOT INCLUDE
Grand lobe limbique	Broca, 1878	Anatomical ring of cortex bordering the brainstem	**No functional / emotional claim at all**
Papez circuit	Papez, 1937	A closed loop as the substrate of emotion (now read as a memory and contextual-emotion loop)	**No amygdala, no nucleus accumbens**
Limbic system	MacLean, 1949	Papez ring PLUS amygdala, septum, orbitofrontal cortex	Boundaries deliberately loose

The three-step lineage examiners reward: Broca named the lobe, Papez gave it a circuit, MacLean gave it the modern name and the amygdala. Knowing who added the amygdala is a classic one-mark discriminator.

The structures sit, in the words of the standard description, **lateral to the thalamus, beneath the cerebral cortex and above the brainstem**. By embryological origin they split into *telencephalic* components (hippocampus, parahippocampal and entorhinal cortex, olfactory bulb, fornix, mammillary body, septum pellucidum, amygdala, cingulate), *diencephalic* components (hypothalamus, anterior thalamic nuclei, habenula) and *mesencephalic* inputs. Modern neuroscience increasingly retires "the limbic system" as a unitary entity, preferring a revised **three-network model**: a hippocampal-diencephalic and parahippocampal-retrosplenial network for memory and spatial orientation, a temporo-amygdala-orbitofrontal network binding emotion to cognition, and the default-mode network for autobiographical memory and introspection (Catani and colleagues). For the exam, you can name this as the contemporary refinement while still using the classical structures as your scaffold.

⚠ COMMON TRAP

Do not credit Papez with the amygdala or with coining "limbic system". Papez (1937) described a loop and never used the amygdala; MacLean (1949) named the system and added the amygdala. Equally, do not say Broca proposed an emotional function: he made a purely anatomical observation about a bordering lobe.

3.2 Hippocampal formation: subfields and the trisynaptic preview

Structure. The **hippocampal formation** is an *allocortical* (three-layered) structure, phylogenetically older than the six-layered neocortex, curled along the floor of the inferior horn of the lateral ventricle in the medial temporal lobe. It has three classical regions: the **dentate gyrus**, the **hippocampus proper (cornu Ammonis)** and the **subiculum** (the transition back to entorhinal cortex). The cornu Ammonis is divided cytoarchitecturally into four fields, **CA1, CA2, CA3 and CA4**, running from the subiculum inward toward the dentate hilus. Each field is a

single sheet of pyramidal neurons; the dentate gyrus, by contrast, is a sheet of small *granule* cells and is one of the two adult neurogenic niches (the other being the subventricular zone).

Trisynaptic circuit (preview, expanded in the memory topic). The intrinsic wiring is a near-unidirectional three-synapse cascade that you should be able to draw: entorhinal cortex layer II projects via the *perforant path* to the dentate gyrus (synapse 1); dentate granule cells send *mossy fibres* to CA3 (synapse 2); CA3 pyramidal cells send *Schaffer collaterals* to CA1 (synapse 3); CA1 then projects to the subiculum and back to entorhinal cortex, which feeds the fornix. CA3 also has dense recurrent collaterals, the anatomical basis for pattern completion and autoassociative memory.

SUBFIELD	CELL TYPE / FEATURE	KEY VULNERABILITY
Dentate gyrus	Granule cells; adult neurogenesis	Most resistant to ischaemia; neurogenesis suppressed by chronic stress
CA1	Pyramidal cells; receives Schaffer collaterals	**Most vulnerable to hypoxia-ischaemia (Sommer sector) and to early Alzheimer pathology**
CA2	Resistant pyramidal field; social-memory role	Relatively spared (resistant sector); implicated in schizophrenia
CA3	Pyramidal cells; recurrent collaterals	Selectively vulnerable in mesial temporal sclerosis (with CA1, CA4)
CA4 (hilus / end-folium)	Polymorphic cells in dentate hilus	End-folium sclerosis in temporal-lobe epilepsy
Subiculum	Main output to fornix and entorhinal cortex	Output bottleneck; lesions impair recall

Subfield-by-subfield vulnerability, the high-yield reason to memorise CA1-CA4: CA1 is the hypoxia field (Sommer sector) and the Alzheimer field, whereas CA1, CA3 and CA4 with dentate granule-cell loss define mesial temporal (Ammon's horn) sclerosis in epilepsy.

PEARL

CA1 = the casualty. Two of the most examined facts about the hippocampus both land on CA1: it is the *Sommer sector* selectively killed by global hypoxia-ischaemia and cardiac arrest, and it is the earliest cortical field to accumulate neurofibrillary tangles in Alzheimer disease (after the entorhinal cortex). When a stem mentions cardiac arrest plus new memory loss, the answer is CA1.

3.3 Amygdala: nuclear groups and the fear circuit

Structure. The **amygdala** is an almond-shaped grey-matter mass in the dorsomedial temporal lobe, anterior to the hippocampus and partly continuous with it. It is not homogeneous: textbooks group its dozen-plus nuclei into three functional divisions. The **basolateral group** (lateral, basal and accessory basal nuclei) is the principal sensory *input* station, receiving highly processed cortical and thalamic information. The **centromedial group** (central and medial nuclei)

is the principal *output* station to the hypothalamus and brainstem. The **cortical (and the older corticomedial) group** handles olfactory input via the olfactory bulb.

NUCLEAR GROUP	NUCLEI	ROLE
Basolateral	Lateral, basal, accessory basal	**Sensory INPUT; site of fear-conditioning long-term potentiation**
Centromedial	Central, medial	**OUTPUT to hypothalamus and brainstem; drives autonomic and endocrine fear response**
Cortical / corticomedial	Cortical, nucleus of the lateral olfactory tract	Olfactory and pheromonal input; feeding and reproductive behaviour

Input versus output is the amygdala's organising logic: the basolateral complex takes information in (and is where fear memories are encoded), the centromedial complex sends the alarm out to the autonomic and endocrine machinery.

Mechanism. *Fear conditioning* is the model system. A neutral stimulus paired with an aversive one acquires threat value through **long-term potentiation in the lateral nucleus** of the basolateral complex (LeDoux's work), the cellular correlate of emotional learning. The signal is then relayed to the central nucleus, which fans out to drive the integrated fear response: the lateral hypothalamus for sympathetic activation, the paraventricular nucleus for the HPA cortisol surge, the periaqueductal grey for freezing, and the parabrachial nucleus for respiratory change. The amygdala also modulates the hippocampus so that emotionally arousing events are encoded more strongly, the neural basis of flashbulb memory.

Connections. Two named output tracts matter. The **stria terminalis** is the long, curved efferent that arches with the caudate to reach the hypothalamus and septal area. The **ventral amygdalofugal pathway** is the shorter, more direct route to the hypothalamus, thalamus and brainstem. Afferents arrive from all sensory association cortices, the thalamus (a fast subcortical "low road" for crude threat detection) and the olfactory system.

♡ CLINICAL ANCHOR

Kluver-Bucy syndrome follows **bilateral** destruction of the amygdalae and anterior temporal lobes (originally produced in monkeys by Kluver and Bucy, 1939, after bilateral temporal lobectomy; in humans most often from herpes simplex encephalitis, head injury, Pick disease or temporal-lobe surgery). The classic pentad: **hyperorality** (examining objects with the mouth), **hypersexuality**, **hyperphagia** (including pica), **visual agnosia or "psychic blindness"** (failure to recognise objects despite intact vision), and **placidity or docility** with loss of fear and rage. Amnesia may accompany it when the hippocampi are involved. A useful contrast: the amygdala patient is fearless and placid, whereas amygdala stimulation or temporal-lobe epilepsy can produce ictal fear and rage.

3.4 Cingulate cortex: an anterior-posterior division of labour

The cingulate gyrus arches immediately above the corpus callosum and is functionally split. The **anterior cingulate cortex (ACC)** is an affective-cognitive hub: its dorsal part handles cognitive

control, conflict monitoring and error detection, while its **subgenual and rostral (ventral)** part links to emotion regulation, autonomic control and the affective dimension of pain (the unpleasantness, not the location, of a noxious stimulus). It is the node that links behaviour to motivational outcome, multiplexing reward and action signals. The **posterior cingulate cortex (PCC)**, with the adjacent retrosplenial cortex, is a core hub of the default-mode network, serving autobiographical memory, spatial orientation and self-referential thought.

Clinical relevance. The **subgenual ACC (Brodmann area 25)** is the celebrated target of Mayberg's deep brain stimulation work in treatment-resistant depression, where it is metabolically overactive. ACC volume and activity differences are reported in mood disorders and schizophrenia. Bilateral ACC infarction produces *akinetic mutism*; the older psychosurgical *cingulotomy* targets this region for refractory OCD and chronic pain, exploiting its role in the affective drive of those conditions.

3.5 Fornix, mammillary bodies and the anterior thalamus: the Papez detail

This trio carries the hippocampal output around the Papez ring (drawn whole in Fig 1.2), and each is an exam-relevant lesion site. The **fornix** is the major efferent tract of the hippocampus: subicular and CA axons gather in the fimbria, sweep up as the body of the fornix, and split into precommissural fibres (to the septal nuclei) and postcommissural fibres (the columns that descend to the mammillary bodies). Fornix lesions impair recall memory. The **mammillary bodies** receive this input and relay it via the **mammillothalamic tract (of Vicq d'Azyr)** to the **anterior thalamic nucleus**, which projects to the cingulate, completing the loop. The mammillary bodies are essential for episodic memory and are the structure classically destroyed in thiamine deficiency.

♡ CLINICAL ANCHOR

Wernicke-Korsakoff syndrome is the limbic lesion exams return to most. Thiamine (vitamin B1) deficiency, most often from chronic alcohol use, produces haemorrhagic necrosis of the **mammillary bodies** and the medial dorsal and anterior thalamic nuclei. *Wernicke encephalopathy* is the acute triad of **confusion, ophthalmoplegia and ataxia**; untreated it progresses to *Korsakoff psychosis*, a chronic amnestic state with dense anterograde amnesia, retrograde amnesia and **confabulation**. The lesion sits squarely on the Papez ring, which is why a circuit-level memory loop becomes clinically real here. Always give parenteral thiamine before glucose.

HOLD THIS

Wernicke-Korsakoff is a mammillary-body (Papez-ring) lesion, not a hippocampal one. Give parenteral thiamine before any glucose load.

The **septal nuclei** lie in the septum pellucidum between the lateral ventricles, bidirectionally connected to the hippocampus (via the precommissural fornix and the medial septum, whose cholinergic neurons pace the hippocampal theta rhythm essential for memory encoding), the amygdala and the hypothalamus through the **medial forebrain bundle**. In Olds and Milner's classic 1954 self-stimulation experiments, the septal region and medial forebrain bundle were

among the strongest intracranial "pleasure" sites, and septal lesions in animals produce the *septal rage* syndrome of hyper-reactive aggression.

The **nucleus accumbens** is the ventral striatum, the anatomical interface where limbic emotional input (from the amygdala, hippocampus and prefrontal cortex via glutamate) meets the **mesolimbic dopamine** projection from the ventral tegmental area. It is the final common substrate of motivation, reward prediction and reinforcement, and therefore the convergence point of every drug of dependence. It also sits at the heart of what StatPearls calls the *limbic-motor interface*, the model for how the "emotive brain" recruits motor output to act on a goal.

3.7 Connections in and out, and a functional synthesis

Afferents. The limbic system samples all sensory association cortices, the olfactory bulb (the only sensory modality with a direct, non-thalamic limbic route, a phylogenetic relic), the thalamus and brainstem monoaminergic nuclei (the locus coeruleus, raphe and ventral tegmental area set the emotional gain). **Efferents** exit through three named highways worth listing together: the **fornix** (hippocampus to mammillary bodies and septum), the **stria terminalis** and **ventral amygdalofugal pathway** (amygdala to hypothalamus and brainstem), and the **medial forebrain bundle** (the reward and drive corridor linking septum, accumbens, hypothalamus and ventral tegmentum). The hypothalamus is the principal output relay that converts limbic signals into autonomic, endocrine (HPA axis) and behavioural action.

Functions in one frame

Memory: hippocampal formation and the Papez ring consolidate new declarative memory (they do not store old memory, which is why bilateral lesions spare remote recall). **Emotion and salience:** the amygdala tags threat and reward value and drives the fear response. **Reward and drive:** nucleus accumbens, septal nuclei and the medial forebrain bundle. **Homeostatic and visceral control:** hypothalamic links governing the "four Fs" (feeding, fighting, fleeing, mating). **Olfaction:** the evolutionary origin of the whole system.

3.8 Clinical correlation: temporal-lobe epilepsy and the Gastaut-Geschwind syndrome

Beyond the disorder-by-disorder map already laid out (schizophrenia, depression, PTSD, anxiety, addiction and amnesia), two epilepsy-linked syndromes are high-yield and frequently confused.

Mesial temporal lobe epilepsy is the commonest focal epilepsy, driven by **mesial temporal (Ammon's horn) sclerosis**, that is, neuronal loss and gliosis in CA1, CA3 and CA4 with dentate granule-cell change (subtopic 1.2). Auras are quintessentially limbic: rising epigastric sensation, intense ictal fear, deja vu and jamais vu, and olfactory or gustatory hallucinations (uncinate fits from the amygdala-uncus region), reflecting which limbic node is discharging.

CLINICAL ANCHOR

The **Gastaut-Geschwind interictal personality syndrome** describes an enduring behavioural change in some patients with chronic temporal-lobe epilepsy. The cardinal features are **hyperreligiosity**, **hypergraphia** (compulsive, often detailed writing), **hyposexuality** and **viscosity or "stickiness"** of thought and interpersonal interaction (circumstantiality, difficulty terminating conversations), often with intensified emotionality and a deepened sense of personal destiny. Hold it as the deliberate mirror image of Kluver-Bucy: temporal-lobe *overactivity* in Gastaut-Geschwind produces hyper-religiosity and **hypo**sexuality, whereas bilateral temporal *destruction* in Kluver-Bucy produces placidity and **hyper**sexuality. The construct remains debated and is not in ICD-11 or DSM-5-TR as a formal diagnosis, but it is a reliable viva favourite.

TRAP Confusing the two temporal syndromes. Temporal **overactivity** (Gastaut-Geschwind) gives hyper-religiosity and **hypo**sexuality; bilateral temporal **destruction** (Kluver-Bucy) gives placidity and **hyper**sexuality.

MNEMONIC

Geschwind: "Religion, Writing, no Sex, Sticky" (R-W-S-S)

The four pillars of the interictal personality: hyper-**R**eligiosity, hyper-graphia (compulsive **W**riting), hypo-**S**exuality, and viscosity (**S**tickiness). Contrast Kluver-Bucy with **"Placid Pets Probe with Mouth, Mate, Munch and miss the Memo"**: Placidity, Psychic blindness (visual agnosia), hyperorality (Mouth), hypersexuality (Mate), hyperphagia (Munch), and amnesia (miss the Memo).

4 · Stress circuitry: the amygdala-hippocampus-HPA loop

Stress is not a single organ or hormone but a distributed circuit. A threat cue reaches the **amygdala**, which simultaneously fires a fast neural limb (sympatho-adrenomedullary, seconds) and a slow endocrine limb (the HPA axis, minutes to hours), while the hippocampus and ventromedial prefrontal cortex keep both limbs on a leash through inhibitory feedback. This is the neuroanatomical substrate of the neurobiology of stress, and it is where depression, PTSD and the anxiety disorders converge at the level of wiring.

The endocrine chemistry of the slow limb, the CRH-ACTH-cortisol cascade and the dexamethasone suppression test, are detailed on the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes (Neuroendocrinology). This topic stays on the neural loop: which nucleus drives which, who inhibits whom, and what chronic drive does to the tissue. Cross-reference the limbic system and prefrontal cortex topics of these notes for the parent anatomy of the amygdala, hippocampus and vmPFC.

4.1 The two arms: fast sympatho-adrenomedullary vs slow HPA

The stress response fires along two systems that overlap in trigger but differ in speed and mediator. Both are launched by the same threat appraisal but restore homeostasis on different clocks.

Sympatho-adrenomedullary (SAM) arm. A near-instant neural response: descending drive from the paraventricular nucleus, locus coeruleus and rostral ventrolateral medulla reaches preganglionic sympathetic neurons and the adrenal medulla, releasing catecholamines (adrenaline is roughly 80% of adrenal-medullary output in humans, with noradrenaline making up the rest) within seconds for alertness, vigilance and the "fight-or-flight" mobilisation first described by Cannon (Cannon 1915).

HPA (glucocorticoid) arm. A slower hormonal cascade that takes about 3 to 4 minutes to begin reaching organ systems through the circulation and produces amplified, protracted glucocorticoid effects lasting hours to days. The neural drivers are given below; the CRH-ACTH-cortisol chemistry sits on the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes.

4.2 The core neural loop: drive, feedback and the sustained-anxiety switch

The loop has a threat-drive limb and an inhibitory-control limb converging on one hypothalamic integrator, the paraventricular nucleus (PVN).

Amygdala drive. The central nucleus of the amygdala (CeA) is the output hub for the threat response. Its projections (mostly relayed indirectly through GABAergic cell groups in the bed nucleus of the stria terminalis and peri-PVN hypothalamus) reach the PVN to trigger the HPA axis, and reach brainstem autonomic nuclei plus the periaqueductal grey to organise the behavioural threat response (Ulrich-Lai and Herman 2009; LeDoux 2012).

Top-down inhibitory feedback. The hippocampus (CA1 and subiculum) and the ventromedial prefrontal cortex (prelimbic and infralimbic in rodents) exert top-down control. Both are dense in glucocorticoid receptors and send largely indirect projections that inhibit the PVN, so that rising cortisol shuts the axis down: a negative-feedback brake. After intense psychological stress this brake can fail, and the circuit switches from top-down (cortical restraint) to bottom-up (amygdala-driven) control.

Sustained anxiety and the BNST. The bed nucleus of the stria terminalis is the switch between phasic fear and sustained, contextual anxiety: the CeA handles acute cued fear, while the BNST mediates the longer, uncertain, anticipatory state. Its subnuclei are functionally opposed, the posterior BNST inhibiting and the anteroventral BNST exciting the HPA axis (Choi et al 2007).

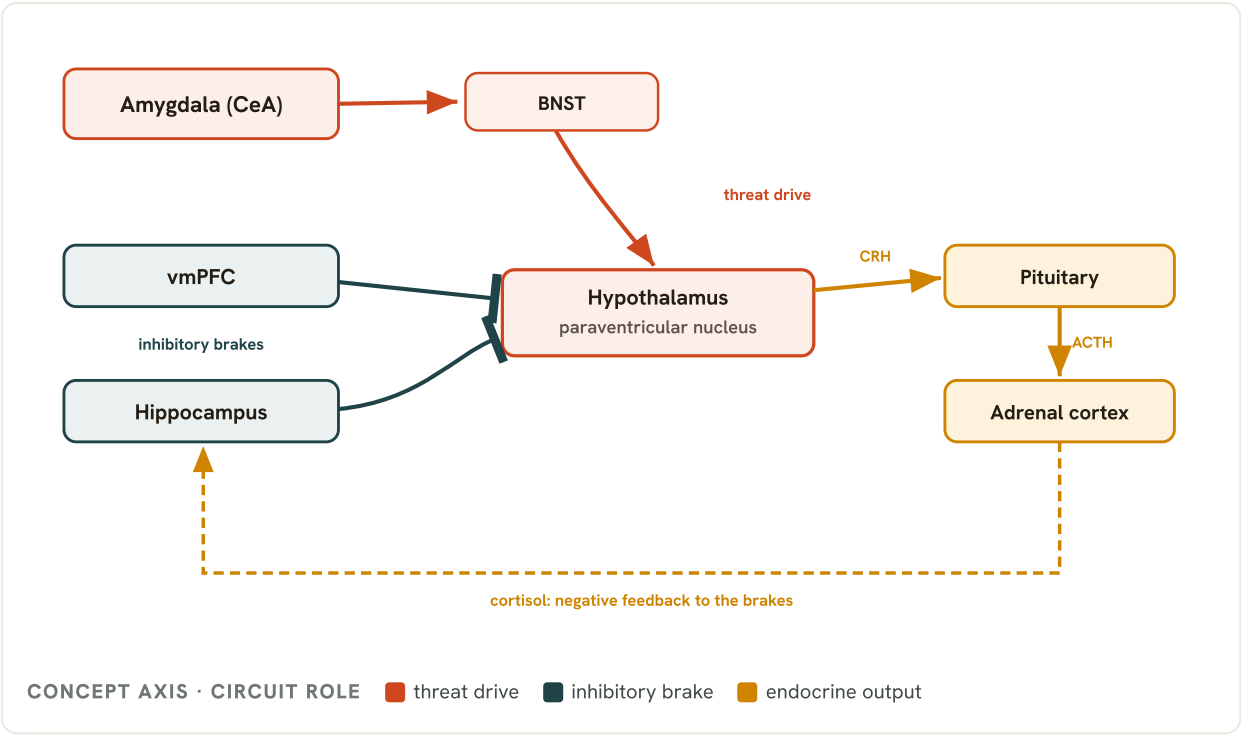


Fig 1.4 The stress loop. The amygdala (coral) drives the paraventricular nucleus, relayed through the BNST for sustained anxiety; the hippocampus and vmPFC (petrol) apply inhibitory brakes; the cortisol output limb (marigold) closes the loop by feeding back onto its own brakes, so that when chronic stress shrinks the hippocampus and vmPFC the brake weakens and the drive runs unopposed.

FEATURE	SYMPATHO-ADRENOMEDULLARY ARM	HPA ARM
Mediator	Adrenaline, noradrenaline	**Glucocorticoid (cortisol)**
Onset	Seconds	**About 3 to 4 minutes to reach organs**
Duration	Short-lasting	Hours to days (amplified, protracted)
Effector	Adrenal medulla, sympathetic nerves	Adrenal cortex
Main relay nucleus	Locus coeruleus	Paraventricular nucleus
Termination	Parasympathetic (vagal) opposition	Glucocorticoid negative feedback

The fast and slow arms of the stress response differ in mediator, speed, duration and how each is switched off.

4.3 Glucocorticoid action on the brain: MR, GR and the inverted-U

Cortisol acts on the brain through two intracellular receptor types with different affinities, and its effect on cognition is dose-dependent rather than linear.

Two receptors, two affinities. Reul and DeKloet (1985) established two adrenal-steroid receptors: the **mineralocorticoid receptor** (MR, Type I), high-affinity and roughly 80 to 100% occupied at basal cortisol, densely expressed in hippocampus, so it sets baseline excitability and tone; and the **glucocorticoid receptor** (GR, Type II), lower-affinity, expressed everywhere,

occupancy rising from about 10% up to 80% only as cortisol climbs, making GR the stress-responsive receptor. Both are cytoplasmic; on binding, cortisol drives dimerisation, nuclear translocation and transcription, with additional rapid non-genomic membrane effects.

The inverted-U. Because MR is engaged first and GR only at higher loads, glucocorticoids show a biphasic, inverted-U dose-response on hippocampal excitability, LTP and memory: moderate physiological rises enhance performance, while very low or very high levels impair it (Diamond et al 1992).

Structural remodelling under chronic stress. Chronic stress remodels the tissue in opposite directions across the loop (Vyas et al 2002). The hippocampal CA3 (and CA1) show dendritic retraction, spine loss and, over time, volume reduction; the medial prefrontal cortex similarly shows dendritic atrophy, both largely reversible in young animals. The basolateral amygdala does the reverse, hypertrophy with dendritic expansion and increased spine density, which is far less reversible and tracks with heightened anxiety. Prolonged cortisol elevation predicts hippocampal atrophy and memory decline in ageing humans (Lupien et al 1998), the clinical face of Sapolsky's glucocorticoid cascade hypothesis (Sapolsky et al 1986).

PEARL

One line for the viva: chronic stress shrinks the hippocampus and prefrontal cortex but grows the amygdala. Loss of the inhibitory brake plus a stronger threat driver is a self-reinforcing loop, and it maps directly onto why depression and PTSD are hard to switch off.

HOLD THIS

Chronic stress shrinks hippocampus and prefrontal cortex but hypertrophies the amygdala. A weaker brake plus a stronger driver is why stress disorders self-perpetuate.

TRAP Assuming every stress disorder runs high cortisol. Depression and Cushing's do, but PTSD classically shows **low or blunted** cortisol, and low cortisol at the trauma predicts later PTSD.

4.4 Allostasis, allostatic load and early-life programming

The system is designed to defend stability through change, and the cost of that defence is what damages the brain over a lifetime.

Allostasis and allostatic load. **Allostasis** (Sterling and Eyer 1988; McEwen and Stellar 1993) is achieving stability through change: the set-point itself shifts to meet demand, unlike the fixed set-point of homeostasis. **Allostatic load** is the cumulative wear-and-tear of repeated or inefficient stress responses; **allostatic overload** is the pathological extreme where that burden produces disease. The same mediators (glucocorticoids, catecholamines) that are protective acutely become damaging when chronically over-secreted or poorly switched off.

Early-life programming. Early-life stress and the quality of maternal care set the lifelong gain of the HPA axis through epigenetic mechanisms, an epigenetic-allostasis model in which early experience programs each individual onto a different stress-reactivity trajectory. Elevated

hippocampal MR levels in juvenile animals, for instance, predict anxiety-like behaviour in adulthood, linking developmental programming to later vulnerability.

4.5 The circuit in disorders: depression, PTSD and anxiety

The same three nodes, drive (amygdala), brake (hippocampus, vmPFC) and output (HPA), are read differently across the major stress-related disorders.

Depression. A hyperactive HPA axis: hypercortisolaemia and dexamethasone-suppression-test non-suppression (the DST itself is a the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes endocrine topic), with reduced hippocampal volume and amygdala overactivity (Drevets and Raichle 1992). Cushing's syndrome, a pathological hypercortisol state, produces reduced hippocampal volume with memory dysfunction (Starkman et al 1992) and a high psychiatric comorbidity, the clinical proof-of-concept that sustained cortisol harms the loop. In ICD-11 this is depressive disorders (6A70-6A7Z); DSM-5-TR major depressive disorder.

PTSD. A drive-and-brake imbalance: amygdala hyperreactivity with deficient vmPFC-mediated fear extinction (the infralimbic-to-amygdala extinction pathway; Santini and Quirk 2008), so threat associations fail to be inhibited. The low-cortisol paradox is exam-favourite: contrary to the "stress equals high cortisol" heuristic, low glucocorticoid levels at the time of trauma predict a higher chance of developing PTSD (Yehuda et al 1998), and a timed glucocorticoid dose given soon after trauma can be protective. ICD-11 post-traumatic stress disorder (6B40); DSM-5-TR PTSD.

Anxiety disorders. A sustained, anticipatory version of the same loop: amygdala and BNST over-drive with weak prefrontal inhibition. Amygdala volume falls when anxiety is successfully treated, showing the change is state-linked and reversible. ICD-11 anxiety and fear-related disorders (6B00-6B0Z); DSM-5-TR anxiety disorders.

> **COMMON TRAP**
>
> Do not assume every stress disorder is a high-cortisol state. Depression and Cushing's run high, but PTSD classically shows low or blunted cortisol, and low cortisol at the moment of trauma is a risk factor for later PTSD, not a protective sign. The lesion in PTSD is failed prefrontal inhibition of the amygdala, not simply too much cortisol.

5 · Prefrontal cortex: subdivisions and syndromes

The prefrontal cortex (PFC) is the brain's executive: it holds goals online, suppresses prepotent responses, and weighs reward against consequence. Three subdivisions map onto three classic lesion syndromes, and naming them cleanly is the fastest route through any frontal-lobe question.

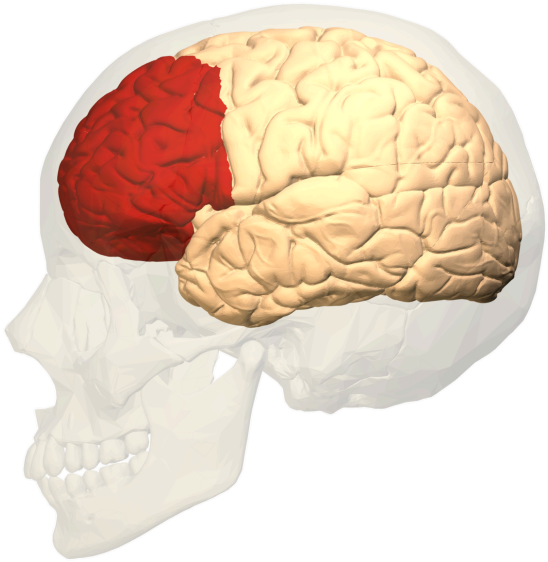


Image: Database Center for Life Science (DBCLS), CC BY-SA 2.1 Japan, via Wikimedia Commons

Fig 1.5 The prefrontal cortex (highlighted) lies anterior to the motor strip. Its three functional zones map to the three lesion syndromes in Tab 1.1: dorsolateral (executive, dysexecutive on lesion), orbitofrontal and ventromedial (reward and social, disinhibited on lesion), and anterior cingulate and medial (drive, apathetic on lesion).

REGION	FUNCTION	LESION SYNDROME	BEDSIDE PICTURE
DLPFC	Working memory, planning, set-shifting, abstraction	**Dysexecutive (dorsolateral)**	Poor planning, perseveration, concrete thinking, reduced verbal fluency
OFC / VMPFC	Reward valuation, impulse control, social judgement	**Disinhibited (orbitofrontal / pseudopsychopathic)**	Impulsivity, tactlessness, poor judgement, emotional lability (Phineas Gage)
ACC / medial	Drive, motivation, conflict monitoring	**Apathetic (medial / pseudodepressed)**	Apathy, abulia, akinetic mutism in severe cases

Tab 1.1 · The three frontal syndromes. Discriminating syndrome shaded.

HOLD THIS

DLPFC dysexecutive, orbitofrontal disinhibited, medial-cingulate apathetic. Three zones, three syndromes; the DLPFC is both the schizophrenia hypofrontality site and the rTMS target in depression.

♡ CLINICAL ANCHOR

The DLPFC is the convergence point of psychiatry's two commonest "frontal" stories: **hypofrontality** in schizophrenia (reduced DLPFC activation on working-memory tasks, the neural basis of negative and cognitive symptoms) and the DLPFC as the standard target of **therapeutic rTMS** in depression. If you can place the DLPFC, you can answer both.

5.1 Cytoarchitecture and the Brodmann map

The PFC is *granular heteromodal association cortex*: its defining histological feature is a well-developed internal granular layer (layer IV), the marker that separates true prefrontal cortex from the agranular motor and premotor fields behind it. It is the last cortex to myelinate, with **synaptic pruning** continuing into the mid-twenties, which is the structural reason adolescent judgement and impulse control mature late. For exams, anchor each functional zone to its Brodmann area (BA) rather than to vague surface names.

Dorsolateral (BA 9, 46, with 8 and 10)

Middle and superior frontal gyri. BA 46 sits in the middle frontal gyrus, ringed by BA 9 like an island (von Economo). The executive core.

Ventrolateral (BA 44, 45, 47)

Inferior frontal gyrus. BA 44 and 45 of the dominant hemisphere form *Broca area* (note: Broca is premotor association cortex, not prefrontal proper). BA 47 contributes to response inhibition and semantic retrieval.

Orbitofrontal (BA 11, 12, 47/12)

Gyrus rectus and orbital gyri on the inferior surface. Reward valuation and social-emotional appraisal.

Ventromedial and medial (BA 10, 11m, 25, 32, 24)

BA 24 and 32 are the anterior cingulate; BA 25 (subgenual cingulate) is the deep-brain-stimulation target in refractory depression (Mayberg). BA 10 is the frontopolar pole.

MNEMONIC

"9-46 to DELIBERATE, 11 to DESIRE, 24/32 to DRIVE"

BA 9 and 46 = dorsolateral deliberation (working memory, planning). BA 11 = orbitofrontal desire and reward. BA 24 and 32 = anterior cingulate drive and conflict monitoring. Three numbers, three syndromes.

5.2 DLPFC and working memory: the Baddeley link

The DLPFC (BA 9, 46) is the cortical substrate of the **central executive** in Baddeley and Hitch's multicomponent model of working memory. In that model a central executive allocates attention between two slave systems, the *phonological loop* (verbal rehearsal) and the *visuospatial sketchpad*, with a later *episodic buffer* binding them to long-term memory. The DLPFC does not store the items; it holds goals online and manipulates the contents, which is why single-item recognition survives a DLPFC lesion but any task requiring comparison, updating, or rule-switching fails (Goldman-Rakic; delayed-response work in macaques).

Lateralisation. Verbal working-memory tasks load the left DLPFC, visuospatial tasks the right (Smith, Jonides and Koeppe 1996); ageing reduces this lateralisation, interpreted as compensatory recruitment of the opposite hemisphere. **Bedside and test correlates.** DLPFC integrity is probed by the Wisconsin Card Sorting Test (perseveration to the old rule on lesion), Trail Making B, the Stroop interference task, phonemic verbal fluency (FAS), digit span backward and the Tower of London. The classic lesion signature is **perseveration, set-shifting failure and**

stimulus-bound behaviour, summarised by Goldman-Rakic as a failure to guide behaviour by internal representations rather than by the immediate environment.

> **PEARL**
> The DLPFC dysexecutive picture can mimic depression (psychomotor slowing, apathy, poverty of speech), which is why older texts called the dorsolateral syndrome *pseudodepressed*. Distinguish it: the DLPFC patient lacks the pervasive low mood, guilt and diurnal variation of a primary depressive episode, and fails executive tests out of proportion to affect.

5.3 OFC, VMPFC and the somatic marker hypothesis

The orbitofrontal cortex (BA 11, 47/12) and the ventromedial PFC (BA 10m, 11m, 25) handle reward valuation, impulse control and the emotional tagging of decisions. The OFC receives convergent input from amygdala, hippocampus and all sensory association cortices, and projects to ventral striatum, mediodorsal thalamus and hypothalamus: it is the node where a stimulus acquires its current motivational value, and it updates that value rapidly (reversal learning).

Somatic marker hypothesis (Damasio). Damasio proposed that the VMPFC links external situations to bodily-emotional states (*somatic markers*) that bias decisions before conscious reasoning completes. A VMPFC lesion severs this link, so the patient reasons normally in the abstract yet chooses disastrously in real life: intact IQ, catastrophic judgement. The laboratory signature is the **Iowa Gambling Task**, on which VMPFC patients keep drawing from high-reward, high-penalty decks and fail to develop the anticipatory skin-conductance response that healthy subjects generate before a risky choice. This dovetails with the *frontal lobe paradox*: preserved performance on structured bedside testing alongside disabling real-world failure, a knowing-doing dissociation.

> **COMMON TRAP**
> OFC and VMPFC are not interchangeable. Lateral OFC lesions correlate with disinhibition, irritability, OCD-type and even manic phenomena; ventromedial lesions classically produce **confabulation** and the somatic-marker decision deficit. A question describing spontaneous false memories told without intent to deceive is pointing at the ventromedial pole, not the dorsolateral.

5.4 Anterior cingulate cortex: dorsal versus rostral

The ACC (BA 24, 32) is the limbic-cognitive interface, and exam questions hinge on its functional split. The **dorsal/cognitive ACC** performs **conflict monitoring** and error detection: it lights up on the incongruent Stroop trial and on the post-error slowing that follows a mistake, then signals the DLPFC to tighten control (the conflict-monitoring model, Botvinick and Carter). The **rostral/ventral-affective ACC** (including subgenual BA 25) processes emotional salience, autonomic regulation and reward, and its dysfunction tracks with depression; pre-treatment rostral-ACC metabolism is a much-cited predictor of antidepressant response.

Damage to the medial ACC drive system gives the third frontal syndrome: **apathy, abulia and, when bilateral and severe, akinetic mutism**, a patient awake with eyes open but neither moving

nor speaking. ACA-territory infarcts and superior-sagittal-sinus-region lesions are the typical culprits.

5.5 Frontopolar cortex (BA 10) and connections

The frontopolar cortex (BA 10) is the largest single architectonic area in the human frontal lobe and is disproportionately enlarged in humans versus other primates. It supports the most abstract executive operations: prospective memory (holding a delayed intention), multitasking between two ongoing goals, relational reasoning and metacognitive self-monitoring. It is a transitional node coupling the default-mode network (self-referential thought) to the multiple-demand executive network.

Connections to memorise. The PFC's long association bundles are high-yield: the *uncinate fasciculus* links OFC to anterior temporal lobe and amygdala (limbic-orbitofrontal); the *cingulum* runs within the cingulate gyrus; the *superior longitudinal/arcuate fasciculus* links DLPFC to parietal and temporal association cortex. The whole system runs as parallel, segregated **cortico-striato-pallido-thalamo-cortical loops** (dorsolateral, orbitofrontal and anterior-cingulate circuits of Alexander and DeLong), which is why a caudate, pallidal or thalamic lesion can reproduce a frontal syndrome without touching the cortex (the subcortical frontal syndrome). Blood supply: lateral and orbital surfaces from the MCA, superior and medial surfaces from the ACA.

5.6 The three frontal syndromes, in full

Building on Tab 1.1, the discriminators below are what separate the three syndromes under exam pressure. Each maps to one prefrontal-subcortical circuit, and each carries an alternative classical name worth knowing.

FEATURE	DORSOLATERAL (DYSEXECUTIVE)	ORBITOFRONTAL (DISINHIBITED)	MEDIAL/CINGULATE (APATHETIC)
Classical alias	Pseudodepressed	**Pseudopsychopathic / frontal lobe personality**	Akinetic / abulic
Core deficit	Planning, set-shifting, working memory	**Impulse control, social judgement, reward valuation**	Drive and initiation
Behaviour	Perseveration, concrete thinking, poor fluency	**Tactlessness, impulsivity, hypersexuality, lability, utilisation behaviour**	Apathy, abulia, mutism if severe
Mood mimic	Looks depressed (flat, slow)	Looks manic/psychopathic	Looks profoundly depressed/catatonic
Best bedside test	WCST, Stroop, Trail B, fluency	**Iowa Gambling Task, go/no-go**	Initiation count, spontaneous speech
Typical lesion	Dorsolateral convexity	Orbital surface (TBI, Gage)	Medial/ACA territory, cingulate

The three frontal syndromes by discriminating column (shaded = the orbitofrontal disinhibited picture, the favourite single-best-answer stem).

5.7 Phineas Gage: the founding case

Harlow, on Phineas Gage (1848) LANDMARK

Event. A 25-year-old railway foreman; a tamping iron blasted through his left orbitofrontal and ventromedial cortex, which he survived. **Finding.** Intellect and memory were spared, but his personality changed: previously responsible and capable, he became impulsive, profane, capricious, unable to hold to a plan, "no longer Gage" in his friends' words. **Why it matters.** The first evidence that a circumscribed prefrontal lesion can dissolve personality and social judgement while leaving general cognition intact, the historical root of the orbitofrontal disinhibition syndrome and, a century later, of Damasio's somatic marker work (his wife Hanna Damasio reconstructed Gage's lesion trajectory from the skull).

5.8 Frontal release signs and primitive reflexes

Frontal release signs are primitive reflexes present in infancy, normally suppressed by maturing frontal cortex, and disinhibited again when that cortex is damaged. They support but do not prove frontal pathology, because they also reappear in normal ageing and diffuse cerebral disease, so their diagnostic specificity is limited.

- **Grasp reflex.** Involuntary grasp on stroking the palm; among the most reliable for frontal/contralateral medial-frontal disease.
- **Palmomental reflex.** Ipsilateral mentalis (chin) twitch on scratching the thenar eminence.
- **Snout/pout reflex.** Lip pursing on light tapping over the upper lip.
- **Glabellar tap (Myerson sign).** Failure to habituate to repeated taps between the eyebrows; also seen in Parkinson disease.
- **Rooting and sucking reflexes.** Re-emerge with extensive frontal damage and advanced dementia.

Related frontal behavioural signs that are higher-yield than the reflexes: *utilisation behaviour* and *environmental dependency* (the patient automatically uses an object placed before them), *imitation behaviour*, and failure of the Luria three-step (fist-edge-palm) motor sequence.

5.9 Clinical correlations across disorders

The PFC is the shared substrate behind most of psychiatry's circuit stories. Hold each disorder to its prefrontal signature.

DISORDER	PREFRONTAL SIGNATURE	EXAM HOOK
Schizophrenia	DLPFC **hypofrontality**: reduced activation on working-memory tasks, reduced long-interval cortical inhibition	**Neural basis of negative and cognitive symptoms; the rTMS/DLPFC target**
Major depression	Hypoactive left DLPFC; hyperactive subgenual ACC (BA 25)	BA 25 = Mayberg DBS target; rostral-ACC metabolism predicts response
OCD	Hyperactive OFC, caudate and ACC (the cortico-striato-thalamo-cortical loop)	**OFC hyperactivity normalises with successful SSRI or CBT**
ADHD	DLPFC and fronto-striatal underactivation; weak catecholamine tone	Stimulants and atomoxetine raise prefrontal dopamine/noradrenaline (Arnsten's inverted-U)
bvFTD	Degeneration of OFC and medial PFC; tau or TDP-43 pathology	Disinhibition, apathy, loss of empathy with early preserved memory

Prefrontal correlates of the major disorders, with the single most testable hook per row (shaded = the two most heavily examined).

♡ CLINICAL ANCHOR

Behavioural-variant FTD is the prototype neurodegenerative frontal syndrome: insidious disinhibition, apathy and loss of empathy with relatively preserved memory early, accounting for roughly 20% of early-onset (under-65) dementia, course about 6 to 11 years. Key pharmacological traps: cholinesterase inhibitors may worsen behaviour in bvFTD, benzodiazepines worsen cognition and fall risk, and antipsychotics carry increased mortality in dementia, so SSRIs (sertraline, citalopram) are first-line for the behavioural symptoms.

5.10 rTMS to the DLPFC: the therapeutic target

The left DLPFC is the standard repetitive-TMS target for major depression. The therapeutic logic mirrors the lesion physiology: the depressed left DLPFC is hypoactive, so **high-frequency (10 Hz) excitatory rTMS to the left DLPFC** is the classic protocol, with low-frequency (1 Hz) inhibitory stimulation to the right DLPFC as the alternative. The accelerated intermittent theta-burst variant (iTBS, including the SAINT/SNT schedule) delivers an equivalent dose far faster and is now in routine use.

Localisation, an examinable detail. The original "5 cm rule" measured 5 cm anterior from the motor hotspot, but it overshot the true DLPFC in many heads; the **BeamF3 / EEG 10-20 method** targeting the F3 electrode position is more accurate and is now preferred, with neuronavigation to BA 46/9 the most precise. Note also the diagnostic versus therapeutic distinction: applying TMS to the DLPFC can transiently *impair* working memory and the ability to deceive, the experimental counterpart of the lesion deficit.

RULE **High-frequency excitatory rTMS to the left DLPFC treats depression.** The depressed left DLPFC is hypoactive, so you drive it; low-frequency to the right is the alternative.

INDIA CONTEXT

rTMS is available at most academic and several private psychiatric centres in India and is used chiefly for treatment-resistant depression, auditory hallucinations (low-frequency to left temporoparietal cortex) and OCD. In Indian viva practice the high-yield answers are: target = left DLPFC, high-frequency = excitatory, localisation has moved from the 5-cm rule to BeamF3, and the common contraindication to remember is a personal seizure history or ferromagnetic intracranial metal.

6 · Basal ganglia circuits

The basal ganglia gate cortical output: they decide which motor and cognitive programmes are released and which are suppressed. The same architecture runs in parallel loops for movement, cognition and emotion, which is why this nucleus group sits behind movement disorders, OCD and the motor adverse effects of antipsychotics alike.

Nuclei

Striatum (caudate + putamen; ventral striatum = nucleus accumbens) · globus pallidus externa (GPe) and interna (GPi) · subthalamic nucleus (STN) · substantia nigra pars compacta (SNc, dopamine) and reticulata (SNr).

Three pathways, one question: does the thalamus get released or clamped? The output nuclei (GPi and SNr) are tonically inhibitory on the thalamus. The pathways modulate that brake.

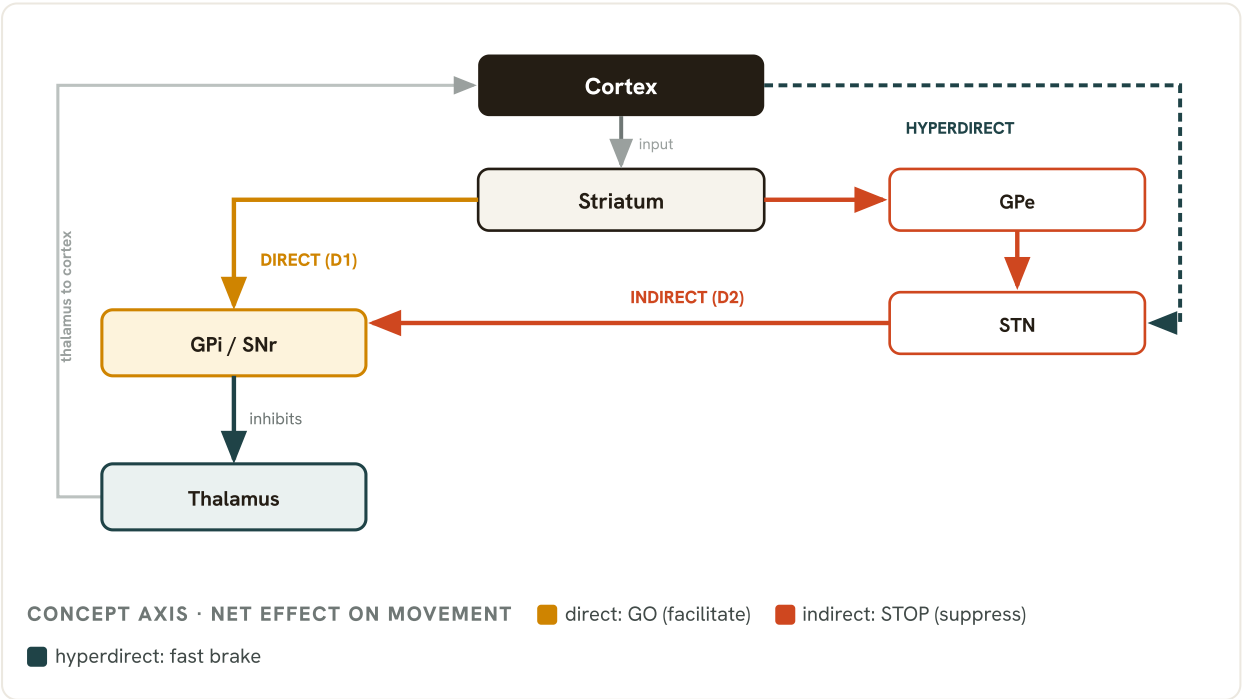


Fig 1.6 The cortico-striato-thalamo-cortical loop. The output nuclei (GPi/SNr) tonically inhibit the thalamus: the direct pathway (marigold, D1) disinhibits it to release movement, while the indirect (coral, D2) and hyperdirect (petrol) pathways raise GPi/SNr output to clamp it. Dopamine via D1 strengthens GO and via D2 weakens STOP, so nigral dopamine loss tips the balance toward suppression (parkinsonism).

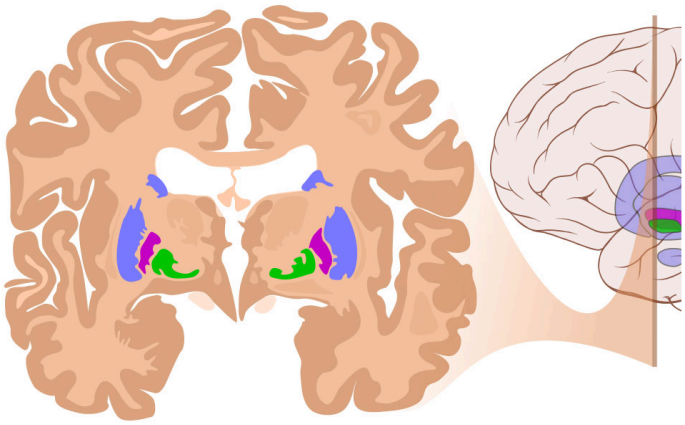


Image: Andrew Meyerson, CC BY-SA 3.0, via Wikimedia Commons

Fig 1.7 The basal-ganglia nuclei in coronal section: the caudate and putamen (together the striatum) and the globus pallidus deep to them. These are the physical structures whose GO and STOP pathways Fig 1.6 traces.

Parallel loops. The motor loop is only one of five cortico-striato-thalamo-cortical (CSTC) circuits. The **dorsolateral prefrontal loop** serves executive function, the **lateral orbitofrontal loop** is implicated in OCD (hyperactivity of the OFC-caudate-thalamus circuit is the leading model, and it normalises with SSRI or CBT response), and the **anterior cingulate loop** serves motivation. **Clinical correlates:** Parkinson's disease (SNc dopamine loss, hypokinesia), Huntington's disease (striatal degeneration, hyperkinesia and psychiatric prodrome), Tourette syndrome, OCD, and the extrapyramidal effects of D2 blockade.

HOLD THIS

Dopamine excites the D1 direct GO pathway and inhibits the D2 indirect STOP pathway, so it favours movement on both arms. Lose nigral dopamine and the thalamus is over-clamped: parkinsonism.

6.1 Components and subdivisions: how the nuclei are named

Exam stems exploit the fact that the basal ganglia carry two naming systems at once, an anatomical one and a functional one, and the two do not map cleanly onto each other. Master both labels for each part and the rest of the topic falls into place. The largest single component is the **striatum**, with a volume of roughly 10 cm cubed, and it is the input station for the whole system (Young 2023).

Neostriatum (dorsal striatum)

Caudate plus putamen, the phylogenetically newest part and the input nucleus for the motor and cognitive (dorsal) loops. The caudate is a C-shaped nucleus (head, body, tail) hugging the lateral ventricle; the putamen sits laterally, separated from the caudate by the internal capsule but joined to it anteriorly at the head.

Paleostriatum (pallidum)

The globus pallidus, the old (pale) striatum, split into **GPe** (external, an intrinsic relay) and **GPi** (internal, an output nucleus). Putamen plus globus pallidus together form the *lentiform (lenticular) nucleus*, a purely anatomical, lens-shaped grouping that crosses the functional divide.

Ventral striatum

Nucleus accumbens plus olfactory tubercle: the input nucleus for the limbic/reward loop, receiving dopamine from the ventral tegmental area rather than the SNc. This is the substrate of addiction, anhedonia and antipsychotic efficacy.

Associated nuclei

Subthalamic nucleus (STN, diencephalon, the only glutamatergic node) and substantia nigra (midbrain), itself split into the dopaminergic **SNc** (pars compacta) and the GABAergic output **SNr** (pars reticulata).

GROUPING	WHAT IT MEANS	MEMBERS
Striatum	Functional: the input nucleus	Caudate + putamen (+ accumbens)
Lentiform nucleus	Anatomical only: a lens-shaped block	Putamen + globus pallidus
Corpus striatum	Older umbrella term	Caudate + lentiform nucleus
Neostriatum	Phylogenetic: newest	Caudate + putamen

The four overlapping names for striatal grey matter. The trap (shaded) is the lentiform nucleus: it pairs the putamen (an input nucleus) with the pallidum (a relay/output), so it never corresponds to a single functional role.

⚠ COMMON TRAP

The *striatum* (caudate + putamen) and the *lentiform nucleus* (putamen + pallidus) overlap only in the putamen. A stem asking "which structure contains both an input nucleus and an output nucleus" wants the **lentiform nucleus**. The amygdala, although developmentally an "archistriatal" relative, is NOT counted as part of the basal ganglia in clinical neuroanatomy.

6.2 The projection neuron and its co-transmitters

About **95%** of striatal neurons are **medium spiny neurons** (MSNs), GABAergic projection cells that are silent at rest and fire only when driven by convergent cortical glutamate plus permissive dopamine. The remaining cells are interneurons, of which the tonically active cholinergic interneuron is the most exam-relevant: it sets the striatal acetylcholine tone that opposes dopamine, the pharmacological basis of anticholinergics in drug-induced parkinsonism (covered in 3.9). MSNs split into two molecularly distinct populations defined by their dopamine receptor and their peptide co-transmitter, and this single fact unlocks both pathways.

FEATURE	DIRECT-PATHWAY MSN	INDIRECT-PATHWAY MSN
Dopamine receptor	**D1 (Gs, excitatory)**	**D2 (Gi, inhibitory)**
Fast transmitter	GABA	GABA
Peptide co-transmitter	Substance P + dynorphin	Enkephalin
Projects to	GPi / SNr (output)	GPe (relay)
Net effect on movement	GO (facilitates)	STOP (suppresses)

The molecular signature of the two MSN populations. Memorise the receptor-peptide-target triplet on each side and the entire circuit is reconstructable.

MNEMONIC

"D1 = Direct = Drives" / "Indirect = Inhibits = Enkephalin"

D1, Direct, Drives movement, carries Dynorphin and substance P. The Indirect pathway Inhibits movement and carries enkephalin. Dopamine excites D1 (GO louder) and inhibits D2 (STOP quieter), so on both arms dopamine favours movement, which is why dopamine loss produces a hypokinetic state.

6.3 Direct pathway: the GO circuit in full synaptic detail

The direct pathway is a chain of three sign changes that ends in **disinhibition** of the thalamus. Trace it synapse by synapse and never memorise it as a black box.

- **Step 1, cortex to striatum.** Excitatory glutamatergic projections from cortical layers III and V depolarise D1 MSNs (Young 2023).
- **Step 2, striatum to GPi/SNr.** The D1 MSN fires GABA onto the output nuclei, *inhibiting* them. Substance P and dynorphin are co-released.
- **Step 3, GPi/SNr to thalamus.** The output nuclei are tonically GABAergic and normally clamp the ventral anterior (VA) and ventrolateral (VL) thalamus. With GPi now silenced, that clamp is lifted: the thalamus is **disinhibited**.
- **Step 4, thalamus to cortex.** Disinhibited VA/VL fire glutamate back to the motor/supplementary motor cortex, releasing the intended movement.

The pallidothalamic axons gather into two white-matter bundles, the *ansa lenticularis* and the *lenticular fasciculus*, which fuse into the *thalamic fasciculus* before entering the thalamus. The logic is a double inhibitory series, so two minus signs make a plus: inhibit the inhibitor and the thalamus is released (the same disinhibition principle the existing Fig 1.6 codes in marigold).

6.4 Indirect pathway: the STOP circuit through GPe and STN

The indirect pathway has two extra relays, the GPe and the STN, which flip the net sign so that the same cortical command now *raises* GPi output and clamps the thalamus harder.

- **Step 1.** Cortex excites the D2 MSN (glutamate).
- **Step 2.** The D2 MSN inhibits GPe (GABA, enkephalin co-released).

- **Step 3.** GPe normally inhibits the STN, so silencing GPe **disinhibits the STN**.
- **Step 4.** The freed STN, the only glutamatergic node, *excites* GPi/SNr.
- **Step 5.** An over-driven GPi clamps VA/VL thalamus even harder, suppressing competing or unwanted movement.

> **PEARL**
> Count the inhibitory synapses to predict the net effect. Direct pathway = two GABA synapses in series (striatum to GPi, GPi to thalamus) = disinhibition = GO. Indirect pathway adds the GPe-to-STN inhibitory synapse, making an **odd number** of inhibitory steps that ends in net excitation of GPi = STOP. The STN is the lone glutamatergic "amplifier" that lets the indirect pathway overshoot.

6.5 Hyperdirect pathway: the fast cortico-subthalamic brake

The hyperdirect pathway is a monosynaptic cortex-to-STN glutamatergic projection that bypasses the striatum entirely, so it is faster than both classical pathways and, importantly, is **not modulated by striatal dopamine** (the SNc cannot tune it). Because it reaches the STN first, it provides an early, diffuse excitatory drive to GPi/SNr that pre-emptively clamps the thalamus before any movement is released.

Functionally it serves a global "hold everything" or stop-signal role: cortex first slams the brake via the hyperdirect route, the direct pathway then carves out the one selected program, and the indirect pathway sharpens the surround by suppressing competitors, yielding a center-surround pattern of focused selection. Chen and colleagues (2020) demonstrated in humans that the prefrontal-subthalamic hyperdirect pathway mediates rapid action cancellation, the neural basis of reactive inhibitory control. Clinically it is the target circuit of *STN deep brain stimulation* in Parkinson disease, where high-frequency stimulation normalises the pathologically over-active STN drive.

6.6 Parallel cortico-striato-thalamo-cortical loops

The same three-pathway architecture is replicated in at least five segregated, parallel loops (the Alexander, DeLong and Strick scheme). Each loop runs cortex to striatum to pallidum/SNr to thalamus and back to its *originating* cortical area, staying topographically separate. This is why a single nuclear group sits behind movement disorders, executive dysfunction, OCD and apathy alike: lesion the limbic loop and you get a psychiatric syndrome with no motor sign.

LOOP	STRIATAL ENTRY	CORTICAL ORIGIN/TARGET	CLINICAL CORRELATE OF DYSFUNCTION
Motor	Putamen	SMA, motor, premotor	Parkinsonism, chorea, dystonia
Oculomotor	Body of caudate	Frontal + supplementary eye fields	Saccade abnormalities
Dorsolateral prefrontal	Dorsolateral caudate head	DLPFC	Executive dysfunction, dysexecutive syndrome
Orbitofrontal (lateral)	Ventromedial caudate	Lateral OFC	**OCD, disinhibition**
Anterior cingulate / limbic	Ventral striatum (accumbens)	ACC, medial OFC	Apathy, abulia, akinetic mutism, addiction

The five parallel loops. The OFC and ACC/limbic loops (lower rows) are the ones psychiatry exams test, linking the basal ganglia to OCD and to motivational disorders rather than to movement.

6.7 Neurotransmitters and modulation at a glance

Three transmitter families run the circuit: glutamate (all cortical inputs plus the STN), GABA (every striatal and pallidal projection), and dopamine (the SNc/VTA modulator). Acetylcholine from striatal interneurons and serotonin from the raphe fine-tune it.

Nigrostriatal dopamine

SNc to striatum: excites D1 (boosts GO) and inhibits D2 (releases the STOP brake). Tonic dopamine release preferentially tunes the D1/direct arm. Loss of this single input is the lesion in Parkinson disease.

Thalamostriatal fibres

From intralaminar (centromedian/parafascicular) thalamic nuclei back to striatum, glutamatergic, providing arousal and attentional gating of the loop.

Dopamine-acetylcholine balance

Striatal cholinergic interneurons oppose dopamine. When dopamine falls (or is blocked), relative cholinergic excess emerges, the rationale for anticholinergics in drug-induced parkinsonism.

6.8 Functions: action selection, habit and reward

The unifying computation is **action selection**: the basal ganglia receive competing candidate programs from cortex and, by default, hold them all under tonic GPi/SNr inhibition, releasing only the winner through focused direct-pathway disinhibition while the indirect and hyperdirect pathways suppress the rest. Three functional themes recur in vivas.

- **Action selection / gating.** "Should this program run?" decided by the dorsal motor and cognitive loops; the GPi is the gate.
- **Habit and procedural learning.** Dorsolateral striatum encodes stimulus-response habits; with overtraining, control migrates from goal-directed prefrontal loops to habitual sensorimotor striatum, a model invoked for compulsions and addiction.
- **Reward and reinforcement.** Phasic dopamine to the ventral striatum encodes a *reward-prediction error* (Schultz's work), the teaching signal of reinforcement learning and the engine

of dopaminergic addiction.

6.9 Clinical correlation: hypokinetic and hyperkinetic disorders

The whole topic distils to one rule: too little GPi output releases excess movement (**hyperkinetic**), too much GPi output clamps movement (**hypokinetic**). Map each disorder onto which pathway or node fails.

TRAP Treating the striatum and lentiform nucleus as the same block. The **lentiform** nucleus (putamen plus pallidus) pairs an input nucleus with an output nucleus and never maps to a single function.

DISORDER	LESION / MECHANISM	NET CIRCUIT EFFECT	PHENOTYPE + KEY FACT
Parkinson disease	SNc dopaminergic loss; alpha-synuclein Lewy bodies	**Less D1 GO + less D2 brake release to GPi over-active to thalamus clamped**	Hypokinetic: bradykinesia, resting tremor, rigidity, postural instability. Rx levodopa.
Huntington disease	CAG repeat, HTT gene, chromosome 4p; early loss of *indirect*-pathway (D2/enkephalin) MSNs in caudate/putamen	Indirect STOP gone to thalamus under-clamped	Hyperkinetic chorea + cognitive/psychiatric decline. Rx tetrabenazine (VMAT2 inhibitor).
Hemiballismus	Lesion of contralateral STN (classically lacunar stroke)	Loss of STN glutamate drive to GPi to indirect STOP fails	Violent flinging proximal-limb movements, contralateral. Often self-limiting.
Tourette syndrome	Cortico-striato-thalamo-cortical dysregulation; relative dopaminergic excess; OFC/limbic loop	Faulty striatal GABAergic gating	Motor + vocal tics, semi-suppressible. Rx alpha-2 agonists, antipsychotics.
OCD	Hyperactive OFC-caudate-thalamus (lateral orbitofrontal) loop	Loop fails to "let go" of an action/thought	Obsessions + compulsions; SSRI/CBT first-line; refractory: anterior capsulotomy/DBS.
Wilson disease	ATP7B mutation; copper deposition in putamen ("face of the giant panda", Kayser-Fleischer rings)	Mixed striatal injury	Young-onset parkinsonism, dystonia, wing-beating tremor + hepatic/psychiatric features. Rx chelation.
Sydenham chorea	Post-streptococcal (rheumatic fever) autoimmune antibodies vs striatal neurons	Striatal dysfunction	Childhood chorea, emotional lability; commonest acquired childhood chorea. Major Jones criterion.

The core movement-disorder differential mapped to circuit logic. The hit cell anchors Parkinson disease as the prototype hypokinetic (GPi over-active) failure against which the hyperkinetic disorders are read.

6.10 Antipsychotic motor adverse effects: the psychiatry-facing payoff

This is where the circuit earns its place in Paper I. D2 blockade in the *nigrostriatal* pathway by antipsychotics pharmacologically mimics dopamine loss in the direct/indirect arms, producing a drug-induced parkinsonian state and its relatives.

SYNDROME	ONSET	MECHANISM	PHENOMENOLOGY + MANAGEMENT
Acute dystonia	Hours to days	Acute striatal dopamine-ACh imbalance	Oculogyric crisis, torticollis, laryngospasm. Rx anticholinergic (IM), young males at risk.
Akathisia	Days to weeks	Mesocortical/striatal dopaminergic dysregulation	Inner restlessness, cannot keep still. Rx propranolol, reduce dose; high suicide-risk red flag.
Drug-induced parkinsonism	Weeks	**Nigrostriatal D2 blockade mimics SNc loss**	Bradykinesia, rigidity, tremor (often symmetrical). Rx anticholinergic, switch to lower-affinity agent.
Tardive dyskinesia	Months to years	Postsynaptic D2 upregulation/supersensitivity after chronic blockade	Choreoathetoid orofacial-lingual movements, often irreversible. Rx VMAT2 inhibitors (valbenazine, deutetrabenazine); stop offending drug cautiously.
Neuroleptic malignant syndrome	Days (idiosyncratic)	Abrupt, profound central D2 blockade (nigrostriatal + hypothalamic)	Rigidity, hyperthermia, autonomic instability, raised CK. Rx stop drug, dantrolene, bromocriptine, supportive.

The extrapyramidal side-effect spectrum, ordered by time course. The hit cell shows the shared root, nigrostriatal D2 blockade reproducing the parkinsonian circuit failure; tardive dyskinesia is the late, opposite (supersensitivity) twist.

HOLD THIS

Antipsychotic EPS is nigrostriatal D2 blockade mimicking dopamine loss. Drug-induced parkinsonism is acute functional deficiency; tardive dyskinesia is the chronic postsynaptic-supersensitivity mirror image.

INDIA CONTEXT

High-potency typicals such as haloperidol and trifluoperazine remain heavily used in Indian public-sector practice for cost reasons, so drug-induced EPS, acute dystonia and tardive dyskinesia are far more common in everyday clinical work and in viva cases here than the second-generation-dominated Western literature implies. Trihexyphenidyl is the ward standard anticholinergic; it carries its own anticholinergic and abuse-liability caveats.

CLINICAL ANCHOR

One examiner-favourite contrast: **NMS is rigidity + fever from too little dopamine** (D2 blockade), whereas **serotonin syndrome is clonus + fever from too much serotonin**. Tardive dyskinesia and drug-induced parkinsonism are pharmacological mirror images: parkinsonism is acute functional dopamine deficiency, tardive dyskinesia is chronic postsynaptic dopamine supersensitivity, which is why adding more dopamine blockade transiently masks tardive dyskinesia but worsens parkinsonism.

7 · Thalamus: nuclei and relay functions

The thalamus is the gateway to the cortex: every sensory modality except smell relays through it, and it is gated by the reticular nucleus and modulated by attention. For psychiatry the headline is the **mediodorsal (MD) nucleus**, the limbic relay to the prefrontal cortex, implicated in schizophrenia (reduced MD volume and neuron number).

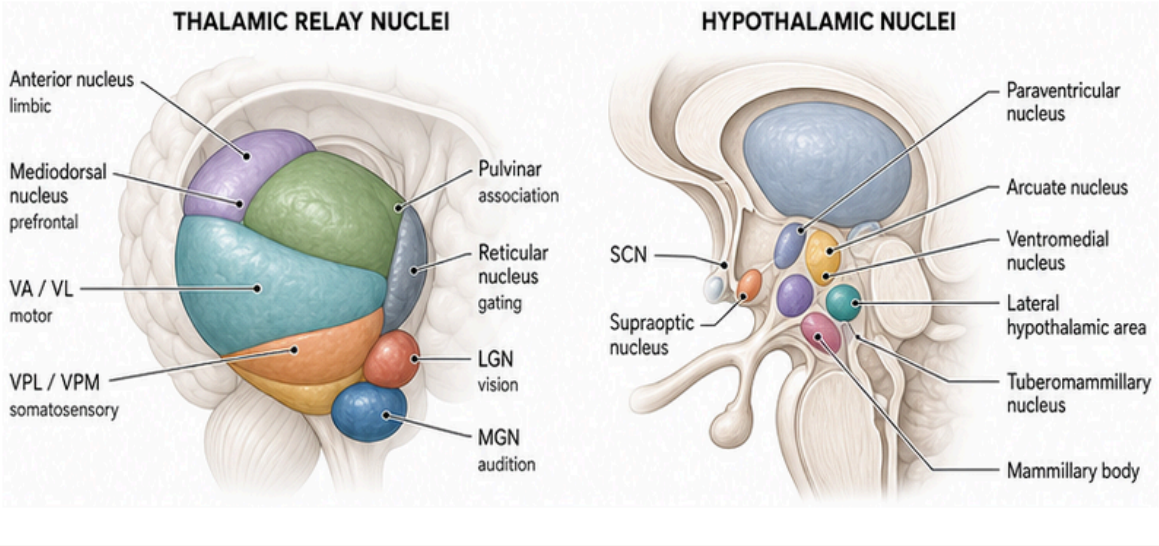


Fig 1.8 Thalamic relay nuclei and hypothalamic nuclei arranged by function: cortical relay and gating on the left, endocrine, autonomic, circadian and homeostatic control on the right.

NUCLEUS	RELAYS	PROJECTS TO
Anterior	Limbic (Papez loop)	Cingulate gyrus
Mediodorsal (MD)	Limbic, emotion, memory	Prefrontal cortex (schizophrenia link)
Ventral anterior / lateral (VA/VL)	Motor (basal ganglia, cerebellum)	Motor and premotor cortex
Ventral posterior (VPL/VPM)	Somatosensory (body / face)	Primary somatosensory cortex
Lateral geniculate (LGN)	Vision	Primary visual cortex
Medial geniculate (MGN)	Hearing	Primary auditory cortex
Pulvinar	Visual attention, integration	Parietal, temporal, occipital
Intralaminar (e.g. centromedian)	Arousal (from RAS)	Diffuse cortex, striatum
Reticular	Gates other thalamic nuclei (GABA)	Thalamus itself (no cortical output)

Tab 1.2 · Thalamic nuclei and their relay functions. MD shaded as the principal psychiatric relay.

HOLD THIS

The mediodorsal nucleus is the thalamus of psychiatry: the limbic relay to prefrontal cortex, with reduced volume and neuron number in schizophrenia. The association nuclei (anterior, MD, pulvinar) carry cognition; the specific relays carry a single modality.

7.1 Three ways to classify the same nuclei

The thalamus holds roughly 60 nuclei, and the trap in exams is that the same nucleus has three names depending on which scheme is in play. The relay table above (anterior, MD, VA/VL, VPL/VPM, LGN, MGN, pulvinar) is the *anatomical* scheme, organised around the **internal medullary lamina**, a Y-shaped sheet of white matter that splits the thalamus into an anterior, a medial and a lateral group, with the intralaminar nuclei buried inside the lamina itself. The two schemes you must layer on top are *functional* (what the nucleus computes) and *connectional* (where its inputs come from). Knowing all three lets you answer "which nucleus" and "why that deficit" from the same fact.

Relay (specific) nuclei

Receive specific, well-defined sensory or motor input from the periphery and project to a discrete, functionally pure cortical area. VA, VL, VPL/VPM, LGN, MGN. These are the "labelled-line" relays: lesion one, lose one modality.

Association nuclei

Receive most input from the cortex itself and project back to higher-order association cortex, regulating integration rather than raw relay. **Anterior nucleus, mediodorsal (MD), pulvinar.** Their lesions produce cognitive and affective syndromes, not pure sensory loss, which is exactly why psychiatry cares about them.

Nonspecific (diffuse-projection) nuclei

Project broadly and diffusely across cortex; subserve global states (arousal, consciousness, attention) rather than content. **Reticular nucleus, intralaminar nuclei, midline nuclei.**

MNEMONIC

The 3 A's are the Association nuclei: Anterior, dorsomedial (Above), pulvinAr

The three association nuclei are the psychiatry-relevant ones (memory, executive, attention). If a question links a thalamic nucleus to a cognitive or psychiatric syndrome rather than to numb skin or a visual-field cut, it is almost always one of these three.

7.2 Anterior nucleus: the Papez relay and its memory role

The **anterior nuclear group** (anteroventral, anteromedial, anterodorsal subnuclei) is the thalamic station of the *Papez circuit*. Its dominant afferent is the **mammillothalamic tract** from the medial mammillary nucleus; it projects reciprocally to the **cingulate gyrus** (Fig 1.2 region) and receives the fornix indirectly. This wires it into episodic and spatial memory, which is why an anterior-thalamic lesion produces an amnestic syndrome that mimics hippocampal damage. Because its input is from the limbic system and its output is to limbic cortex, it is an *association* nucleus despite sitting in its own anatomical group.

CLINICAL ANCHOR

The anterior nucleus and the mammillothalamic tract are the structures that drag diencephalic damage into the memory domain. In Korsakoff and in strategic thalamic infarction, it is interruption of the mammillothalamic tract reaching the anterior nucleus (and damage to MD) that yields anterograde amnesia, not the cortex.

7.3 Mediodorsal nucleus: the prefrontal limbic relay

The **mediodorsal nucleus (MD)** is the single most exam-tested thalamic structure in psychiatry, so deepen it beyond the one-line "schizophrenia link" above. MD is the principal relay to the **prefrontal cortex** and has two functionally distinct parts: a *magnocellular* (medial) part connected to the amygdala, olfactory and limbic cortex and orbitofrontal cortex, and a *parvocellular* (lateral) part connected to dorsolateral prefrontal cortex. Through these it carries affective valence, reward and executive signals into the frontal lobe, and it is the only major route by which olfactory and amygdalar information reaches neocortex.

- **Schizophrenia.** Reduced MD volume and a reduced absolute neuron count are among the more replicated structural findings, fitting the dysconnection model of frontal-thalamic circuitry. Pair this with the reduced thalamic volume seen on MRI.
- **Memory.** MD damage (with the anterior nucleus) is the diencephalic substrate of Korsakoff amnesia; a left MD or paramedian infarct can cause an acute Korsakoff-like amnestic syndrome.
- **Historical surgery.** The MD-to-orbitofrontal connection was the target severed in prefrontal leucotomy, which is why the procedure blunted affect.

7.4 Motor relays (VA/VL) and sensory relays (VPL/VPM, LGN, MGN)

These are the labelled-line specific relays. Beyond the relay table above, the discriminating detail exams want is the exact afferent and the lateralisation of the geniculates.

NUCLEUS	KEY AFFERENT (INPUT)	CORTICAL TARGET	LESION SIGNATURE
VA	Globus pallidus internus + substantia nigra (magnocellular)	Premotor cortex (areas 6, 8)	Movement planning / initiation deficit
VL	Cerebellum (dentate) + globus pallidus	Primary motor cortex (area 4)	Contralateral ataxia / dyscoordination
VIM (ventral intermediate, part of VL)	Cerebellar (dentatothalamic)	Motor cortex	DBS target for essential tremor and tremor-dominant PD
VPL	Medial lemniscus + spinothalamic (body)	S1 (postcentral gyrus)	Contralateral hemianaesthesia of body
VPM	Trigeminal + gustatory (face, taste)	S1 (face area)	Contralateral facial sensory loss, taste loss
LGN	Optic tract (6 layers; crossed nasal + uncrossed temporal)	V1 (calcarine cortex)	Contralateral homonymous hemianopia / quadrantanopia
MGN	Inferior colliculus (auditory, tonotopic)	A1 (temporal lobe)	Subtle bilateral hearing change (auditory input is bilateral)

The specific relays, each tagged with the one afferent that distinguishes it and the deficit that betrays a lesion. Note that LGN and MGN are geniculate "bodies" some authors place in the dorsal diencephalon rather than the thalamus proper.

⚠ COMMON TRAP

Because auditory pathways are bilateral by the level of the inferior colliculus, a unilateral MGN lesion does **not** cause unilateral deafness, unlike the clean contralateral loss seen with VPL, VPM or LGN. This crossed-versus-bilateral asymmetry is a favourite single-best-answer discriminator.

7.5 Pulvinar, intralaminar and reticular nuclei: attention, consciousness, gating

Pulvinar. The largest thalamic nucleus, an *association* nucleus reciprocally connected with parietal, temporal and occipital (association) cortex. It coordinates **visual attention** and cross-cortical synchronisation, and is the site of the imaging "pulvinar sign" (see clinical section).

Intralaminar and midline nuclei. Buried in the internal medullary lamina, the rostral group (central medial, paracentral, central lateral) and caudal group (**centromedian, parafascicular**) take input from the globus pallidus, deep cerebellar nuclei and the reticular activating system, and project diffusely to cortex and striatum. They are the thalamic arm of the ascending arousal system, governing **arousal, consciousness and pain regulation**. The centromedian is part of the motor loop and is a DBS target in some movement and epilepsy work.

Reticular nucleus (TRN). A thin GABAergic shell wrapping the lateral thalamus, with the internal capsule immediately lateral to it. Uniquely it sends **no axons to cortex**: thalamocortical and

corticothalamic fibres pass through it and give off collaterals, and the TRN feeds inhibition back onto the relay nuclei. This makes it the thalamic **gatekeeper**, the structure that decides which relays are open to cortex (sensory gating, selective attention) and the pacemaker that generates **sleep spindles** during NREM stage 2. Its rhythmic GABAergic bursting is also implicated as the generator of generalised spike-and-wave discharges in idiopathic generalised epilepsy.

> PEARL
>
> Two thalamic structures explain why exam stems on consciousness and attention keep returning to the thalamus: the **intralaminar nuclei** (the relay of the ascending reticular activating system into cortex, hence coma with bilateral lesions) and the **reticular nucleus** (the GABAergic gate generating spindles and gating sensory throughput). Specific relays carry content; these two carry state.

7.6 Internal capsule and blood-supply relations

The thalamus is bounded laterally by the **posterior limb of the internal capsule**, which separates it from the lentiform nucleus; the reticular nucleus lies between the two. This proximity matters clinically: a lesion that spreads from thalamus into the adjacent posterior limb adds a *contralateral hemiparesis* (corticospinal fibres) to the sensory loss, and the genu/posterior-limb relationship is why thalamic strokes are rarely purely sensory. Vascular supply comes from four territories: tuberothalamic (anterior), which arises from the **posterior communicating artery**, plus inferolateral/thalamogeniculate (the territory of classic Dejerine-Roussy), paramedian, and posterior choroidal, which arise from **posterior cerebral artery** branches.

> PEARL
>
> The **artery of Percheron** is a single paramedian trunk arising from one PCA that supplies both paramedian thalami; it is present in about 4% to 12% of people. Its occlusion causes **bilateral paramedian thalamic infarction**, classically presenting with the triad of altered consciousness, vertical-gaze palsy and memory impairment, a high-yield stroke vignette.

7.7 Thalamic clinical syndromes

The thalamus earns its psychiatry weight through a handful of named syndromes. Map each to its nucleus or territory.

Dejerine and Roussy (1906) LANDMARK

Description. The thalamic pain syndrome, after a lesion of the thalamogeniculate (inferolateral PCA) territory, typically involving VPL/VPM. **Course.** An initial contralateral hemisensory loss and tingling, then over weeks to months a transition to severe, spontaneous, often burning *central neuropathic pain* (anaesthesia dolorosa), with allodynia and hyperpathia in the numb territory. **Mechanism.** Loss of central cortical inhibition after deafferentation, a disinhibition model. **Why it matters.** It is the prototype of central post-stroke pain and the classic answer to "painful numbness after a thalamic stroke".

- **Mediodorsal in schizophrenia.** Reduced MD volume and neuron number; part of the frontothalamic dysconnection account (see 4.3).
- **Anterior / MD in Korsakoff.** Thiamine-deficiency damage to the mammillary bodies extends via the mammillothalamic tract to the anterior nucleus and MD, producing the diencephalic amnestic syndrome with confabulation. Often nutritional in alcohol use disorder.
- **Fatal familial insomnia.** An autosomal-dominant prion disease from a *PRNP* mutation on chromosome 20p13, with selective degeneration of the **anterior and mediodorsal thalamic nuclei**. Progressive untreatable insomnia, dysautonomia, then panic, paranoia, phobias, hallucinations, total sleeplessness, dementia, mutism and death.
- **Central (thalamic) pain.** The broader category of which Dejerine-Roussy is the prototype; any deafferenting thalamic lesion can drive it.
- **Pulvinar sign.** Symmetrical posterior-thalamic (pulvinar) T2/FLAIR hyperintensity, the "hockey-stick" sign, originally described in variant Creutzfeldt-Jakob disease and also highly specific for Fabry disease with cardiac/renal involvement.

SYNDROME	NUCLEUS / TERRITORY	HALLMARK
Dejerine-Roussy	VPL/VPM (thalamogeniculate)	Numbness then burning central pain
Korsakoff amnesia	Anterior + MD (via mammillothalamic tract)	Anterograde amnesia, confabulation
Fatal familial insomnia	Anterior + MD	Untreatable insomnia, dysautonomia, death
Schizophrenia structural finding	MD (and overall thalamic volume)	Reduced volume / neuron number
Percheron infarct	Bilateral paramedian	Drowsiness, vertical-gaze palsy, amnesia

A one-look map from thalamic syndrome to the responsible nucleus, the level at which most single-best-answer questions are pitched.

RULE **Painful numbness after a thalamic stroke is Dejerine-Roussy (VPL/VPM territory).** Numbness first, then weeks later a burning central pain in the same field.

TRAP Expecting a unilateral MGN lesion to cause unilateral deafness. Auditory pathways are bilateral by the inferior colliculus, so unlike VPL, VPM or LGN, an MGN lesion gives no clean contralateral loss.

PEARL

Notice the convergence: **both** Korsakoff and fatal familial insomnia hit the **anterior and mediodorsal nuclei**, the two association relays for memory and limbic-prefrontal traffic. The same nuclei whose dysconnection is invoked in schizophrenia. The association nuclei are the psychiatry of the thalamus.

8 · Hypothalamus: nuclei and functions

Four grams of tissue that runs homeostasis, the endocrine system and the autonomic and circadian clocks. It is the efferent arm of the limbic system, translating emotion into bodily change (the racing heart of fear is the amygdala speaking through the hypothalamus).

- **Suprachiasmatic nucleus (SCN)** the master circadian clock, entrained by retinal light, driving melatonin via the pineal (topic 14, 25).
- **Supraoptic & paraventricular nuclei** synthesise ADH (vasopressin) and oxytocin; the paraventricular nucleus also drives the HPA stress axis via CRH.
- **Ventromedial nucleus** satiety centre (lesion causes hyperphagia and obesity); **lateral nucleus** hunger centre (lesion causes aphagia).
- **Anterior hypothalamus** heat loss and parasympathetic; **posterior** heat conservation and sympathetic.
- **Preoptic area** thermoregulation and sleep onset (ventrolateral preoptic, VLPO, the sleep switch, topic 14).
- **Mammillary bodies** memory relay on the Papez circuit (Wernicke-Korsakoff).

MNEMONIC

"The HypoThalamus regulates 5 F's"

Feeding (ventromedial satiety, lateral hunger), **F**ighting (rage, defence), **F**leeing (autonomic), **F**ornication (HPG axis, sexual behaviour) and physiological regulation: temperature, fluid and circadian rhythm.

8.1 Anatomical zones and the full nuclear roster

The hypothalamus is parsed two ways at once, and exams test both axes. In the **mediolateral** plane it is divided into three *zones* running parallel to the third ventricle; in the **rostrocaudal** plane it is divided into three *regions* (anterior or supraoptic, middle or tuberal, posterior or mammillary). Any given nucleus sits at the intersection of one zone and one region, and that coordinate is the cleanest way to remember its function.

Periventricular zone

A thin sheet of cells just inside the ependyma of the third ventricle. Functionally **neuroendocrine and autonomic**: its two prominent residents are the *arcuate* nucleus (which extends laterally into the medial zone) and part of the *paraventricular* nucleus.

Medial zone

The cytoarchitectonically richest band, holding most of the named nuclei. Predominantly governs the **autonomic nervous system and neuroendocrine output**.

Lateral zone

Few discrete nuclei, but carries the great longitudinal fibre highways, above all the *medial forebrain bundle*. It is demarcated from the medial zone by the fornix and houses the lateral hypothalamic area (feeding, arousal) and the lateral tuberal complex.

Classical teaching counts **eleven major nuclei**. The table below fixes each to its zone, region and headline function; commit the discriminator column, because single-best-answer items live there.

NUCLEUS	ZONE	REGION	CORE FUNCTION (AND LESION SIGNATURE)
Preoptic	Medial / lateral	Anterior	Heat loss; GnRH; NREM sleep onset; sexual dimorphism
Anterior	Medial	Anterior	**Heat dissipation + parasympathetic; lesion to hyperthermia**
Suprachiasmatic (SCN)	Medial	Anterior	Master circadian clock; lesion to arrhythmic sleep-wake
Supraoptic (SON)	Medial / lateral	Anterior	**Magnocellular ADH (mostly); lesion to central DI**
Paraventricular (PVN)	Periventricular / medial	Anterior to tuberal	Oxytocin + ADH; CRH (HPA), TRH (HPT); autonomic
Dorsomedial (DMH)	Medial	Tuberal	Emotional expression and rage; integrates circadian and feeding
Ventromedial (VMH)	Medial	Tuberal	**Satiety; lesion to hyperphagia, obesity, savage rage**
Arcuate (infundibular)	Periventricular / medial	Tuberal	Energy sensing; GHRH, dopamine (PIF); tuberoinfundibular hub
Lateral hypothalamic area	Lateral	Tuberal	**Hunger; orexin; lesion to aphagia, weight loss, somnolence**
Posterior	Medial	Posterior	Heat conservation + sympathetic; lesion to poikilothermia
Mammillary	Medial	Posterior	Papez memory relay; lesion to anterograde amnesia (Korsakoff)

The eleven hypothalamic nuclei mapped to zone, region and the lesion that betrays each. Discriminator cells carry the exam-favourite consequences.

MNEMONIC

"A SAD PuPPy SeeS"

The four anterior-region nuclei in one breath: **A**nterior, **S**upraoptic, **P**reoptic, **P**araventricular, **S**uprachia**S**matic (SCN). For the autonomic poles: **A**nterior is the **A**ir-conditioner (heat loss, parasympathetic), **P**osterior is the **P**arka and the **P**ush (heat conservation, sympathetic).

8.2 Neuroendocrine output: the two secretory systems

The hypothalamus reaches the pituitary by two anatomically distinct routes, and confusing them is the single most common neuroanatomy trap in this topic. Both arise from specialised neurosecretory cells but differ in cell size, target and vascular plumbing.

Magnocellular system (the neurohypophysis)

Large-bodied neurons of the **SON and PVN** synthesise *vasopressin (ADH)* and *oxytocin*, package them with their carrier neurophysins, and send axons through the *hypothalamo-neurohypophyseal tract* down the infundibulum to terminate on capillaries of the **posterior pituitary**. There is no portal step: the hormone is released directly into the systemic circulation. SON is predominantly ADH; PVN is predominantly oxytocin.

Parvocellular system (the adenohypophysis)

Small-bodied neurons release *releasing and inhibiting factors* into the primary capillary plexus of the **hypophyseal portal system** at the median eminence. Portal veins carry these factors a few millimetres to a second plexus in the **anterior pituitary**, where they tune trophic-hormone output. This portal route, not a direct neural one, is why anterior pituitary control is humoral.

The releasing-factor logic by axis: **HPA**, PVN CRH (plus vasopressin as co-secretagogue) drives ACTH. **HPT**, PVN TRH drives TSH (and prolactin). **HPG**, preoptic and arcuate GnRH, released in pulses, drives FSH and LH; tonic rather than pulsatile GnRH paradoxically suppresses the axis, the pharmacological basis of GnRH-agonist downregulation. **GH**, arcuate GHRH stimulates and periventricular somatostatin inhibits, a push-pull pair. **Prolactin** is the outlier: it is under *tonic inhibition* by arcuate dopamine (the tuberoinfundibular pathway), so anything that lowers dopamine, including stalk compression or dopamine-antagonist antipsychotics, releases the brake and raises prolactin.

PEARL

Prolactin is the only anterior pituitary hormone whose default hypothalamic signal is *inhibitory*. A pituitary stalk lesion therefore drops every trophic hormone except prolactin, which **rises** (loss of dopamine delivery). This "stalk effect" hyperprolactinaemia is usually modest, under about 150 ng/mL, and helps distinguish a non-functioning macroadenoma compressing the stalk from a true prolactinoma, which typically pushes far higher.

HOLD THIS

Prolactin is the only anterior-pituitary hormone under tonic dopaminergic inhibition. So a stalk lesion, or D2-blocking antipsychotics, drops every trophic hormone except prolactin, which rises.

8.3 Autonomic control and thermoregulation

The hypothalamus is the head ganglion of the autonomic nervous system and the efferent arm of the limbic system (the topic 8 head note frames this well; here is the mechanism). The polarity is anatomical and reciprocal. The **anterior and preoptic hypothalamus** is the parasympathetic and heat-dissipating pole: warming of its thermosensitive neurons triggers cutaneous vasodilation, sweating and panting-equivalent heat loss. The **posterior hypothalamus** is the sympathetic and heat-conserving pole: cooling triggers vasoconstriction, piloerection and shivering thermogenesis, and it also mediates the diffuse sympathetic arousal of the Cannon fight-or-flight response. The preoptic area holds the body's thermostatic **set point**; pyrogens (prostaglandin E2) raise this set point to generate fever, which is why the febrile patient feels cold and shivers despite a rising core temperature.

POLE	AUTONOMIC LIMB	THERMAL ROLE	LESION PRODUCES
Anterior / preoptic	Parasympathetic	Heat loss (vasodilation, sweat)	**Hyperthermia (cannot dump heat)**
Posterior	Sympathetic	Heat conservation (shiver, vasoconstrict)	**Hypothermia / poikilothermia**

The reciprocal thermoregulatory and autonomic poles. Note the lesion paradox: destroy the cooling centre and the patient overheats.

⚠ COMMON TRAP

Students reverse the lesion logic. The rule: a lesion produces the *opposite* of the centre's function because the centre is destroyed. **Anterior** lesion (loss of heat loss) gives **hyperthermia**; **posterior** lesion (loss of heat conservation, and it also disrupts the descending sympathetic tract) gives **hypothermia or poikilothermia**. For psychiatry, this circuitry is the substrate of antipsychotic-induced thermal dysregulation and of the hyperthermia in neuroleptic malignant syndrome.

8.4 Feeding regulation: the satiety and hunger axis

Energy balance is a dual-centre system layered onto a hormone-sensing front end. The **ventromedial nucleus (VMH)** is the satiety centre: stimulation stops feeding, and bilateral lesions produce the classic *hypothalamic obesity* triad of hyperphagia, weight gain and, because the VMH abuts the DMH, savage irritability ("VMH rage"). The **lateral hypothalamic area (LHA)** is the hunger centre: stimulation drives feeding, and lesions cause aphagia, weight loss and somnolence (the LHA is also the source of orexin/hypocretin). The aphorism is that the VMH says *stop* and the LHA says *go*.

The decisive integrator, and the modern exam favourite, is the **arcuate nucleus**, which sits at the median eminence outside the blood-brain barrier and therefore directly samples circulating energy signals. It contains two antagonistic neuron populations: anorexigenic **POMC/CART** neurons and orexigenic **NPY/AgRP** neurons. Circulating signals act here: *leptin* (from adipocytes, a long-term adiposity signal) and *insulin* activate POMC and suppress NPY/AgRP, reducing appetite; *ghrelin* (from the stomach, the "hunger hormone", rising before meals) does the reverse. The arcuate then relays to the PVN and to the VMH/LHA, coordinating intake.

SIGNAL	SOURCE	TIMESCALE	NET EFFECT ON APPETITE
Leptin	Adipose tissue	Long-term (adiposity)	**Decreases (anorexigenic)**
Insulin	Pancreatic beta cells	Meal to medium-term	Decreases
Ghrelin	Gastric fundus	Short-term (pre-meal)	**Increases (orexigenic)**
Orexin / hypocretin	Lateral hypothalamus	State (arousal-linked)	Increases + promotes wakefulness

The arcuate-sensed peripheral signals. Leptin and ghrelin are the reciprocal long- and short-term poles examiners contrast.

RULE **Ventromedial nucleus says stop (satiety), lateral hypothalamus says go (hunger).** A VMH lesion causes hyperphagia and obesity; an LHA lesion causes aphagia.

CLINICAL ANCHOR

Counterintuitively, common obesity is a state of **high leptin with leptin resistance**, not deficiency; congenital leptin deficiency is rare but causes severe early-onset obesity that responds to recombinant leptin. This circuitry is also why second-generation antipsychotics (olanzapine, clozapine) drive weight gain partly through H1 and 5-HT2C antagonism acting on these arcuate and VMH circuits, a daily clinical reality in Indian psychiatric practice where metabolic monitoring is often under-resourced.

8.5 Circadian control: the SCN and melatonin

The **suprachiasmatic nucleus (SCN)**, sitting just above the optic chiasm, is the body's master clock. Its neurons hold an intrinsic, self-sustaining rhythm: in constant darkness they free-run at close to, but not exactly, 24 hours (roughly 25 hours in classic human data), which is why daily entrainment is needed. The molecular engine is a transcription-translation feedback loop of the *CLOCK*, *BMAL1*, *PER* and *CRY* genes. Entrainment to the external light-dark cycle comes via the **retinohypothalamic tract**, a non-rod, non-cone input from intrinsically photosensitive retinal ganglion cells using the pigment *melanopsin*.

The melatonin output pathway is a favourite multi-synapse traceable question. Light activates the SCN, whose *inhibitory* GABAergic projection suppresses the PVN; the PVN drives sympathetic preganglionic neurons in the T1-T2 intermediolateral column; these reach the **superior cervical ganglion**, whose noradrenergic fibres innervate the **pineal gland**, where noradrenaline acting on beta-1 and alpha-1 receptors *stimulates* melatonin synthesis. In daylight, therefore, SCN activity holds this sympathetic limb down and melatonin stays low. In darkness SCN firing falls, the inhibition on the PVN lifts, sympathetic drive to the pineal rises, and melatonin rises with it, peaking overnight. Melatonin is therefore the chemical signal of darkness, and exogenous melatonin and the MT1/MT2 agonists (ramelteon, agomelatine which is also 5-HT2C antagonist) exploit this to phase-shift the clock.

PEARL

The SCN to pineal route runs *caudally first*: the signal descends to the upper thoracic cord before ascending through the superior cervical ganglion to the pineal. This is why a high cervical cord or sympathetic lesion abolishes the normal nocturnal melatonin surge. For psychiatry, SCN-mediated phase disturbance underlies delayed sleep phase syndrome, the diurnal mood variation of melancholic depression, and the rationale for chronotherapy and bright-light therapy in seasonal affective disorder.

8.6 Clinical correlation by syndrome

Hypothalamic disease is read off the nucleus involved. The high-yield set spans water balance, energy, sleep and the named eponymous syndromes; ICD-11 codes the underlying endocrine or sleep disorder rather than "hypothalamic syndrome" as a unitary entity.

- **Central diabetes insipidus.** Destruction of the ADH-secreting SON and PVN, occurring in about 1 per 25,000 people, most often idiopathic (probably autoimmune). Presents with polyuria, polydipsia and nocturia; serum sodium stays high-normal while thirst is intact but climbs to *hypernatraemia* if thirst is impaired or access to water is denied (children, CNS-lesion patients). Distinguish from nephrogenic DI by the desmopressin response, and from primary polydipsia by the water-deprivation test. Psychiatric relevance: lithium causes *nephrogenic* (not central) DI; carbamazepine, by contrast, can cause SIADH.
- **SIADH.** Inappropriately high ADH relative to osmolality gives euvolaemic *hyponatraemia* (nausea, headache, confusion, seizures). Common psychiatric culprits: carbamazepine, oxcarbazepine and the SSRIs (especially in the elderly); also small-cell lung carcinoma and CNS insults. Correct slowly, capping the rise at roughly 8 mEq/L in 24 hours, to avoid *osmotic demyelination (central pontine myelinolysis)*. One study attributed up to a third of in-hospital hyponatraemia to SIADH.
- **Hyperprolactinaemia.** Loss of dopaminergic inhibition (stalk compression, or antipsychotic D2 blockade) disinhibits prolactin, causing galactorrhoea, oligo/amenorrhoea, and hypogonadism with reduced libido in men. The commonest psychiatric cause is medication, and risperidone, paliperidone and amisulpride are the worst offenders; switch to a prolactin-sparing agent (aripiprazole) where feasible.
- **Functional hypothalamic amenorrhoea.** Suppressed pulsatile GnRH from low energy availability (anorexia nervosa, over-exercise) or chronic stress (raised cortisol, low IGF-1) accounts for around 35% of secondary amenorrhoea. The result is hypogonadotropic hypogonadism with oestrogen deficiency, low bone density and infertility, a core link between eating disorders and reproductive endocrinology.
- **Frohlich syndrome (adiposogenital dystrophy).** A tuberal-region/medial-basal lesion (classically craniopharyngioma, also other suprasellar masses) producing the combination of *obesity and hypogonadism*, often with growth failure in children, from coupled disruption of the satiety circuitry and the GnRH axis.

- **Prader-Willi syndrome.** Loss of paternally expressed genes at 15q11-q13 (paternal deletion or maternal uniparental disomy) with hypothalamic dysfunction. The hallmark course is neonatal hypotonia and poor feeding giving way to insatiable *hyperphagia* and early obesity, with short stature, hypogonadism and intellectual disability; ghrelin levels are characteristically elevated. It is a leading genetic cause of syndromic obesity and the classic example of genomic imprinting in viva.
- **Kleine-Levin syndrome.** A rare relapsing-remitting disorder of presumed hypothalamic origin, mostly in adolescent males, defined by recurrent episodes of *hypersomnia* with cognitive change (derealisation, apathy) plus, in many, hyperphagia and hypersexuality during episodes, with normal function between them. ICD-11 classes it under recurrent hypersomnia; the syndrome is largely self-limiting over years.
- **Hypothalamic obesity.** A distinct, treatment-resistant obesity following VMH/arcuate damage (postsurgical for craniopharyngioma, irradiation, trauma), with intractable hyperphagia, low metabolic rate and dysautonomia, far harder to manage than common obesity because the set-point machinery itself is broken.

INDIA CONTEXT

In Indian neuropsychiatric practice, two hypothalamic-region causes deserve a low threshold of suspicion: **tuberculoma and tubercular meningitis** involving the suprasellar cistern, which can present with DI, hypopituitarism or hypersomnia, and **craniopharyngioma**, a common paediatric suprasellar tumour producing Frohlich-type pictures and postsurgical hypothalamic obesity. Any young patient with new polyuria-polydipsia, amenorrhoea or unexplained hypersomnia plus visual field signs warrants pituitary-hypothalamic imaging before the picture is attributed to a primary psychiatric disorder.

9 · Cerebellum and the cognitive-affective syndrome

The cerebellum is no longer "just coordination". It modulates cognition and affect through cerebello-thalamo-cortical loops, much as it smooths movement. **Schmahmann's cerebellar cognitive affective syndrome (CCAS)**[3] follows posterior-lobe and vermal lesions and has four components: executive dysfunction, impaired visuospatial cognition, language difficulties (agrammatism, dysprosodia) and affective dysregulation (blunting or disinhibition, the vermis being the "limbic cerebellum"). Schmahmann frames the unifying deficit as *dysmetria of thought*: the cerebellum keeps cognition and emotion around a homeostatic baseline just as it keeps movement on target.

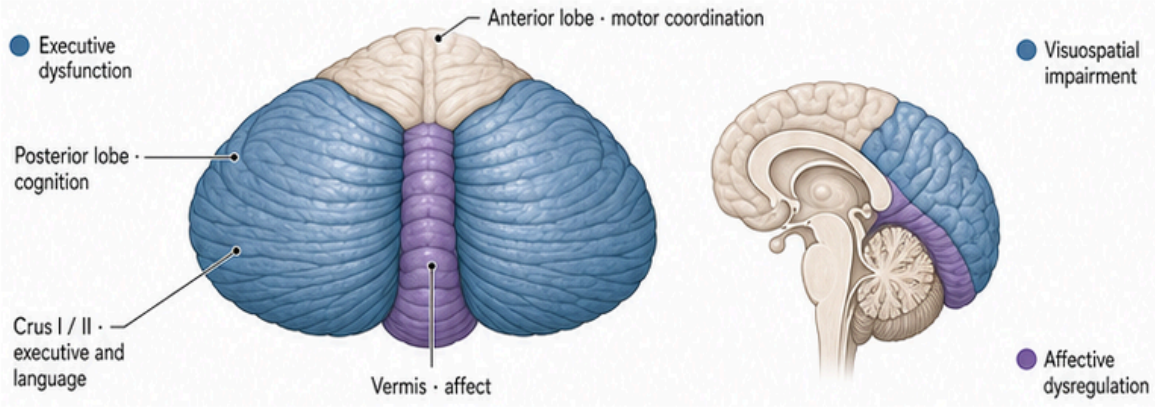


Fig 1.9 Cerebellar cognitive-affective topography. Motor coordination maps anteriorly; executive, language and visuospatial functions map posteriorly; affective regulation is concentrated in the vermis.

HOLD THIS

CCAS follows posterior-lobe and vermal lesions: executive, visuospatial, linguistic and affective deficits with a structurally normal cerebrum. The vermis is the "limbic cerebellum"; anterior-lobe lesions spare cognition.

Schmahmann & Sherman (1998) LANDMARK · CCAS

Design. Clinical and neuropsychological study of 20 patients with focal cerebellar disease. **Finding.** A reproducible syndrome of executive, visuospatial, linguistic and affective impairment, worst with posterior-lobe and vermal damage. **Why it matters.** Established the cerebellum's role in cognition and emotion; underpins the "cognitive dysmetria" model of schizophrenia (Andreasen) and the cerebellar findings in autism.

9.1 Gross anatomy: lobes, vermis, hemispheres and deep nuclei

The cerebellum sits in the posterior fossa, attached to the brainstem by three peduncles (inferior, middle, superior). Two transverse fissures divide its cortex into three lobes: the *anterior lobe* (above the primary fissure), the larger *posterior lobe* (between primary and posterolateral fissures), and the small *flocculonodular lobe*. Sagittally, a midline **vermis** is flanked by two **hemispheres**, with a transitional paravermal (intermediate) strip in between. Each hemisphere is folded into ten lobules (Larsell I to X); for the exam the cognitively loaded ones are **lobule VII** in the posterior lobe, whose hemispheric extensions are *Crus I* and *Crus II*.

Deep nuclei. Buried in the white matter are four paired deep cerebellar nuclei, the sole output of the cerebellum. From medial to lateral they are **fastigial, globose, emboliform, dentate** (the globose and emboliform together form the *nucleus interpositus*). The dentate is by far the largest and phylogenetically newest, developing in parallel with the association areas of the frontal cortex.

MNEMONIC

"Fat Globs Eat Donuts" (medial to lateral)

Fastigial, **G**lobose, **E**mboliform, **D**entate. Pair it with function: Fastigial = limbic/emotion, interposed (Globose + Emboliform) = motor, Dentate = cognition.

9.2 Functional zones: vestibulo-, spino- and cerebrocerebellum

The cerebellum is read three ways at once: by lobe (above), by phylogeny, and by the functional longitudinal zone that maps onto a specific deep nucleus and output target. The functional scheme is the one examiners reward.

FUNCTIONAL ZONE	PHYLOGENY / REGION	DEEP NUCLEUS	ROLE	LESION PICTURE
Vestibulocerebellum	Archicerebellum (flocculonodular lobe)	Fastigial (and direct to vestibular nuclei)	Balance, vestibulo-ocular reflex, axial tone	**Truncal ataxia, nystagmus, gait instability with preserved limb coordination**
Spinocerebellum	Paleocerebellum (vermis + paravermal strip)	Fastigial (vermis), interposed (paravermal)	Trunk and limb tone, ongoing movement correction	**Gait and truncal ataxia (vermis); appendicular dysmetria, dysarthria (paravermal). Affect change with vermal lesions**
Cerebrocerebellum	Neocerebellum (lateral hemispheres, Crus I/II)	Dentate	Motor planning, timing, and non-motor cognition	**Dysmetria, intention tremor, dysdiadochokinesia; and CCAS when posterior**

The three functional cerebella, their output nuclei and the dissociated clinical syndromes each produces. The cerebrocerebellum is the zone that generates CCAS.

9.3 Cerebello-thalamo-cortical loops: the closed circuit

The non-motor reach of the cerebellum is wholly a matter of its wiring. Schmahmann and Pandya described a **two-stage feedforward and two-stage feedback** loop. **Feedforward.** Layer V pyramidal neurons of the cerebral cortex (sensorimotor regions and, crucially, association and limbic cortices) project through the cerebral peduncle to the ipsilateral *basis pontis*; pontine axons then cross and enter via the **contralateral middle cerebellar peduncle**, terminating in cerebellar cortex as mossy fibres. **Feedback.** Cerebellar cortex projects to a deep nucleus (the corticonuclear microcomplex), which exits through the **superior cerebellar peduncle** to the contralateral ventrolateral thalamus, which closes the loop back onto the originating cortex. Because both crossings happen, cerebellar function is referred to the *contralateral* cerebral hemisphere.

The cognitively relevant feeder cortices are specific and worth memorising: posterior parietal cortex (spatial awareness), superior temporal gyrus supramodal areas (language), posterior

parahippocampal cortex (spatial memory), parastriate visual association cortex (higher visual processing), and prefrontal cortex (reasoning, attention, working memory), with cingulate projections to the pons supplying the affective limb. Parallel, largely non-overlapping loops therefore link the cerebellum with motor, prefrontal, parietal and limbic territory, the anatomical basis for topographic specialisation of function within one structure.

> **PEARL**
> Two decussations (pontine crossing in, superior peduncle crossing out) make the loop functionally contralateral. A right cerebellar hemisphere lesion produces left-cortical-type deficits, hence right hemisphere damage tends to impair language (left-dominant cortex) and left hemisphere damage impairs visuospatial function.

RULE **Cerebellar motor signs are ipsilateral to the lesion; cognitive-affective deficits are referred contralateral** because the two decussations make the loop functionally contralateral to cortex.

9.4 The cerebellar cognitive affective syndrome (CCAS / Schmahmann syndrome)

CCAS, first delineated by Schmahmann and Sherman (1998) and also called *Schmahmann syndrome*, is the constellation of cognitive and affective deficits that follows cerebellar injury without any primary cerebral lesion. It overturned the dogma that the cerebellum is purely motor. It is defined across **four domains**.

1. Executive dysfunction

Impaired planning, set-shifting, abstract reasoning, verbal fluency and working memory, with perseveration, distractibility and inattention. Usually the most prominent and persistent domain.

2. Visuospatial impairment

Visuospatial disorganisation and impaired visuospatial memory (for example deficits copying or constructing figures).

3. Linguistic deficits

Dysprosodia (flat or abnormal speech melody), agrammatism and mild anomia; in children, transient cerebellar mutism after posterior fossa surgery sits on this spectrum.

4. Affective and personality change

Blunting of affect or, conversely, disinhibited, inappropriate behaviour: distractibility, impulsivity, anxiety, ritualistic and obsessive behaviours, dysphoria, apathy, and childlike conduct with poor reading of social boundaries.

The net effect is a general lowering of intellectual function. Lesion localisation matters: **posterior lobe** and bilateral or pancerebellar lesions produce the severest syndrome, whereas anterior-lobe lesions (the sensorimotor cerebellum) cause little cognitive change. Within the deep nuclei the dissociation holds, the **dentate** serves cognition, the **fastigial** and vermis serve affect (the "limbic cerebellum", an idea anticipated by Robert Heath), and the interposed nucleus is motor. Symptoms are typically moderate after acute injury and attenuate over months, supporting a regulatory rather than generative role for the cerebellum in cognition.

CLINICAL ANCHOR

Suspect CCAS in any patient with a posterior fossa stroke (PICA territory), resected medulloblastoma or astrocytoma, cerebellitis, or hereditary ataxia who presents with new executive, affective or "frontal-like" changes but a structurally normal cerebrum. A bedside Schmahmann CCAS/CCAS-Scale screen can flag it; in children, medulloblastoma carries worse neuropsychological outcomes than astrocytoma.

9.5 Dysmetria of thought and the universal cerebellar transform

Schmahmann's **dysmetria of thought** hypothesis is the unifying mechanism. Just as the motor cerebellum smooths the rate, force, rhythm and accuracy of movement (its absence yielding limb dysmetria and intention tremor), the cognitive cerebellum is proposed to apply the same computation to thought and emotion. The cerebellum performs one stereotyped operation, a *universal cerebellar transform*, on whatever information the connected loop carries; the behavioural consequence depends only on which cortical territory it is wired to. Damage therefore produces **dysmetria of thought**: thought and affect that are poorly modulated, overshooting or undershooting, mistimed, and inconsistent, exactly mirroring the unsteadiness of an ataxic limb. This elegantly explains how a single lesion can disorganise executive, spatial, linguistic and emotional output simultaneously, and why cerebellar pathology can mimic frontal-subcortical syndromes.

COMMON TRAP

"Dysmetria of thought" is not a vague metaphor for confusion. It is a specific claim that the cerebellum regulates the **consistency and calibration** of cognition by the same mechanism it uses for movement. Do not equate CCAS with dementia: CCAS is a regulatory, dysmodulatory syndrome, often partially reversible, not a degenerative loss of cortical knowledge.

9.6 Clinical correlations in psychiatric and neurological disorders

Through the same loops, cerebellar dysfunction is implicated across psychiatry, lending the cerebellum a transdiagnostic role.

- **Schizophrenia.** Andreasen's *cognitive dysmetria* model proposes a disrupted **cortico-cerebellar-thalamo-cortical circuit (CCTCC)** producing poor coordination of mental activity, a candidate "fundamental cognitive deficit" of the illness. Post-mortem work shows reduced anterior vermis size, smaller inferior vermis with loss of normal hemispheric asymmetry, and reduced Purkinje cell size and density in the vermis (Tran et al. 1998).
- **ADHD.** Structural studies show smaller posterior-inferior cerebellar lobules and reduced vermal volume, with vermis size correlating inversely with symptom severity (Berquin et al. 1998), consistent with cerebellar contribution to attention and timing.
- **Mood disorders.** Vermal and cerebellar volume reductions and the "limbic cerebellum" (vermis to fastigial nucleus) tie cerebellar dysfunction to depression and bipolar disorder; cerebellar vermis TMS has shown preliminary mood and cognitive benefit in schizophrenia samples.

- **Autism and neurodevelopment.** Purkinje cell loss is among the most replicated neuropathological findings in autism; cerebellar dysfunction is also reported in dyslexia (reduced PET activation on motor tasks), Fragile X and Down syndrome, framing the developing cerebellum as a node for neurodevelopmental disorders.
- **Ataxias (acquired and hereditary).** CCAS accompanies the motor syndrome in hereditary disease, classically the spinocerebellar ataxias and Friedreich ataxia, and in acquired causes (cerebellar stroke, tumour, cerebellitis, trauma, alcohol-related anterior-vermis degeneration, paraneoplastic cerebellar degeneration, and neurodegenerations such as multiple system atrophy and progressive supranuclear palsy). The cognitive-affective burden is an independent contributor to disability and should be screened for, not assumed absent because the presentation looks "just motor".

INDIA CONTEXT

In Indian practice the cerebellum surfaces most often through alcohol-related cerebellar (anterior superior vermis) degeneration, where chronic dependence produces a wide-based gait and, frequently, an under-recognised cognitive-affective component layered on Wernicke-Korsakoff. Screen for executive and affective change in these patients rather than charting gait alone.

10 · Large-scale brain networks (DMN, salience, central-executive)

Modern psychiatry thinks in networks, not regions. Three intrinsic connectivity networks dominate, and Menon's **triple network model**[6] proposes that much psychopathology is a disorder of switching between them.

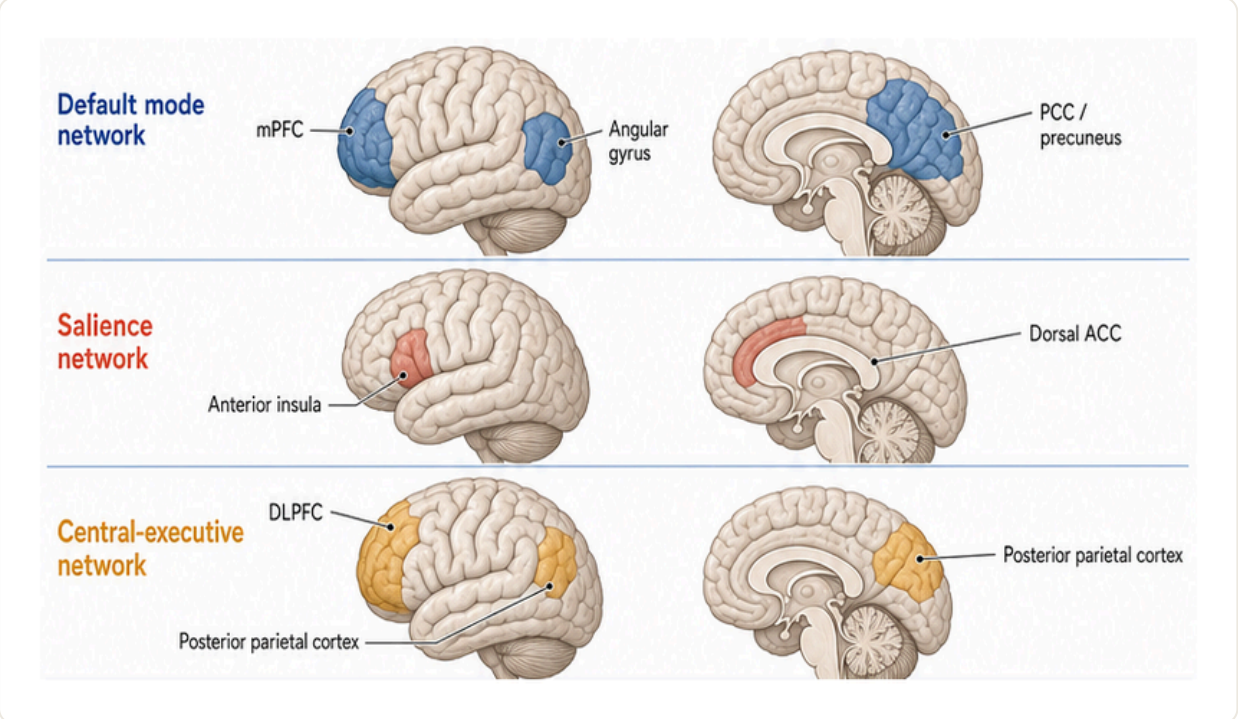


Fig 1.10 The principal anatomical nodes of the default-mode, salience and central-executive networks, shown on matched lateral and medial views.

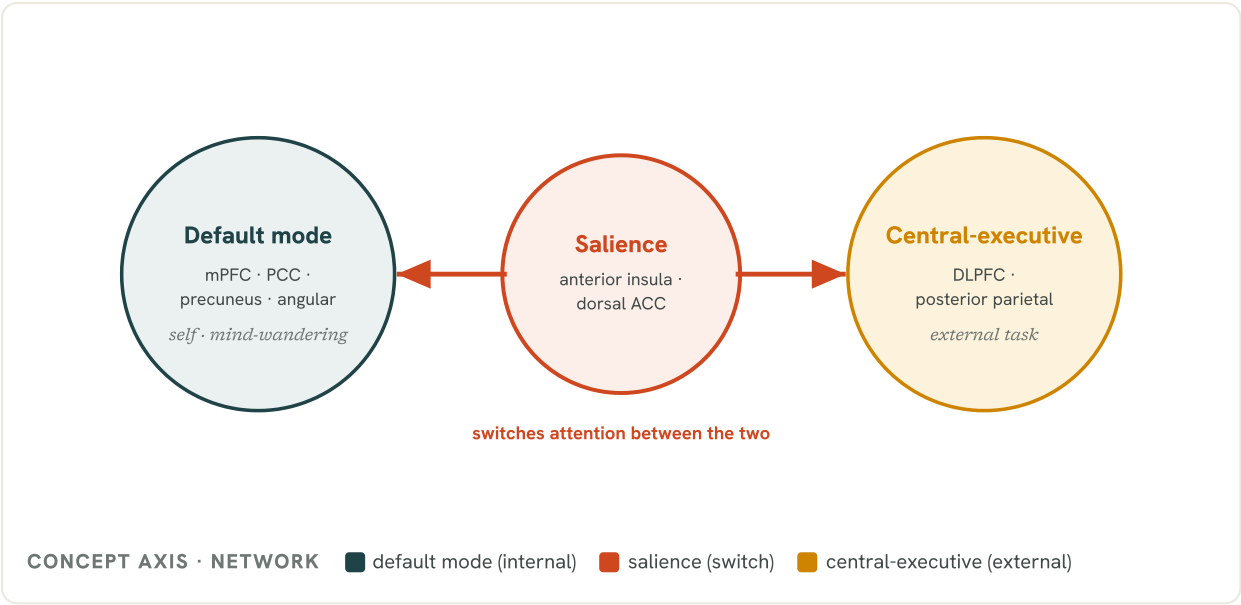


Fig 1.11 The triple network. The salience network (anterior insula, dorsal ACC) detects what matters and toggles the brain between inward self-referential processing (DMN) and outward task control (CEN).

- **Depression.** DMN hyperconnectivity and difficulty disengaging from it map onto rumination.
- **Schizophrenia.** Aberrant salience (Kapur): the salience network misattributes significance to neutral stimuli, the proposed engine of delusion formation; failure to suppress the DMN during tasks correlates with cognitive deficits.
- **Anxiety.** Salience-network (insula) hyperactivity heightens threat detection.

HOLD THIS

The salience network (anterior insula, dorsal ACC) is the switch that toggles the inward DMN and the outward central-executive network. Menon frames much psychopathology as failed switching between the three.

10.1 The default mode network: anatomy and the self-referential mind

The **default mode network (DMN)** is the brain's "task-negative" or intrinsic system: it is most active at rest and during internally directed cognition, and it deactivates reliably whenever attention turns to a demanding external task. It was discovered backwards, as the set of regions that consistently *decreased* their activity across diverse tasks in early PET and fMRI studies (Raichle 2001, Shulman). Its three principal hubs are the **medial prefrontal cortex (mPFC)**, the **posterior cingulate cortex (PCC) and adjoining precuneus** (the network's metabolic core and densest hub), and the bilateral **inferior parietal lobule, especially the angular gyrus**, with the lateral temporal cortex and hippocampal formation as a medial temporal subsystem.

Anterior (mPFC) subsystem

Self-relevance tagging, affective valuation, "thinking about my own mental states". Ventral mPFC carries strong limbic and ventral striatal connections.

Posterior (PCC/precuneus) hub

The integrative core; couples the anterior subsystem to the medial temporal subsystem and is the highest-metabolic-rate cortical region at rest.

Medial temporal subsystem (hippocampus, parahippocampus, retrosplenial, angular gyrus)
Episodic and autobiographical memory retrieval, scene construction, and prospection (mental time travel).

Functional role. The DMN constructs and maintains the autobiographical self: it underlies mind-wandering, autobiographical memory, future simulation, theory of mind, and moral reasoning. The unifying account is that it supports cognition decoupled from the immediate environment, internally generated thought that draws on memory rather than perception.

Rumination. When self-referential processing becomes negatively biased and perseverative, it is experienced as **rumination**, the cognitive symptom most tightly mapped onto DMN function. Hamilton and colleagues showed that depressive rumination tracks sustained DMN dominance and, specifically, elevated activity of the subgenual anterior cingulate (sgACC) embedded within the ventromedial DMN. The DMN is therefore the network where the inward, self-critical preoccupations of depression and anxiety are physically expressed (expanded in 7.6).

> **PEARL**
> The single best one-line exam answer for the DMN is "task-negative network, active at rest and during self-referential thought, hubs at mPFC, PCC/precuneus and angular gyrus". The PCC/precuneus is the metabolic and connectional core, and the sgACC is the affective node that links DMN overactivity to depression.

10.2 The salience network: anterior insula, dorsal ACC and von Economo neurons

The **salience network (SN)** is the brain's relevance detector and the engine of network switching. Its two cortical anchors are the **anterior insula (specifically the frontoinsular cortex)** and the **dorsal anterior cingulate cortex (dACC)**; its subcortical partners include the amygdala, ventral striatum, hypothalamus, the substantia nigra / ventral tegmental area (SN/VTA dopaminergic nuclei) and the thalamus. This wiring lets the SN integrate interoceptive, autonomic, emotional and reward signals and decide what deserves the brain's limited processing resources.

Cytoarchitecture. The frontoinsular cortex and dACC are uniquely populated by **von Economo neurons (VENs)**, large bipolar spindle-shaped projection neurons. They are found in great numbers in humans, present in lesser numbers in great apes, and largely absent in other primates, an evolutionary signature consistent with rapid relaying of integrated salience signals to distant cortex (Allman 2010). VENs are selectively vulnerable in the *behavioural-variant frontotemporal dementia*, which is the clinical proof that loss of this exact cell population produces the apathy, disinhibition and loss of social salience that define bvFTD.

Interoception and the insula. The anterior insula is functionally split into a **dorsal salience subnetwork** (attention, cognitive control, switching between resources) and a **ventral salience subnetwork** (densely connected to limbic and paralimbic cortex, subserving affect and emotion). The dorsal anterior insula and dACC co-activate to signal "this matters, change what you are doing", driving the switch described next.

CLINICAL ANCHOR

Von Economo neurons tie three otherwise unrelated exam facts together: the salience network, selective degeneration in behavioural-variant FTD, and the aberrant salience model of psychosis. A question that names "spindle neurons in frontoinsular and anterior cingulate cortex" is testing this one cell type.

MNEMONIC

"AI on the dACC desk"

Anterior **I**nsula and **dACC** are the two cortical chairs of the salience "desk"; the von Economo neurons are the fast messengers that run between them and the rest of cortex.

10.3 The central executive (frontoparietal) network

The **central executive network (CEN)**, equivalently the **frontoparietal control network**, is the brain's "task-positive" system. Its anchors are the **dorsolateral prefrontal cortex (DLPFC)** and the **posterior parietal cortex (PPC), including the intraparietal sulcus and superior parietal lobule**. It activates during cognitively demanding, externally directed operations: working memory, sustained and selective attention, planning, rule-based decision-making and goal maintenance. The DLPFC node integrates information arriving from occipital, parietal and temporal cortices and imposes top-down control, the neural substrate of Miller and Cohen's prefrontal model of cognitive control.

The CEN is functionally and anatomically distinct from two neighbours that exams love to confuse with it: the *dorsal attention network* (frontal eye fields and intraparietal sulcus, for spatial orienting) and the *cingulo-opercular network* (tonic task-set maintenance). In the triple-network shorthand, the CEN is simply "the outward-facing worker" that the salience network recruits when a task needs doing.

10.4 Menon's triple network model

Vinod Menon's **triple network model** (Menon 2011, building on Sridharan, Levitin and Menon 2008) is the organising framework for systems-level psychiatry. Its claim is parsimonious: a large fraction of psychopathology across diagnoses can be understood as **aberrant organisation of, and switching between, three core networks**, the DMN, the CEN and the SN. The salience network sits at the apex of this architecture as the dynamic controller. On detecting a behaviourally salient event (external or internal), the SN, via the anterior insula and dACC, generates a transient control signal that *engages the CEN* for goal-directed processing while simultaneously *disengaging the DMN*. Effective dynamic causal modelling studies place the right anterior insula as the causal outflow hub initiating this switch.

The model's explanatory power is that it converts region-by-region findings into a small set of failure modes: a network can be internally hyper- or hypo-connected, the antagonism between two networks can be lost, or the salience switch itself can misfire by tagging the wrong stimuli or

failing to toggle at the right time. Different disorders sit at different points in this space, which is the unifying thread of 7.6.

Menon (2011) LANDMARK · TRIPLE NETWORK

Design. Synthesis in *Trends in Cognitive Sciences* integrating resting-state and task fMRI across psychiatric and neurological disorders. **Finding.** Proposed that dysfunction of the DMN, salience and central-executive networks, and of the salience network's control over the other two, is a common substrate across schizophrenia, depression, anxiety, dementia and autism. **Why it matters.** Reframed psychopathology as a disorder of large-scale network dynamics rather than discrete lesions; the dominant transdiagnostic systems framework and the conceptual parent of the figure in this section (Fig 1.11).

10.5 DMN to CEN anticorrelation: the antagonistic brain

A defining property of intrinsic brain organisation is that the DMN and the task-positive CEN are **anticorrelated**: when one rises, the other falls. Fox and Raichle's landmark 2005 study showed the resting human brain is intrinsically organised into two dynamic, anticorrelated systems, a task-negative (default mode) system and a task-positive (frontoparietal) system, whose spontaneous fluctuations oscillate out of phase. This anticorrelation is the physiological correlate of an everyday fact: the brain cannot be deeply inward (ruminating, daydreaming) and sharply outward (concentrating on a task) at the same instant.

Why it matters clinically. The salience network is what enforces the antagonism. When SN switching is healthy, the two networks trade off cleanly; when it falters, the anticorrelation weakens and the DMN intrudes into task states. **Reduced (or lost) DMN to CEN anticorrelation is one of the most replicated transdiagnostic findings**, reported in ADHD, depression, schizophrenia and ageing. The "default mode interference" hypothesis frames attentional lapses as moments where an inadequately suppressed DMN breaks through into the task-positive state.

⚠ COMMON TRAP

"Anticorrelation" is between the DMN and the CEN, not between the salience network and either one. The salience network is the *switch* that produces the anticorrelation; it is not itself the anticorrelated partner. A second trap: some of the apparent anticorrelation magnitude is an artefact of global-signal regression, so phrase it as a robust but methodologically debated finding, not an absolute.

10.6 Clinical correlation: network signatures across disorders

The triple-network model earns its keep by giving each major disorder a characteristic network signature. These are tendencies, not diagnostic tests, but they recur across the literature and are high-yield.

DISORDER	DMN	SALIENCE NETWORK	CEN / SWITCHING	CLINICAL READING
Major depression	Hyperconnectivity, sgACC-anchored dominance	Variable, often hyperreactive to negative cues	Hypoactive CEN, weak DMN suppression	**Rumination = a DMN that will not switch off; the network basis of "stuck" negative self-focus**
Schizophrenia / psychosis	Failure to deactivate during tasks	Aberrant salience attribution (Kapur)	Impaired SN control over DMN/CEN switching	**Misfiring salience tags neutral stimuli, the proposed substrate of delusion formation**
Anxiety disorders	Self-referential threat loops	Hyperactive insula/dACC threat detection	Reduced top-down CEN regulation of amygdala	**An overtuned salience network that over-tags threat**
ADHD	Default-mode interference, poor suppression	Weakened SN to CEN coupling	Reduced DMN to CEN anticorrelation and segregation	**Attentional lapses = inward thought intruding on outward task**
OCD	Increased intra-DMN connectivity	Increased SN to DMN and SN to CEN coupling	Difficulty disengaging, poor set-switching	**The brain cannot let go of an internally generated signal**
bvFTD / MCI / AD	DMN breakdown (AD)	SN degeneration (bvFTD, von Economo loss)	Disrupted salience control in MCI predicts decline	**A double dissociation: AD targets the DMN, bvFTD targets the salience network**

Transdiagnostic network signatures under the triple-network model: each disorder is a different failure mode of network connectivity, antagonism, or salience-driven switching.

Depression. The depressed brain shows **DMN hyperconnectivity**, with the subgenual ACC drawn abnormally tightly into the network; this anchors the perseverative, self-critical rumination that defines the cognitive phenotype. Effective antidepressant treatment, pharmacological and TMS to the DLPFC node of the CEN, is associated with normalisation of this DMN dominance, and sgACC connectivity is a target in deep brain stimulation for treatment-resistant depression (Mayberg).

Psychosis and Kapur's aberrant salience. Shitij Kapur's 2003 framework is the most examinable single idea here. It proposes that hyperdopaminergic firing in the mesolimbic system (ventral striatum, an SN partner) causes **aberrant assignment of salience** to innocuous internal and external stimuli. Stimuli that should be ignored acquire urgent significance; *delusions are the*

patient's cognitive effort to explain this aberrant salience, and antipsychotics work by dampening the dopaminergic salience signal (a "dissolution of salience") rather than directly erasing beliefs. This maps cleanly onto a salience network that tags the wrong things, and it explains why insight is partial and why relapse follows medication discontinuation as salience returns.

RULE **In Kapur's model, delusions are the patient's explanation of aberrant salience.** Hyperdopaminergic firing tags neutral stimuli as urgent; antipsychotics dampen the salience signal, not the belief directly.

Anxiety. Anxiety disorders show an **over-tuned salience network**: hyperreactive anterior insula and dACC over-detect threat, coupled with insufficient CEN/DLPFC top-down regulation of the amygdala. The phenomenology, hypervigilance and the sense that ordinary cues are dangerous, is salience misallocation toward threat.

ADHD. ADHD is the prototype of a **switching disorder**: reduced DMN to CEN anticorrelation, attenuated SN to DMN antagonism, and weakened SN to CEN coupling. The "default-mode interference" hypothesis holds that an inadequately suppressed DMN intrudes into task-positive states, producing the periodic attentional lapses, mind-wandering and variable performance that characterise the disorder. Stimulants increase catecholaminergic tone in the frontoparietal CEN and improve DMN suppression, a network reading of why they sharpen sustained attention.

INDIA CONTEXT

For Indian MD vivas, the triple-network model is most often probed through three anchors: name the three networks and their hubs, explain Kapur's aberrant salience hypothesis of psychosis (a recurrent theory question), and state that depression shows DMN hyperconnectivity driving rumination. Resting-state fMRI remains a research tool, not bedside, in most Indian centres, so frame these as mechanistic and explanatory rather than diagnostic.

11 · Reticular activating system and arousal

Consciousness needs both content (cortex) and a level (arousal). The level is set by the **ascending reticular activating system (ARAS)**, a set of brainstem and hypothalamic nuclei projecting diffusely upward through two routes: a dorsal route via the thalamus (intralaminar nuclei) and a ventral route via the hypothalamus and basal forebrain to the cortex.

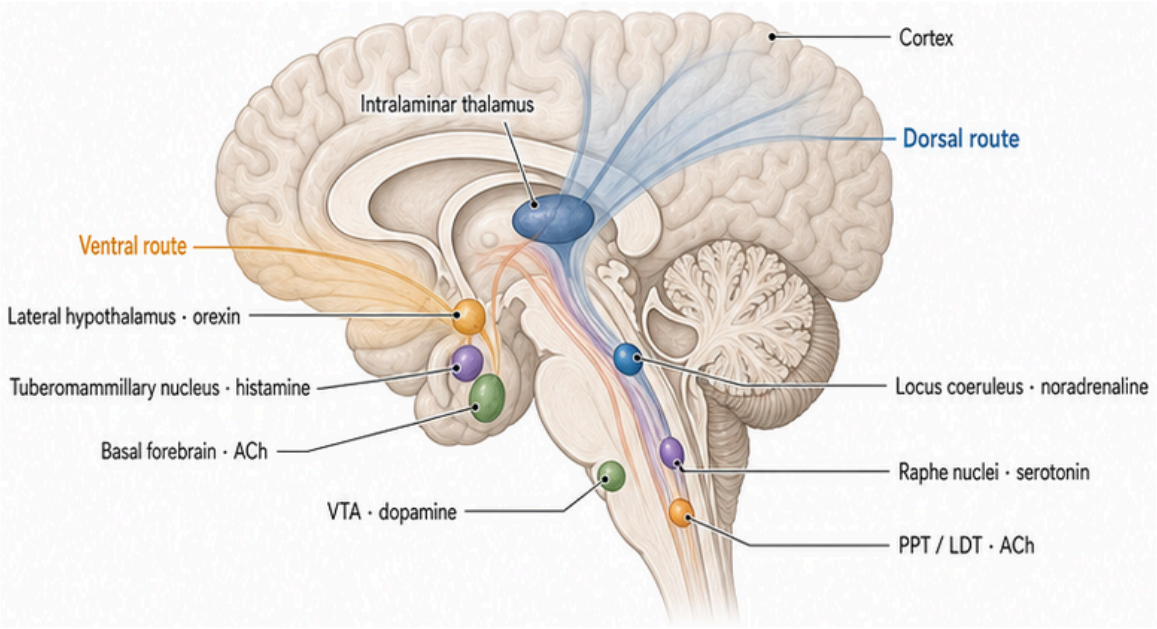


Fig 1.12 The ascending arousal and modulatory systems. Dorsal and ventral routes carry diffuse cholinergic and monoaminergic projections from compact brainstem and hypothalamic nuclei to thalamus, basal forebrain and cortex.

- **Cholinergic** (pedunculopontine and laterodorsal tegmental nuclei) drive cortical activation and REM sleep.
- **Noradrenergic** (locus coeruleus) for vigilance and stress arousal; **serotonergic** (raphe nuclei); **dopaminergic** (VTA); **histaminergic** (tuberomammillary nucleus, the target of sedating antihistamines); **orexin/hypocretin** (lateral hypothalamus), the wakefulness stabiliser whose loss causes narcolepsy and whose blockade by the dual orexin receptor antagonists (DORAs, e.g. suvorexant, daridorexant) is the newest hypnotic mechanism.

A lesion of the ARAS (e.g. paramedian midbrain) causes coma; this is why brainstem strokes can abolish consciousness while small cortical lesions do not.

HOLD THIS

Consciousness needs arousal (ARAS, the level) and awareness (cortex, the content). A small upper-brainstem lesion can abolish consciousness; a small cortical lesion cannot.

11.1 ARAS anatomy and the dual route to cortex

The level-setting machinery for consciousness is not a single nucleus but a distributed core within the rostral brainstem tegmentum, the **reticular formation**, a loose meshwork (Latin *reticulum*, "little net") of interneurons whose individual cells each synapse with hundreds of others, generating the diffuse, non-topographic connectivity that lets a small volume of tissue tune the entire cortical mantle. The functional dividing line sits at the **trigeminal nerve entry zone** in the pons: the reticular formation *rostral* to this point is the arousal-relevant ARAS, while the *caudal* portion serves premotor, cardiovascular and respiratory roles (Yeo, Chang and Jang

2013). This is why a paramedian midbrain or upper pontine lesion abolishes consciousness, whereas a medullary reticular lesion kills by autonomic failure, not by coma.

The dorsal (thalamic) route. The classic ARAS ascends from the pontine reticular formation through the mesencephalic tegmentum, running just **posterior to the red nucleus**, and relays in the **intralaminar and other non-specific (midline) thalamic nuclei**, chiefly the central lateral, centromedian and parafascicular (CM-Pf), and paracentral nuclei. These nuclei project diffusely and non-topographically across the whole cortex, modulating the *gain* of thalamocortical transmission rather than carrying any sensory content. Human diffusion-tensor tractography confirms this single ascending bundle is symmetric between hemispheres and does not atrophy with normal ageing (Yeo, Chang and Jang 2013).

The ventral (extrathalamic) route. A second, thalamus-bypassing stream runs ventrally through the *lateral hypothalamus* and into the **basal forebrain** (nucleus basalis of Meynert, medial septum, diagonal band), from where cholinergic and GABAergic fibres fan out directly to cortex. The two routes are partly redundant: experimentally, cortical activation can survive loss of one if the other is intact, which is the physiological basis for why ARAS lesions must be substantial and usually bilateral or midline to extinguish arousal completely.

> PEARL
>
> The intralaminar nuclei are the single most exam-relevant relay station of the ARAS. Their bilateral destruction (e.g. thalamic infarction, paramedian artery of Percheron occlusion) produces a profound, often persistent disorder of consciousness despite an intact cortex, the inverse of the cortical-content lesions seen in the network topic: the salience and default-mode networks degrade *content*, whereas the ARAS sets *level*.

11.2 The neuromodulatory nuclei in full

Six chemically defined nucleus groups, each releasing a different transmitter, constitute the ascending arm. Their shared signature is **slow, tonic, state-dependent firing** that is fastest in waking, slower in non-REM sleep, and (for the aminergic cells) nearly silent in REM, while the cholinergic cells reactivate in REM. This is the chemical "code" of the sleep-wake switch.

NUCLEUS	TRANSMITTER	LOCATION	FIRING ACROSS STATES	FUNCTIONAL ROLE / CLINICAL HOOK
Locus coeruleus (LC)	Noradrenaline	Dorsolateral upper pons	**Wake > NREM, silent in REM**	Vigilance, stress arousal, attention; acts on cortical alpha and beta receptors. Degenerates early in Alzheimer and Parkinson disease; noradrenergic hyperactivity in PTSD.

NUCLEUS	TRANSMITTER	LOCATION	FIRING ACROSS STATES	FUNCTIONAL ROLE / CLINICAL HOOK
Dorsal & median raphe	Serotonin	Midline, full brainstem	Wake > NREM, silent in REM	Tonic cortical activation, mood, links to suprachiasmatic nucleus for circadian timing.
PPT & LDT	Acetylcholine	Mesopontine tegmentum	**Active in BOTH wake and REM**	Cortical desynchronisation (low-voltage fast EEG) and REM generation; the "REM-on" cholinergic cells.
Tuberomammillary nucleus (TMN)	Histamine	Posterior hypothalamus	Wake > NREM, off in REM	Sole brain source of histamine; the target of sedating (first-generation) antihistamines, which cause drowsiness by blocking it.
Ventral tegmental area (VTA)	Dopamine	Ventral midbrain	Wake-active (motivation-linked)	Wakefulness with behavioural salience; implicated in anaesthesia emergence and delirium.
Lateral hypothalamus	Orexin (hypocretin)	Posterior-lateral hypothalamus	Wake-active, the stabiliser	Excites all the above and inhibits sleep-promoting cells; its loss causes narcolepsy type 1; its blockade by DORAs is the newest hypnotic class.

The six ascending neuromodulatory systems: aminergic cells (LC, raphe, TMN) fall silent in REM while cholinergic cells (PPT, LDT) stay active, the cellular basis of REM's "wake-like cortex, paralysed body" paradox.

Orexin as the conductor. Orexin (hypocretin) neurons are few (tens of thousands) but pivotal. They do not drive arousal directly so much as **stabilise** it: they place excitatory tone on LC, raphe, TMN, VTA and the cholinergic nuclei, and simultaneously, through a feed-forward circuit, indirectly *inhibit* the sleep-promoting **ventrolateral preoptic nucleus (VLPO)** (sleepneuro optogenetic mapping). Loss of this stabilising hand is why narcolepsy is best understood not as simple sleepiness but as *state instability*, rapid, inappropriate intrusions of one state into another.

MNEMONIC

"A HAND of Orexin"

The arousal transmitters orexin holds together: **A**cetylcholine (PPT/LDT), **H**istamine (TMN), **A**drenergic-noradrenaline (LC), **N** for "5-HT" raphe (the serotonin nucleus), **D**opamine (VTA). Orexin is the hand; the five fingers are the wake systems it grips.

11.3 The flip-flop switch and state stability

Wakefulness and sleep are held apart by mutual inhibition, the **flip-flop switch** model (Saper). The arousal nuclei of 8.2 inhibit the sleep-active VLPO, and the VLPO, using GABA and the peptide *galanin*, inhibits all of them back. Two mutually inhibitory poles produce a bistable system that snaps cleanly between states and resists the middle ground, biologically advantageous (no half-asleep predator). Orexin is the external **finger on the switch** that weights it toward waking; remove orexin and the switch becomes leaky, flipping unpredictably, which is precisely the narcoleptic phenotype.

CLINICAL ANCHOR

Every sedative-hypnotic acts somewhere on this switch. Benzodiazepines and Z-drugs enhance GABA (reinforce the VLPO pole); first-generation antihistamines and low-dose mirtazapine block histamine (weaken the TMN finger); DORAs (suvorexant, lemborexant, daridorexant) remove the orexin finger so the switch falls naturally toward sleep, a more physiological route that better preserves sleep architecture than GABAergic agents.

11.4 Ascending versus descending reticular systems

"Reticular activating system" names only the *ascending* arousal function. The same brainstem reticular formation also runs powerful **descending** outputs, and exams reward the candidate who keeps the two separate.

Ascending (the ARAS proper)

Alertness, arousal, consciousness, sleep-wake and circadian modulation, and *habituation* (the active filtering-out of repetitive meaningless stimuli so attention can shift to what changes).

Descending (reticulospinal tracts)

Modulation of muscle tone, posture, locomotion and autonomic rhythm. The **medial (pontine) reticulospinal tract** facilitates extensor (anti-gravity) tone; the **lateral (medullary) reticulospinal tract** inhibits it and helps drive respiration. Loss of descending balance produces the textbook posturing signs.

Internally the reticular formation is organised in three sagittal columns: the midline *raphe* (serotonergic, mood and arousal), the *gigantocellular* medial column (large cells, motor coordination), and the lateral *parvocellular* column (small cells, respiratory and cranial-nerve modulation). A medial-to-lateral tegmental division maps onto eye/head-coordination (medial) versus visceral/cranial-nerve premotor functions (lateral). The ocular gaze centres live here: **mesencephalic** reticular formation for vertical gaze, **paramedian pontine reticular formation**

(PPRF) for horizontal gaze, with the medullary region for gaze-holding (cross-reference the PPRF in the fine-grain topic).

> ⚠ **COMMON TRAP**
>
> Decerebrate versus decorticate posturing is a descending-reticulospinal sign, not an ARAS-arousal sign. **Decerebrate** (extension of arms and legs) follows a lesion *at or below the red nucleus*, releasing the pontine extensor-facilitating tract. **Decorticate** (arms flexed, legs extended) follows a lesion *above the red nucleus*. The rule: the higher (decorticate) lesion carries the better prognosis; progression from decorticate to decerebrate signals caudal deterioration.

11.5 The two axes of consciousness: arousal and awareness

Consciousness is conventionally factorised into two dissociable components, and the ARAS topic exists to teach the first.

Arousal (wakefulness, the "level")

Set by the ARAS, expressed as eye-opening and sleep-wake cycling, indexed clinically by the eye component of the Glasgow Coma Scale and by EEG background. It is a *brainstem-thalamic* function.

Awareness (content)

The contents of experience, of environment and of self, requiring an intact and connected *cortex* (the fronto-parietal and default-mode/salience networks of the network topic). It is the "what" of consciousness.

The clinical power of the distinction lies in its dissociations. The two can come apart in either direction, and the disorders of consciousness are precisely the cells of that two-by-two table: arousal can be present without awareness (vegetative state), or awareness present while motor output is lost (locked-in), or both abolished (coma).

11.6 Clinical correlation per disorder

Coma. A state of unarousable unresponsiveness, no eye-opening, no sleep-wake cycle, lasting more than an hour (distinguishing it from syncope). Mechanistically it requires one of two things: a **bilateral** hemispheric/diencephalic insult, or a single lesion of the **ARAS in the upper brainstem** (paramedian midbrain or pontine tegmentum). A small unilateral cortical stroke never causes coma; a small paramedian midbrain stroke can. Supratentorial mass lesions cause coma indirectly, by *transtentorial herniation* compressing the midbrain ARAS, the reason a fixed dilated pupil and falling consciousness in a head-injury patient is a neurosurgical emergency.

STATE	AROUSAL (ARAS)	AWARENESS (CORTEX)	MOTOR OUTPUT	LESION / MECHANISM
Coma	**Absent**	Absent	Absent (reflexive only)	Upper-brainstem ARAS or bilateral hemispheric
Vegetative state / UWS	**Present (cycles, eyes open)**	Absent	Reflexive, non-purposeful	Diffuse cortical / thalamic damage, ARAS preserved
Minimally conscious state	Present	Fluctuating, partial	Inconsistent but reproducible	Severe but incomplete cortical disconnection
Locked-in syndrome	Present	**Fully intact**	Quadriplegia, anarthria; vertical gaze/blink spared	Ventral pons lesion (basilar occlusion), ARAS spared
Brain death	Absent (irreversible)	Absent	Absent, no brainstem reflexes, apnoea	Whole-brain including brainstem

The disorders of consciousness as a dissociation matrix: the vegetative state and locked-in syndrome are mirror images, the former has arousal without awareness, the latter awareness without expressible output.

Locked-in versus vegetative state / unresponsive wakefulness syndrome. The single most examined and most clinically consequential distinction in this topic. In the **vegetative state** (now preferably termed *unresponsive wakefulness syndrome, UWS*, to avoid the pejorative connotation), the ARAS is intact so the patient opens their eyes and cycles through sleep and wake, but the cortex is too damaged or disconnected to generate awareness; responses are reflexive only. In **locked-in syndrome**, a ventral pontine lesion (classically basilar artery thrombosis) severs the descending motor (corticospinal and corticobulbar) tracts while sparing the dorsally placed ARAS and the oculomotor pathways: the patient is *fully conscious and aware* but can move only the eyes (vertical gaze and blinking), through which communication can be established. Mistaking locked-in for vegetative is a catastrophic error; careful examination for purposeful vertical eye movement is the safeguard.

CLASSIC TRAP Reading locked-in syndrome as vegetative. Locked-in has **full awareness** (ventral pons lesion, ARAS spared); test for purposeful vertical gaze and blinking before concluding there is no awareness.

Narcolepsy. The paradigmatic ARAS-stabiliser disorder. ICD-11 (7A20) and DSM-5-TR define *narcolepsy* as recurrent irrepressible sleep attacks. **Type 1** reflects near-total loss of orexin (hypocretin) neurons (CSF orexin-A low or undetectable) and is defined by *cataplexy*, sudden bilateral loss of muscle tone triggered by emotion (often laughter), representing REM atonia intruding into wakefulness. **Type 2** has preserved CSF orexin and no cataplexy. The wider *narcoleptic tetrad* adds sleep paralysis and hypnagogic (sleep-onset) and hypnopompic (waking) hallucinations, with sleep paralysis and hallucinations reported by roughly 50 to 60 percent of patients; onset is typically adolescent (before age 10 in 10 to 15 percent). On the multiple sleep

latency test the hallmark is short sleep latency with two or more sleep-onset REM periods. Management: modafinil or armodafinil (and newer wake-promoters such as pitolisant, an H3 inverse agonist that raises histamine, and solriamfetol) for daytime sleepiness, and sodium oxybate for cataplexy and disrupted nocturnal sleep.

HOLD THIS

Narcolepsy type 1 is orexin loss with cataplexy and low CSF orexin; type 2 keeps orexin and has no cataplexy. Cataplexy is REM atonia intruding into wakefulness, and the MSLT shows two or more sleep-onset REM periods.

INDIA CONTEXT

CSF orexin assay and formal polysomnography with MSLT are available only in tertiary sleep centres in India, so narcolepsy is frequently under-recognised and mislabelled as depression, "laziness" or epilepsy (cataplexy mistaken for an atonic seizure). For exams, anchor the diagnosis on the clinical tetrad plus MSLT; modafinil is the widely available first-line agent. Sodium oxybate access remains limited.

Anaesthesia. General anaesthetics do not simply "switch off" the brain; they hijack the same arousal circuitry. Most act by potentiating GABA-A transmission, which suppresses the ascending arousal nuclei and engages the sleep-promoting VLPO, producing an EEG that progresses from waking activation to slow waves and burst-suppression as dose rises. Crucially, *emergence* from anaesthesia is not passive drug washout alone but an active reactivation of arousal nuclei: orexin and VTA dopamine systems drive the return of consciousness, and disturbance of this reactivation is linked to delayed emergence and to post-operative delirium (sleepneuro animal work on LH-orexin and VTA-dopamine in anaesthesia-induced sleep-wake and delirium-like behaviour). Dexmedetomidine, an alpha-2 agonist, is illustrative: it sedates by inhibiting the locus coeruleus, mimicking a natural non-REM-like state, which is why its sedation is more rousable.

Delirium. Delirium (ICD-11 6D70) is, at the level of this topic, an *acute, fluctuating failure of the arousal-attention system*, a disturbance of consciousness and attention with a characteristic diurnal (often sundowning) pattern. The leading neurochemical account is **cholinergic deficiency with relative dopaminergic and glutamatergic excess**, which maps directly onto ARAS chemistry: anticholinergic burden is a major precipitant (the reason anticholinergic drugs are deliriogenic in the elderly), and dopaminergic overactivity is why low-dose antipsychotics (e.g. haloperidol, quetiapine) target the agitated phenotype, though they treat symptoms, not the underlying cause. The fluctuating arousal level and the EEG generalised slowing both reflect destabilisation of the ascending modulatory systems. Management is identification and correction of the precipitant first, then non-pharmacological measures (orientation, sleep-wake normalisation, sensory aids), with antipsychotics reserved for distressing agitation, consistent with NICE CG103 and the IPS delirium guidance.

Yeo, Chang and Jang (2013) LANDMARK

Design. Diffusion-tensor tractography in 26 healthy adults reconstructing the lower (pontine reticular formation to thalamus) component of the ARAS. **Finding.** A discrete, hemispherically symmetric tract ascends from the pontine reticular formation through the mesencephalic tegmentum posterior to the red nucleus to terminate in the intralaminar thalamic nuclei, without age-related decline. **Why it matters.** It is the first in-vivo human depiction of the ARAS bundle, giving an imaging substrate for prognosticating disorders of consciousness, where ARAS tract integrity tracks recovery potential.

12 · Brainstem monoamine nuclei of origin

The cortex does not manufacture its own neuromodulators. A handful of small, phylogenetically ancient nuclei buried in the brainstem and basal forebrain synthesise noradrenaline, serotonin, dopamine, acetylcholine and histamine, then fan those signals out over the entire neuraxis through diffuse, poorly-topographic projections. This is the anatomy of **ascending modulatory (diffuse projection) systems**: a nucleus of a few thousand neurons tunes the gain of millions of downstream cells. For the exam, learn each nucleus as a triplet: where it sits, where it projects, and the one disorder or drug class it is famous for.

Why this is high-yield. Every major psychotropic drug class and every degenerative dementia is, at heart, a story about one of these nuclei failing or being manipulated. The recurring principle, confirmed across tract-tracing work, is *one nucleus, one transmitter, one diffuse job*: the source is discrete and the target is the whole forebrain (Dafny et al. 2024 frame the dorsal raphe, locus coeruleus and ventral tegmental area as the respective serotonergic, noradrenergic and dopaminergic sources of the reward circuit). The transmitter pathways in full and the receptor pharmacology are taught on the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes Neurochemistry; here we learn only the nuclei of origin.

HOLD THIS

One nucleus, one transmitter, one diffuse forebrain job. Locus coeruleus (noradrenaline), raphe (serotonin), VTA and substantia nigra (dopamine), basal forebrain (acetylcholine), tuberomammillary (histamine).

12.1 Locus coeruleus: the sole major noradrenaline source

The **locus coeruleus** ("blue spot", cell group A6) lies in the posterior rostral pons, in the lateral floor of the fourth ventricle; its blue colour comes from neuromelanin, the polymer of noradrenaline analogous to the dopamine-based pigment of the substantia nigra. It is the principal, effectively the sole, site of brain noradrenaline synthesis, and despite holding only in the order of tens of thousands of pigmented neurons it projects almost everywhere: cortex, hippocampus, amygdala, thalamus, hypothalamus, cerebellum, brainstem and spinal cord. Because a single small nucleus innervates the entire forebrain, its output is genuinely diffuse rather than point-to-point.

Function. The locus coeruleus-noradrenergic system sets **arousal, vigilance and attention**, times the sleep-wake cycle (it is quiescent in REM sleep), and drives the central limb of the stress

response. Emotional and stressful input reaches it from the amygdala and cingulate, and its excitatory noradrenergic output primes cortical neurons to respond to salient stimuli. The projection from the locus coeruleus to the basolateral amygdala is implicated in the fear-circuitry of PTSD (ICD-11 6B40; DSM-5-TR posttraumatic stress disorder), and the nucleus is a target of the noradrenergic and dual-action antidepressants and of atomoxetine.

CLINICAL ANCHOR

The locus coeruleus degenerates early and heavily in neurodegeneration. In Alzheimer disease (ICD-11 8A20; DSM-5-TR major neurocognitive disorder due to Alzheimer disease) there is up to roughly 80% loss of locus coeruleus neurons, and tau neurofibrillary tangles appear here decades before clinical symptoms, arguably the earliest tangle-bearing site of all. It also degenerates in idiopathic Parkinson disease, progressive supranuclear palsy and Pick disease. Loss of its noradrenergic, anti-inflammatory tone is thought to accelerate amyloid deposition, the basis of the "noradrenergic theory of cognitive reserve".

TRAP Swapping the two dopamine nuclei. The medial **VTA** seeds mesolimbic and mesocortical (reward, psychosis); the lateral **substantia nigra pars compacta** seeds nigrostriatal (Parkinson motor loss).

12.2 Raphe nuclei: the midline serotonin source

The **raphe nuclei** are a chain of serotonergic cell groups strung along the midline (raphe = "seam") of the brainstem, running from midbrain to medulla. Their exam-critical organising fact is a **rostral versus caudal division of labour**. The rostral group, above all the *dorsal raphe* and the *median raphe* in the midbrain and upper pons, sends the ascending serotonergic projection to the whole forebrain: cortex, striatum, limbic system and hypothalamus. The caudal group in the lower pons and medulla (for example the raphe magnus) projects downward to the brainstem and spinal cord, where it gates descending pain modulation and autonomic and motor tone.

Function. Through its forebrain-projecting rostral output the serotonergic system regulates **mood, the sleep architecture, appetite**, impulse control, anxiety and aggression, which is why the raphe is the conceptual home of the SSRIs and of the monoamine hypothesis of depression. The caudal, cord-projecting output belongs more to analgesia and autonomic regulation than to affect. The dorsal raphe is the serotonergic source of the reward circuit in the framework of Dafny et al. (2024).

12.3 Ventral tegmental area and substantia nigra pars compacta: the two dopamine sources

Midbrain dopamine arises from two adjacent but functionally distinct pigmented cell groups, and the discriminator examiners want is *which nucleus seeds which pathway*. The **ventral tegmental area** (VTA, cell group A10), medial in the midbrain tegmentum, seeds the **mesolimbic pathway** (to the nucleus accumbens and limbic system, the reward and psychosis-relevant projection) and the **mesocortical pathway** (to the prefrontal cortex, relevant to cognition and negative symptoms). The **substantia nigra pars compacta** (SNc, cell group A9), lateral to it, seeds the **nigrostriatal pathway** to the dorsal striatum, the motor loop. (The fourth, tuberoinfundibular,

dopamine pathway arises from the hypothalamus, not the midbrain.) The full four-pathway map with its receptor pharmacology is the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes Neurochemistry.

CLINICAL ANCHOR

The two nuclei fail in opposite directions clinically. Degeneration of the neuromelanin-containing SNc neurons is the defining lesion of Parkinson disease, producing nigrostriatal dopamine loss and the motor triad. VTA-driven mesolimbic overactivity is the dopaminergic correlate of positive psychotic symptoms in schizophrenia (ICD-11 6A20; DSM-5-TR schizophrenia), while mesocortical underactivity is invoked for negative and cognitive symptoms.

12.4 Nucleus basalis of Meynert and the septal-diagonal band groups: the cholinergic source

The diffuse cortical cholinergic supply comes from the **basal forebrain cholinergic complex**, learned as Mesulam's Ch1 to Ch4 groups. The **nucleus basalis of Meynert** (Ch4), in the substantia innominata beneath the globus pallidus, gives the principal **cholinergic projection to the whole neocortex and the amygdala**. The **medial septal nucleus (Ch1) and the vertical and horizontal limbs of the diagonal band of Broca (Ch2, Ch3)** project chiefly to the **hippocampus** (via the fornix) and cingulate. Together they carry acetylcholine to cortex and hippocampus for **memory encoding, learning and cortical arousal**. (A separate brainstem cholinergic group, the pedunculopontine and laterodorsal tegmental nuclei, drives thalamic arousal and REM sleep, but the memory-relevant source is the basal forebrain.)

CLINICAL ANCHOR

Degeneration of the nucleus basalis of Meynert with loss of cortical cholinergic input is the neurochemical core of Alzheimer disease and the rationale for cholinesterase inhibitors (donepezil, rivastigmine, galantamine). This "cholinergic hypothesis" is also why anticholinergic drug burden worsens cognition and can precipitate delirium in the elderly.

12.5 Tuberomammillary nucleus: the histamine source, and the unifying map

The **tuberomammillary nucleus**, in the posterior hypothalamus, is the sole source of histaminergic neurons in the brain and, like the others, projects diffusely to cortex and much of the neuraxis to promote **wakefulness and arousal**. Its silencing is central to how sedating, H1-antagonist antihistamines and many antipsychotics cause somnolence, and the wake-promoting orexin (hypocretin) system acts partly by exciting it, the link to narcolepsy. It completes the shared blueprint of these systems: a small, discrete brainstem or basal-forebrain nucleus, a single signature transmitter, and one broad, gain-setting job across the forebrain.

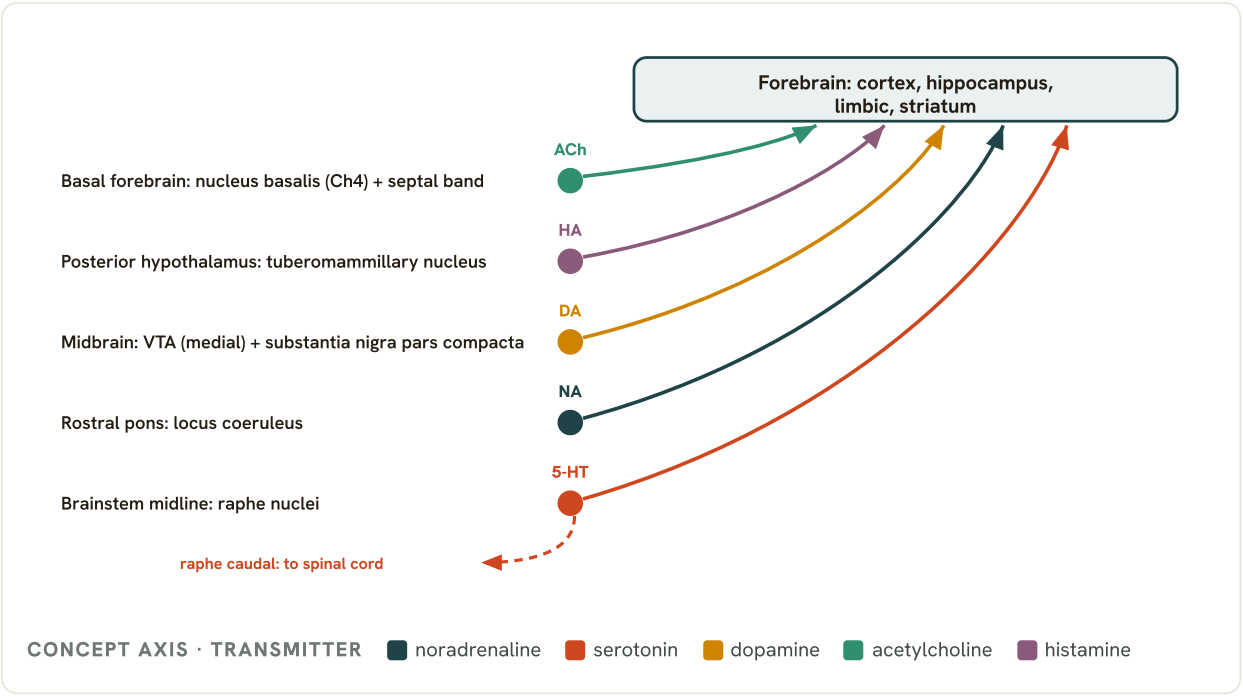


Fig 1.13 The nuclei of origin, plotted rostral to caudal. Each discrete nucleus (colour = transmitter) fans a diffuse ascending projection over the whole forebrain: one nucleus, one transmitter, one gain-setting job. The raphe alone splits its output, rostral to the forebrain and caudal to the cord. The transmitter pathways and receptors are developed on the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes.

NUCLEUS	TRANSMITTER	MAIN PROJECTION	SIGNATURE CLINICAL LINK
Locus coeruleus (pons, A6)	Noradrenaline	**Sole major NA source; diffuse to whole cortex, hippocampus, cord**	~80% loss and earliest tau in Alzheimer disease; arousal, PTSD, stress
Raphe nuclei (midline brainstem)	Serotonin	**Rostral to forebrain, caudal to spinal cord**	Mood, sleep, appetite; SSRIs and depression
Ventral tegmental area (A10)	Dopamine	Mesolimbic and mesocortical	Mesolimbic overactivity in psychosis
Substantia nigra pars compacta (A9)	Dopamine	Nigrostriatal (to dorsal striatum)	Degenerates in Parkinson disease (motor)
Nucleus basalis of Meynert plus septal-diagonal band	Acetylcholine	Neocortex (Meynert) and hippocampus (septal-diagonal band)	Cholinergic loss in Alzheimer disease; cholinesterase inhibitors
Tuberomammillary nucleus (posterior hypothalamus)	Histamine	Diffuse to cortex, wake-promoting	H1 blockade causes sedation; orexin and narcolepsy

MNEMONIC

Big Brains Make Slow Thoughts Hesitate

Reads the six sources rostral-to-caudal by transmitter home, but easier as a source-to-transmitter cue: **B**lue spot (locus coeruleus) makes noradrenaline; **B**asalis of Meynert makes acetylcholine; **M**idline raphe makes serotonin; **S**ubstantia nigra and VTA make dopamine; **T**uberomammillary makes histamine. The single principle to carry: one nucleus, one transmitter, one diffuse job.

COMMON TRAP

Do not swap the two dopamine nuclei: the VTA (medial) seeds the mesolimbic and mesocortical pathways, the substantia nigra pars compacta (lateral) seeds the nigrostriatal. A stem describing a resting tremor and rigidity is pointing at the nigra; a stem about reward, salience or positive psychotic symptoms is pointing at the VTA. Also do not call the locus coeruleus a dopamine nucleus because it is pigmented: its neuromelanin is noradrenaline-derived, and it is the noradrenergic, not dopaminergic, source.

13 · Blood supply and cerebrovascular territories

The vascular map is the single most examinable overlay on the anatomy of these notes, because a stroke is a natural lesion experiment: an artery closes and a defined block of tissue falls silent, so the deficit reads the territory back to you. For psychiatry this is not a neurology detour. Vascular lesions produce syndromes that arrive at the psychiatric clinic first, misfiled as depression, apathy, psychosis or an amnestic dementia, and the marks in the exam go to the candidate who can localise a behavioural change to an arterial territory and name the collateral routes that decide whether an occlusion is silent or catastrophic. The brain has no fuel store of its own and consumes roughly 15% of resting cardiac output (Yu and Lui, StatPearls 2022), which is why even brief hypoperfusion carves out predictable border-zone lesions.

Learn the arteries by the deficit they abolish, not by the sulci they cross. The scheme below moves from the anastomotic ring that lets one territory rescue another, out to each of the three cerebral arteries, and finishes with the border-zone and small-vessel disease that underlie much of vascular cognitive impairment. Post-stroke depression, mania, psychosis and apathy are developed as a management arc on the Stroke, TBI, delirium & focal brain syndromes notes; here the task is localisation and its behavioural signature.

13.1 The circle of Willis: anterior and posterior circulation and the communicating arteries

Four vessels feed the brain: the two **internal carotid arteries** (ICA) forming the anterior circulation and the two vertebral arteries, which fuse into the basilar artery, forming the posterior (vertebrobasilar) circulation (Konan, Reddy and Mesfin, StatPearls 2023). At the skull base these two systems close into an anastomotic ring, the circle of Willis, whose sides are the two anterior cerebral arteries joined across the midline by the single **anterior communicating artery** (AComm), and the two posterior cerebral arteries joined to each ICA by the paired **posterior communicating arteries** (PComm). Each ICA gives three terminal branches, the anterior cerebral, middle cerebral and anterior choroidal arteries; the posterior cerebral arteries are the

terminal branches of the basilar. The anterior circulation supplies about 80% of the brain and the posterior about 20%, which is mirrored in stroke epidemiology, roughly 80% of ischaemic strokes are anterior and 20% posterior (Yu and Lui, StatPearls 2022).

Why the ring matters clinically. The communicating arteries are collateral channels: a complete circle lets an occluded ICA be perfused across the AComm from the other side or up the PComm from the posterior circulation, so a slowly occluding vessel can be clinically silent. A complete, symmetric circle is present in only a minority of people; hypoplasia or absence of one or both communicating or precommunicating segments is the norm, which is why the same occlusion is silent in one patient and devastating in another.

PEARL

Common variants worth the mark: a **fetal PCA** (the PCA is fed mainly by the PComm from the ICA rather than the basilar, so an anterior-circulation clot can produce an occipital, posterior-territory infarct); an **azygos ACA** (a single unpaired A2 trunk supplying both medial hemispheres, so one occlusion causes bilateral leg weakness); and the **artery of Percheron** (a single trunk supplying both paramedian thalami, whose occlusion produces bilateral thalamic infarction, see 13.4).

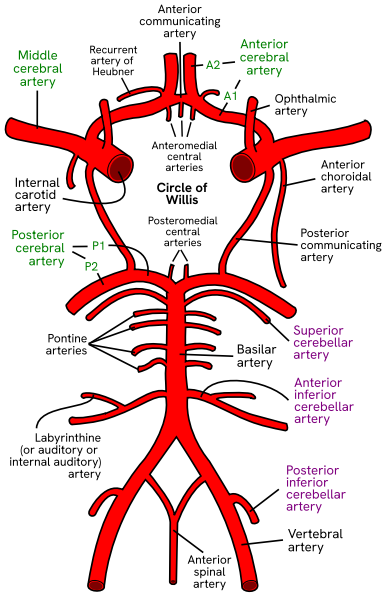


Image: Rhcastilhos, public domain, via Wikimedia Commons

Fig 1.14 The circle of Willis: the anastomotic ring where the anterior (internal carotid) and posterior (vertebrobasilar) circulations meet. The communicating arteries are the collateral channels that decide whether an occlusion is silent or symptomatic.

13.2 Anterior cerebral artery: the medial hemisphere and the frontal-behavioural syndromes

The ACA sweeps over the corpus callosum to supply the **medial** surface of the frontal and parietal lobes, the territory that includes the leg area of the motor and sensory homunculus, the supplementary motor area and the anterior cingulate. Its deep recurrent artery of Heubner (off A1 or proximal A2) supplies the head of the caudate and the anterior limb of the internal capsule

(Konan, Reddy and Mesfin, StatPearls 2023). ACA infarcts are the least common of the three cortical strokes, largely because the AComm allows cross-filling.

Motor signature. Because the leg homunculus sits on the medial surface, an ACA infarct gives contralateral weakness that is *leg-predominant*, sparing the face and arm, the mirror image of the MCA pattern in 13.3.

RULE **ACA infarct is leg-predominant weakness; MCA is face-and-arm predominant.** The homunculus splits at the interhemispheric fissure, so the territory reads the weakness pattern back to you.

Behavioural signature. Medial-frontal and anterior cingulate involvement produces **abulia**, a loss of drive and spontaneous behaviour that is readily mistaken for depression, and in bilateral or extensive lesions **akinetic mutism**, a state of preserved wakefulness with almost no spontaneous movement or speech. Left-sided supplementary-motor-area damage gives a **transcortical motor aphasia**: sparse, non-fluent output with preserved repetition, the hallmark that separates it from Broca aphasia. These are exactly the presentations that reach psychiatry mislabelled as catatonia or a depressive stupor.

13.3 Middle cerebral artery: the lateral hemisphere and the commonest stroke of psychiatric interest

The MCA is the direct continuation of the ICA and the largest cerebral artery. It supplies almost the entire **lateral** convexity of the hemisphere, the face and arm areas of the homunculus, the language cortices on the dominant side and the attentional cortices on the non-dominant side, while its deep **lenticulostriate** perforators supply the basal ganglia and the internal capsule (Konan, Reddy and Mesfin, StatPearls 2023). It is both the commonest site of large-vessel stroke and the one whose deficits most often present as a psychiatric or neuropsychiatric picture.

Motor and sensory signature. Contralateral weakness and sensory loss that is *face and arm predominant*, sparing the leg, because the trunk and leg sit on the medial (ACA) surface.

The dominant versus non-dominant split. A dominant (usually left) MCA stroke produces aphasia: Broca (non-fluent) with frontal opercular lesions, Wernicke (fluent, empty, poorly comprehended) with superior temporal lesions. A non-dominant (usually right) MCA stroke produces **hemispatial neglect**, anosognosia (denial of the deficit) and affective flattening of prosody, a cluster repeatedly mistaken for indifference, confusion or a functional presentation. Deep lenticulostriate occlusion instead produces a **lacunar** syndrome, classically pure motor hemiparesis from an internal-capsule infarct, with no cortical signs.

13.4 Posterior cerebral artery: occipital vision, medial-temporal memory and the disconnection syndromes

The PCA supplies the **occipital** lobe (primary visual cortex around the calcarine fissure), the inferomedial **temporal** lobe including the hippocampus, and, through its proximal perforators, much of the thalamus and rostral midbrain (Benjamin, Tadi and Singh, StatPearls 2026). Its deficits are therefore a mixture of visual, amnestic and neuropsychiatric signs.

Visual signature. A unilateral occipital infarct gives contralateral **homonymous hemianopia with macular sparing**; the macular representation survives because the occipital pole receives collateral supply from the MCA (Benjamin, Tadi and Singh, StatPearls 2026). A dominant occipital lesion that also takes the splenium of the corpus callosum disconnects the intact visual cortex from the language areas, producing **alexia without agraphia**, the patient can write but cannot read what they wrote.

Bilateral and amnestic signatures. Bilateral occipital infarction causes cortical blindness, and when the patient denies the blindness and confabulates a visual world it is **Anton syndrome** (Das and Naqvi, StatPearls 2023). Bilateral parieto-occipital border-zone damage produces **Balint syndrome**: simultanagnosia, optic ataxia and oculomotor apraxia. Because the PCA feeds the hippocampus, infarction here (especially bilateral or dominant) produces an **amnestic syndrome** that mimics a rapidly progressive dementia. Occlusion of an artery of Percheron gives bilateral paramedian thalamic infarcts presenting with impaired memory, altered arousal and vertical gaze palsy, a classic psychiatry-of-confusion trap.

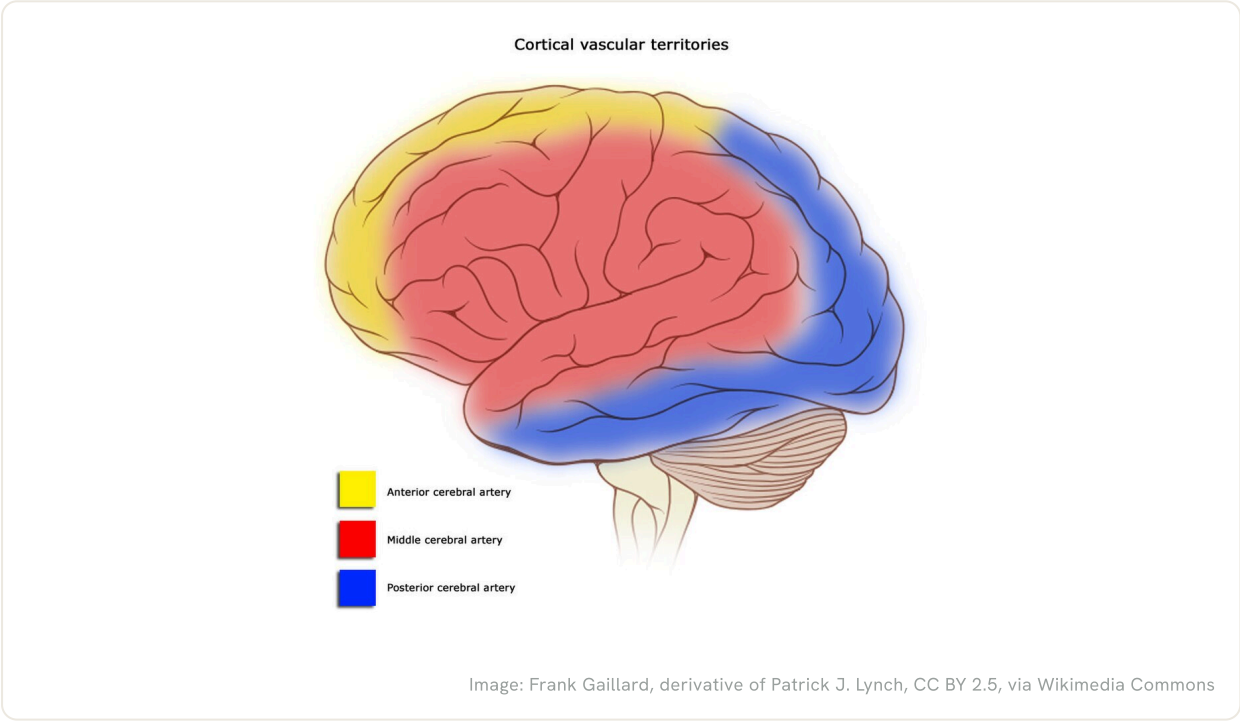


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Fig 1.15 Cortical arterial territories on the lateral surface: anterior cerebral (medial strip over the top), middle cerebral (lateral convexity, face and arm), posterior cerebral (occipital and inferior temporal). The border zones between colours are the watershed regions that fail first in global hypoperfusion.

13.5 Watershed infarcts, small-vessel disease and strategic-infarct dementia

Between adjacent arterial territories lie **border-zone** (watershed) regions perfused at the far end of two supplies, so they are the first to fail during global hypoperfusion (cardiac arrest, profound hypotension, carotid occlusion). The **anterior (ACA-MCA)** border zone runs in the superior frontal and parasagittal cortex; the **posterior (MCA-PCA)** border zone sits in the parieto-occipital region. The internal (subcortical) border zone lies in the deep white matter of the corona radiata.

Signatures. Bilateral anterior watershed infarction spares the distal limbs but takes the proximal shoulder and hip cortex, producing proximal weakness with distal sparing, the **"man in a barrel"** pattern. Posterior watershed damage produces the visual-integration failure of Balint syndrome (13.4), and a left temporal-parietal border-zone lesion gives **transcortical sensory aphasia**: fluent speech with preserved repetition but impaired comprehension. The transcortical aphasias are the border-zone signature, repetition survives because the perisylvian language core is intact while its connections to association cortex are cut.

Small-vessel disease and vascular cognitive impairment. Chronic hypertension and diabetes damage the deep penetrating arterioles (lenticulostriate, thalamoperforators), giving lacunar infarcts and confluent white-matter change (leukoaraiosis). The cumulative burden underlies much **vascular cognitive impairment**, classically a dysexecutive, apathetic, psychomotor-slowed picture with gait disturbance, distinct from the amnestic onset of Alzheimer disease. Under ICD-11 this is captured as vascular dementia (6D81 within neurocognitive disorders), cross-mapping to DSM-5-TR Major or Mild Vascular Neurocognitive Disorder. A single small infarct in a functionally critical site, the **strategic infarct**, can cause disproportionate cognitive collapse: a dominant thalamic (paramedian) infarct produces a dense amnestic and dysexecutive state, and a dominant angular gyrus infarct can reproduce the full Gerstmann tetrad (acalculia, agraphia, finger agnosia, left-right disorientation) with fluent aphasia, mimicking a cortical dementia.

COMMON TRAP

Do not read a fluent, comprehending, repeating patient as intact. Preserved repetition with impaired comprehension (transcortical sensory) or impaired output (transcortical motor) points to a border-zone lesion, not a psychiatric mutism or thought disorder. Likewise, an abulic or akinetic-mute patient after a medial-frontal ACA event is not depressed, and a right-MCA patient denying a left hemiplegia has anosognosia, not denial in the psychodynamic sense.

The table below is the single highest-yield object of this topic: read it left to right to localise from a deficit, or use the last column to see why each territory recurs in the psychiatric clinic.

ARTERY	TERRITORY	SIGNATURE DEFICIT	PSYCHIATRIC RELEVANCE
Anterior cerebral (ACA)	Medial frontal and parietal, leg homunculus, anterior cingulate, SMA	Leg-predominant weakness; transcortical motor aphasia (dominant)	**Abulia and akinetic mutism mistaken for depression or catatonia**
Middle cerebral (MCA)	Lateral convexity, face and arm homunculus; deep lenticulostriate to capsule and basal ganglia	Face and arm weakness; aphasia (dominant) or neglect and anosognosia (non-dominant)	**Right-MCA neglect and aprosodia misread as indifference; post-stroke depression (the Stroke, TBI, delirium & focal brain syndromes notes)**
Posterior cerebral (PCA)	Occipital cortex, medial temporal and hippocampus, thalamus, rostral midbrain	Homonymous hemianopia with macular sparing; alexia without agraphia; Anton or Balint if bilateral	**Hippocampal amnesia mimicking dementia; cortical blindness with confabulation (Anton)**
Border zone (ACA-MCA, MCA-PCA)	Parasagittal frontal and parieto-occipital cortex after global hypoperfusion	Proximal weakness ("man in a barrel"); transcortical (repetition-sparing) aphasias; Balint	Post-arrest cognitive-executive syndromes and language errors misfiled as functional
Deep perforators (small vessel)	Lenticulostriate, thalamoperforators, deep white matter	Lacunar syndromes; leukoaraiosis; strategic infarcts (thalamus, angular gyrus)	**Vascular cognitive impairment: dysexecutive, apathetic, slowed, gait-affected**

Artery-to-deficit map for the five clinically grouped cerebrovascular territories, with the discriminating psychiatric presentation of each highlighted; localise from a deficit by reading left to right, or trace a psychiatric presentation back to its territory using the final column.

HOLD THIS

ACA abulia mistaken for depression, right-MCA neglect mistaken for indifference, PCA hippocampal amnesia mistaken for dementia. Every arterial territory has a psychiatric mimic that arrives at the clinic first.

14 · Fine-grain neuroanatomy worth a quick mark

Four structures that recur as 10-mark spotters.

Medial longitudinal fasciculus (MLF)

Links the cranial-nerve nuclei that move the eyes conjugately. A lesion (classically demyelination in MS) causes *internuclear ophthalmoplegia*: failure of adduction on the lesioned side with nystagmus of the abducting eye.

Pineal gland

Secretes melatonin under SCN control (dark-onset), the chronobiotic hormone; calcifies with age (a midline radiological landmark).

Cortical control of eye movement

Frontal eye fields drive voluntary saccades to the contralateral side; the parietal eye fields and the pontine paramedian reticular formation (PPRF, the horizontal-gaze centre) execute them. Smooth-pursuit and antisaccade abnormalities are replicated findings in schizophrenia.

CSF circulation

Choroid plexus (lateral, third, fourth ventricles) makes roughly 500 mL/day; flow runs lateral to third (foramina of Monro) to fourth (aqueduct) to subarachnoid space (foramina of Luschka and Magendie), absorbed at the arachnoid granulations. Normal-pressure hydrocephalus gives the triad of gait apraxia, urinary incontinence and dementia (a treatable cause of cognitive decline).

14.1 The MLF and internuclear ophthalmoplegia, in full

The *medial longitudinal fasciculus* (MLF) is the brainstem's master cable for conjugate eye movement. It is a paired, heavily myelinated bundle running near the midline through the dorsal tegmentum of all three brainstem segments (ventral to the cerebral aqueduct in the midbrain, ventral to the fourth ventricle in the pons and medulla) and reaching caudally into the upper cervical cord. The defining paragraph in the existing section gives the headline; here is the wiring that makes it a recurring 10-mark answer.

Structure and contents. Beyond being a conduit, the rostral MLF houses two nuclei the examiner loves: the **interstitial nucleus of Cajal (INC)** (oculomotor control, head posture, the neural integrator for vertical and torsional gaze-holding) and, just rostral to it, the **rostral interstitial nucleus of the MLF (riMLF)**, the vertical-gaze burst centre (detailed in 9.2). The trochlear nucleus (CN IV) is embedded within the MLF between the superior and inferior colliculi.

Connections. The MLF is the main central connection of CN III, IV and VI. The key horizontal loop: the PPRF excites the *ipsilateral* abducens nucleus, which sends one signal to the ipsilateral lateral rectus and a second via abducens excitatory interneurons that *decussate* and ascend in the *contralateral* MLF to the medial rectus subnucleus of the oculomotor nucleus. The MLF also carries ascending vestibulo-ocular fibres from the vestibular nuclei to CN III, IV and the INC, coordinating eyes with head movement.

Mechanism of INO. A lesion of one MLF interrupts the ascending interneuron before it reaches the medial rectus subnucleus. The result is failure or slowing of **adduction on the side of the lesion** with **dissociated abducting nystagmus of the other eye.** The nystagmus is best explained by Hering's law of equal innervation: the brain drives the weak adducting eye harder, and the yoked contralateral lateral rectus is over-innervated, producing the jerks. Convergence may be preserved because near-response medial rectus drive enters above the MLF lesion; preserved convergence with failed adduction on saccades is the sign that confirms an MLF (rather than medial rectus or third-nerve) lesion. The older Cogan split (anterior INO, lesion above CN III, lost convergence; posterior INO of Cogan, lesion below, retained convergence) has been disproven, but the eponyms still appear in question stems.

FEATURE	TRUE INO (MLF LESION)	PSEUDO-INO
Adduction deficit	Present, ipsilateral	Present (mimics)
Convergence	**Often preserved (dissociation)**	Variable / preserved
Abducting nystagmus	**Dissociated, a few beats**	Usually absent
Classic cause	MS (young, bilateral); infarct (older, unilateral)	Myasthenia gravis; partial CN III palsy
Fatigability / ptosis	Absent	**Present in myasthenia**

How to separate a real MLF lesion from the great mimic, myasthenia gravis, on the bedside saccade-versus-convergence test.

Epidemiology and cause. Roughly one-third of INO cases are infarcts (typically **unilateral, older patients**) and another third are demyelinating, classically multiple sclerosis (typically **bilateral, young adults and adolescents**); INO is seen in about **23% of MS patients** in some series. Remaining causes: trauma, tentorial herniation, infections (HIV, syphilis, neurocysticercosis, tuberculoma, herpes zoster), tumours (medulloblastoma, pontine glioma, lymphoma, metastases), and vasculitis (SLE, Sjogren). Incidence is roughly equal between sexes, and nearly half of cases resolve within one year. MRI shows a visible lesion in up to **75%**; proton-density sequences are best for demyelinating plaques.

HOLD THIS

The side of an internuclear ophthalmoplegia equals the side of failed adduction equals the side of the MLF lesion. Bilateral INO in a young adult is multiple sclerosis until proven otherwise; unilateral in an older patient is a pontine infarct.

INO-plus syndromes. When the lesion spreads to adjacent structures the picture extends:

- **One-and-a-half syndrome.** Lesion of the MLF plus the ipsilateral PPRF or abducens nucleus: an ipsilateral horizontal gaze palsy ("one") plus an INO on looking the other way ("a half"). The only surviving horizontal movement is abduction of the contralateral eye. With a facial nerve lesion added it becomes the "eight-and-a-half syndrome".
- **INO with trochlear syndrome.** Caudal-midbrain lesion taking out the MLF and the embedded ipsilateral CN IV nucleus, adding a contralateral hyperdeviation (CN IV decussates, so its nucleus serves the opposite superior oblique).
- **WEBINO.** Wall-eyed bilateral INO: bilateral MLF lesions (usually a demyelinating plaque between the trochlear and abducens nuclei) sparing the ocular motor nuclei, producing bilateral adduction failure plus exotropia (the "wall-eyed" divergence) from disrupted otolithic input.

Management is cause-directed, not symptomatic. Acute stroke needs admission and a vascular workup; MS, infection and vasculitis are treated on their own lines. Persistent diplopia can be helped with Fresnel prisms or botulinum toxin, and WEBINO exotropia with strabismus surgery.

PEARL

Side of the INO equals side of the failed adduction equals side of the MLF lesion. Bilateral INO in a young woman is multiple sclerosis until proven otherwise; unilateral INO in an older hypertensive is a paramedian pontine infarct.

MNEMONIC

MLF = My Lagging Friend

The eye on the side of the MLF lesion *lags* (fails to adduct); the other eye runs ahead and jerks (abducting nystagmus). The lagging friend is always on the lesioned side.

14.2 The gaze centres: FEF, PPRF, riMLF

Conjugate gaze is built in two tiers: cortical command and brainstem execution. The existing section names the FEF and PPRF; the examinable depth is who commands what, and the clean horizontal-versus-vertical split.

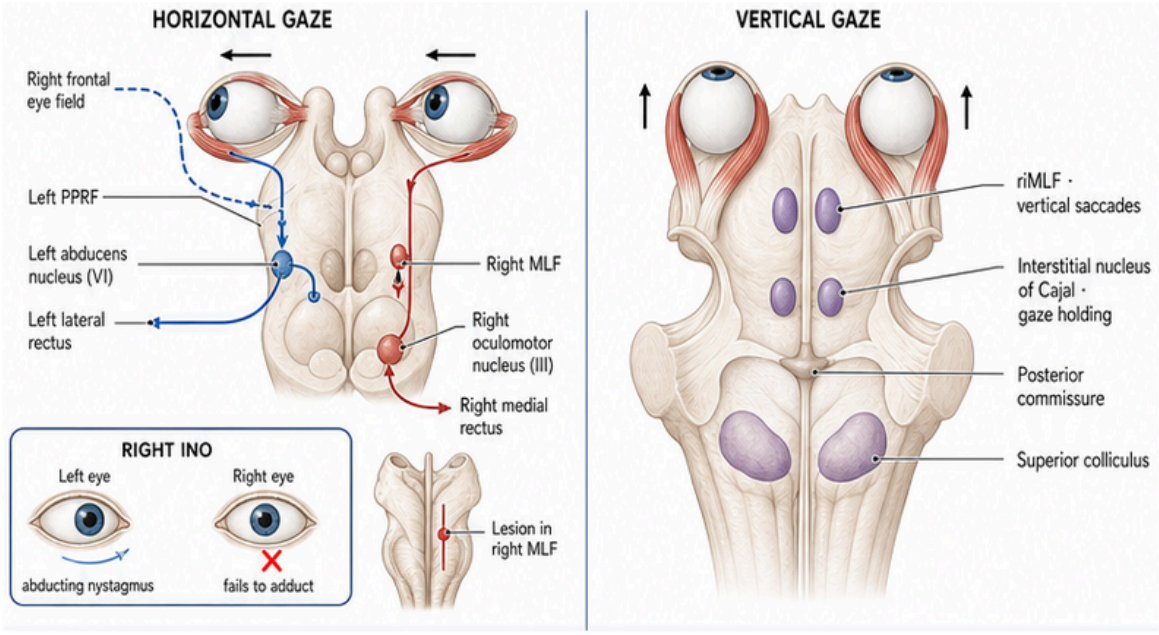


Fig 1.16 Horizontal and vertical conjugate gaze systems. The horizontal pathway links frontal eye field, contralateral PPRF, abducens nucleus and the opposite oculomotor nucleus through the medial longitudinal fasciculus.

Frontal eye field (FEF, Brodmann area 8)

Cortical command centre for voluntary *saccades*. It drives gaze to the **contralateral** side. A destructive FEF lesion (stroke) causes the eyes to deviate **towards** the lesion (the intact opposite FEF wins); an irritative lesion (a seizure focus) drives them **away**. Useful localising rule: a hemisphere stroke patient "looks at the lesion", a seizing patient "looks away from it".

Parietal eye field

Governs reflexive, visually guided saccades and smooth pursuit (ipsilateral pursuit). Smooth-pursuit gain reduction and antisaccade errors are among the most replicated oculomotor endophenotypes in schizophrenia.

PPRF (paramedian pontine reticular formation)

The **horizontal** gaze centre. It receives the FEF command and drives the ipsilateral abducens nucleus, generating a conjugate horizontal saccade to its own side. A PPRF or abducens-nucleus lesion gives an ipsilateral horizontal gaze palsy (the eyes will not cross the midline towards the lesion).

riMLF (rostral interstitial nucleus of the MLF)

The **vertical and torsional** gaze burst centre in the rostral midbrain. It generates vertical saccades; the adjacent *interstitial nucleus of Cajal* is the neural integrator that holds vertical gaze. Bilateral riMLF or dorsal-midbrain damage abolishes vertical saccades and produces the *Parinaud (dorsal midbrain) syndrome*: up-gaze palsy, light-near dissociation of the pupils, convergence-retraction nystagmus and lid retraction (Collier sign), classically from a pineal-region tumour compressing the tectum.

PLANE / FUNCTION	BURST CENTRE	HOLDING INTEGRATOR	LESION SYNDROME
Horizontal saccade	**PPRF (pons)**	Nucleus prepositus hypoglossi	Ipsilateral gaze palsy
Vertical / torsional	**riMLF (midbrain)**	Interstitial nucleus of Cajal	Parinaud syndrome
Cortical command	FEF (area 8)	not applicable	Eyes deviate to side of lesion

The horizontal-pons versus vertical-midbrain dichotomy, the single fact that unlocks most gaze-centre questions.

RULE **Horizontal gaze lives in the pons (PPRF); vertical gaze lives in the midbrain (riMLF).** A destructive stroke makes the eyes look at the lesion; a seizure drives them away.

♡ CLINICAL ANCHOR

A teenager with up-gaze paralysis, big poorly reactive pupils that constrict to a near target (light-near dissociation), and lid retraction has Parinaud syndrome from a pineal germinoma pressing on the dorsal midbrain. Connect this to 9.3.

14.3 Pineal gland and the melatonin axis

The existing entry states the headline (melatonin under SCN control, calcifies with age). Here is the circuit and its clinical traction.

Structure and pathway. The pineal gland is an unpaired midline endocrine organ on the posterior diencephalon, just above the dorsal midbrain. Light information runs a long indirect arc: retina to the **suprachiasmatic nucleus (SCN)** via the retinohypothalamic tract, then SCN to paraventricular nucleus, to the intermediolateral cell column of the upper thoracic cord, to the superior cervical ganglion, whose post-ganglionic *sympathetic* noradrenergic fibres finally reach the pineal. Darkness disinhibits this pathway, so melatonin rises at night and is suppressed by light, including phone-screen blue light.

Mechanism. Pinealocytes convert serotonin to melatonin via two enzymes, with *aralkylamine N-acetyltransferase (AANAT)* the rate-limiting, night-active step. Melatonin acts on MT1 (sleep onset, SCN inhibition) and MT2 (circadian phase-shifting) receptors.

Functional and clinical role. Melatonin is the body's chronobiotic, the darkness signal that entrains the sleep-wake rhythm. Exogenous melatonin and the MT1/MT2 agonist *ramelteon* are used for circadian and sleep-onset problems; *agomelatine* (MT1/MT2 agonist plus 5-HT2C antagonist) is an antidepressant that resynchronises disrupted rhythms. Pineal-region tumours (germinoma, pineocytoma, pineoblastoma) present not with melatonin failure but with **Parinaud syndrome** (mass effect on the tectum, link to 9.2) and obstructive hydrocephalus (compression of the aqueduct, link to 9.5). Pineal calcification is a normal age-related midline radiological landmark whose displacement once flagged space-occupying lesions before cross-sectional imaging.

> **PEARL**
> The pineal is sympathetically driven and the signal is paradoxically a darkness signal: the superior cervical ganglion fires more at night. The SCN is the clock; the pineal is the hand that writes the time in hormone.

14.4 The ventricular system

A clean map of the ventricles is the scaffold the CSF and hydrocephalus answers hang on.

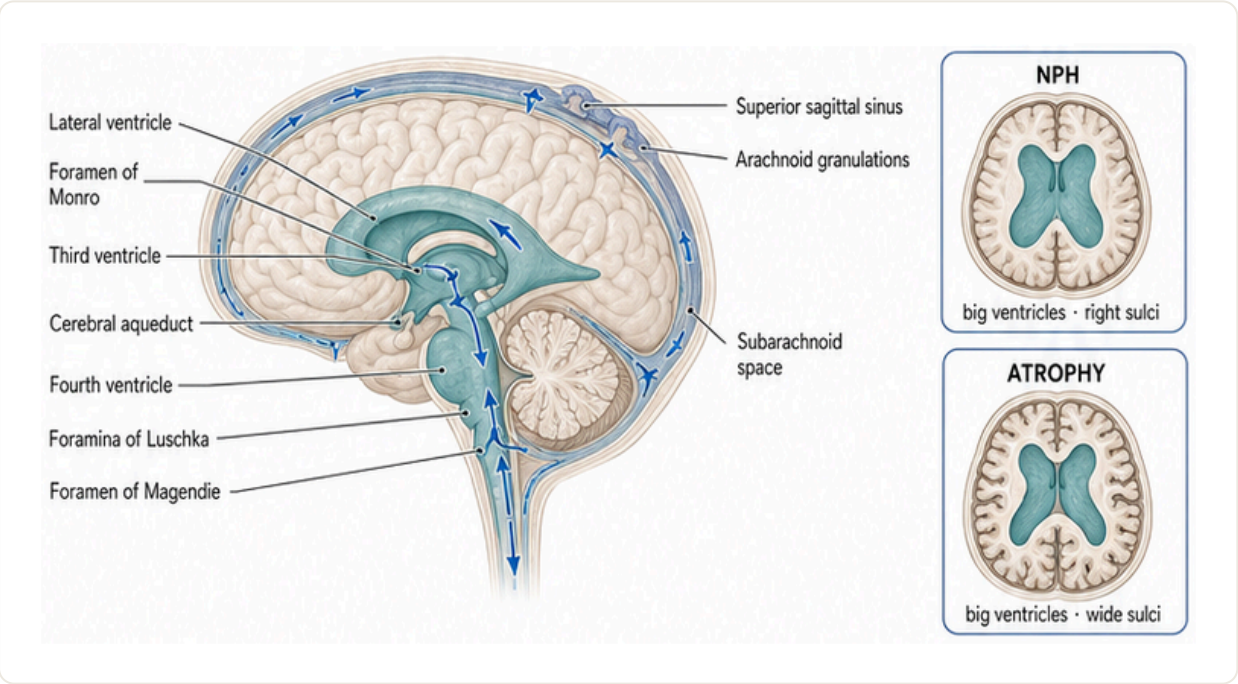


Fig 1.17 Ventricular anatomy and CSF circulation from the lateral ventricles to arachnoid granulations, with the ventricular patterns of normal-pressure hydrocephalus and cerebral atrophy contrasted at right.

- **Two lateral ventricles.** One in each hemisphere, each with a frontal (anterior) horn, body, atrium (trigone), and occipital (posterior) and temporal (inferior) horns. They drain through the paired *foramina of Monro* (interventricular foramina).
- **Third ventricle.** A midline slit between the two thalami, bounded by the hypothalamus below; it connects to the fourth via the *cerebral aqueduct (of Sylvius)* through the midbrain, the narrowest point and the commonest site of obstructive block.

- **Fourth ventricle.** A diamond-shaped space between the pons/medulla in front and the cerebellum behind; CSF exits to the subarachnoid space through the two lateral *foramina of Luschka* and the single midline *foramen of Magendie*.

> **PEARL**
>
> Lateral to Luschka, medial to Magendie: the two lateral foramina of Luschka sit at the sides, the single Magendie sits in the midline. Both are in the fourth ventricle.

14.5 CSF: production, circulation, absorption and hydrocephalus

The existing CSF line gives the route and the NPH triad. The depth a question demands is the volume bookkeeping and the obstructive-versus-communicating logic.

Production

The **choroid plexus** in the lateral, third and fourth ventricles makes most CSF by active secretion (carbonic anhydrase dependent, hence the use of acetazolamide to reduce production). Output is roughly 500 mL/day; the total CSF volume is about 150 mL, so the whole pool is turned over several times a day.

Circulation

Lateral ventricles to third (foramina of Monro), third to fourth (cerebral aqueduct), fourth to subarachnoid space (foramina of Luschka and Magendie), then over the convexities and around the cord. Bulk flow is pulsatile, driven by arterial pulsation.

Absorption

Classically at the *arachnoid granulations (villi)* projecting into the dural venous sinuses, draining into venous blood; recent work adds a meningeal lymphatic (glymphatic) route.

Hydrocephalus by mechanism. Separate the two families cleanly:

- **Non-communicating (obstructive).** A block within the ventricular system, most often at the aqueduct (congenital stenosis, tectal or pineal tumour) or fourth-ventricle outlets. CSF cannot reach the subarachnoid space; ventricles upstream of the block dilate.
- **Communicating.** Flow reaches the subarachnoid space but absorption fails, classically after subarachnoid haemorrhage or meningitis scarring the granulations, or rarely from a CSF-secreting choroid plexus papilloma (overproduction).

Normal-pressure hydrocephalus (NPH). A communicating hydrocephalus with ventricular enlargement but normal opening pressure on lumbar puncture. The triad, the heavily examined one, is **gait apraxia, urinary incontinence and dementia** ("wet, wacky and wobbly", though gait usually comes first and responds best). The gait is magnetic and shuffling; cognition is a subcortical, frontal-executive slowing. It is one of the few *reversible* causes of dementia: a high-volume diagnostic LP (the tap test) that transiently improves gait predicts benefit from ventriculoperitoneal shunting. In a psychiatry exam it appears as the dementia not to miss because it is treatable.

COMMON TRAP

NPH ventriculomegaly is out of proportion to any sulcal atrophy; in Alzheimer atrophy the ventricles enlarge *ex vacuo* with widened sulci. Do not call enlarged ventricles plus widened sulci "hydrocephalus": that is atrophy. NPH is big ventricles with tight sulci and a normal opening pressure.

HOLD THIS

Normal-pressure hydrocephalus is the dementia not to miss because it is treatable: gait apraxia, incontinence, dementia with a normal opening pressure. Gait comes first and responds best to shunting.

MNEMONIC

Wet, Wacky, Wobbly

Wet = urinary incontinence; Wacky = dementia; Wobbly = gait apraxia. The NPH triad. Wobbly tends to appear first and recover best after shunting.

14.6 Corpus callosum and the alien-hand sign

Structure. The corpus callosum is the brain's largest commissure, roughly 200 million axons joining homologous cortical areas across the hemispheres. Front to back: *rostrum, genu, body, splenium*; the genu's fibres (forceps minor) link the frontal poles and the splenium's (forceps major) the occipital poles. It carries the bulk of interhemispheric integration that lets one hemisphere know what the other is doing.

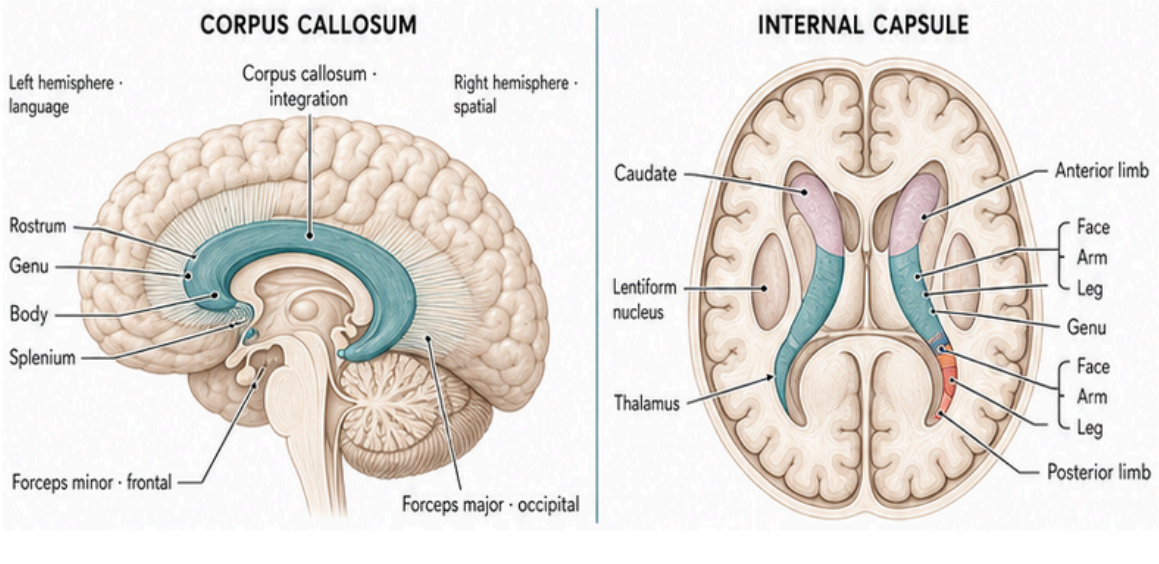


Fig 1.18 The corpus callosum and internal capsule. Callosal sectors connect homologous cortical regions; fibres in the internal capsule are ordered through the anterior limb, genu and posterior limb.

Disconnection phenomena. When the callosum is severed (surgical commissurotomy for intractable epilepsy, or damaged by infarct or a demyelinating or toxic lesion such as *Marchiafava-Bignami disease* in chronic alcohol use), the hemispheres lose their conversation.

Classic split-brain findings include left-hand *agraphia* and *tactile anomia* (the verbal left hemisphere cannot name what the right hemisphere feels in the left hand) and the **alien-hand sign**: a hand, usually the non-dominant left, performs goal-directed acts the patient disowns and may have to restrain with the other hand (it unbuttons a shirt the right hand just buttoned). Anterior callosal and medial frontal (supplementary motor area) lesions are the usual culprits.

CLINICAL ANCHOR

A patient whose left hand acts against their stated intent and who cannot name objects placed in that hand has a callosal disconnection. In a chronic drinker think Marchiafava-Bignami (callosal demyelination and necrosis); in a psychiatry viva, separate this organic alien hand from a conversion or dissociative presentation.

14.7 Internal capsule somatotopy

Structure. The internal capsule is the dense white-matter sheet funnelling almost all fibres between cortex and brainstem/cord. On an axial slice it is a boomerang pointing medially, with an *anterior limb* (between caudate and lentiform nucleus), a *genu*, and a larger *posterior limb* (between thalamus and lentiform nucleus), then retrolentiform and sublentiform parts.

PART	MAJOR FIBRES	CLINICAL NOTE
Anterior limb	Frontopontine; anterior thalamic radiation (to prefrontal cortex)	Target of capsulotomy for refractory OCD
Genu	**Corticobulbar fibres (face, head)**	Genu lesion = contralateral lower facial weakness
Posterior limb	**Corticospinal (arm then leg, front to back); sensory radiation; optic and auditory radiations posteriorly**	Lacune here = dense contralateral hemiplegia

Somatotopy of the internal capsule: corticobulbar at the genu, then arm-to-leg laid out anteroposteriorly through the posterior limb, with sensory and special-sense radiations behind.

Clinical correlation. The posterior limb is supplied largely by the lenticulostriate branches, so a small-vessel lacune here produces a *pure motor stroke*: a dense contralateral face-arm-leg hemiplegia with no cortical signs (no aphasia, no neglect), a high-yield localising pattern. The psychiatric relevance is twofold: the anterior limb is the lesion target of *anterior capsulotomy* and the path of deep-brain stimulation for treatment-refractory OCD and depression, and capsular lacunes contribute to vascular cognitive impairment and post-stroke depression.

MNEMONIC

Face at the Genu, then Arm before Leg

Corticobulbar (face) sits at the genu; corticospinal fibres run through the posterior limb arm-first, leg-last (anterior to posterior). Sensory and the optic-auditory radiations trail behind.

14.8 Blood supply of key structures

A handful of named arteries account for the strokes that produce the syndromes above.

- **Lenticulostriate arteries.** Small perforators from the proximal middle cerebral artery supplying the basal ganglia, internal capsule and corona radiata. They are the classic site of hypertensive lacunar infarcts (pure motor stroke from a posterior-limb lacune) and of hypertensive intracerebral haemorrhage; the largest is sometimes called Charcot's artery of cerebral haemorrhage.
- **Recurrent artery of Heubner.** A perforator from the anterior cerebral artery supplying the anterior limb of the internal capsule and head of the caudate.
- **Anterior choroidal artery.** From the internal carotid; supplies the posterior limb of the internal capsule, optic tract and parts of the thalamus and hippocampus, hence its strokes can give a triad of contralateral hemiplegia, hemianaesthesia and homonymous hemianopia.
- **Artery of Percheron.** An anatomical variant in which a single dominant perforator off one posterior cerebral artery (P1) feeds **both** paramedian thalami (and often the rostral midbrain). Its occlusion infarcts both medial thalami at once, producing the striking picture of acute amnesia, vertical-gaze palsy and fluctuating consciousness or hypersomnolence, an easily missed "thalamic" stroke that mimics a metabolic or psychiatric encephalopathy.

> **CLINICAL ANCHOR**
> Sudden bilateral medial-thalamic infarction from an artery of Percheron occlusion presents as abrupt amnesia, drowsiness and up-gaze trouble, and is repeatedly mistaken for delirium, Wernicke encephalopathy or a primary psychiatric stupor. The symmetry on imaging is the giveaway.

> **PEARL**
> Match the artery to the structure: lenticulostriate to the posterior limb (pure motor stroke), Heubner to the anterior limb and caudate, anterior choroidal to the posterior limb and optic tract, and Percheron to both paramedian thalami. Each pairing is a ready-made one-mark spotter.

15 · Localizing lesions by sign

Everything earlier in these notes zoomed *into* structures. This topic runs the ladder the other way: it starts from a bedside sign and asks the one question every localisation stem is really testing, which is *at what level of the neuraxis does this sit?* The skill examined is discrimination, not recall. A candidate who has memorised twenty syndromes still fails if a weak, wasted, fasciculating hand does not immediately read as "anterior horn or below" while a weak, spastic, hyperreflexic hand reads as "corticospinal, above." Build the ladder once and the syndrome lists collapse into a single decision tree.

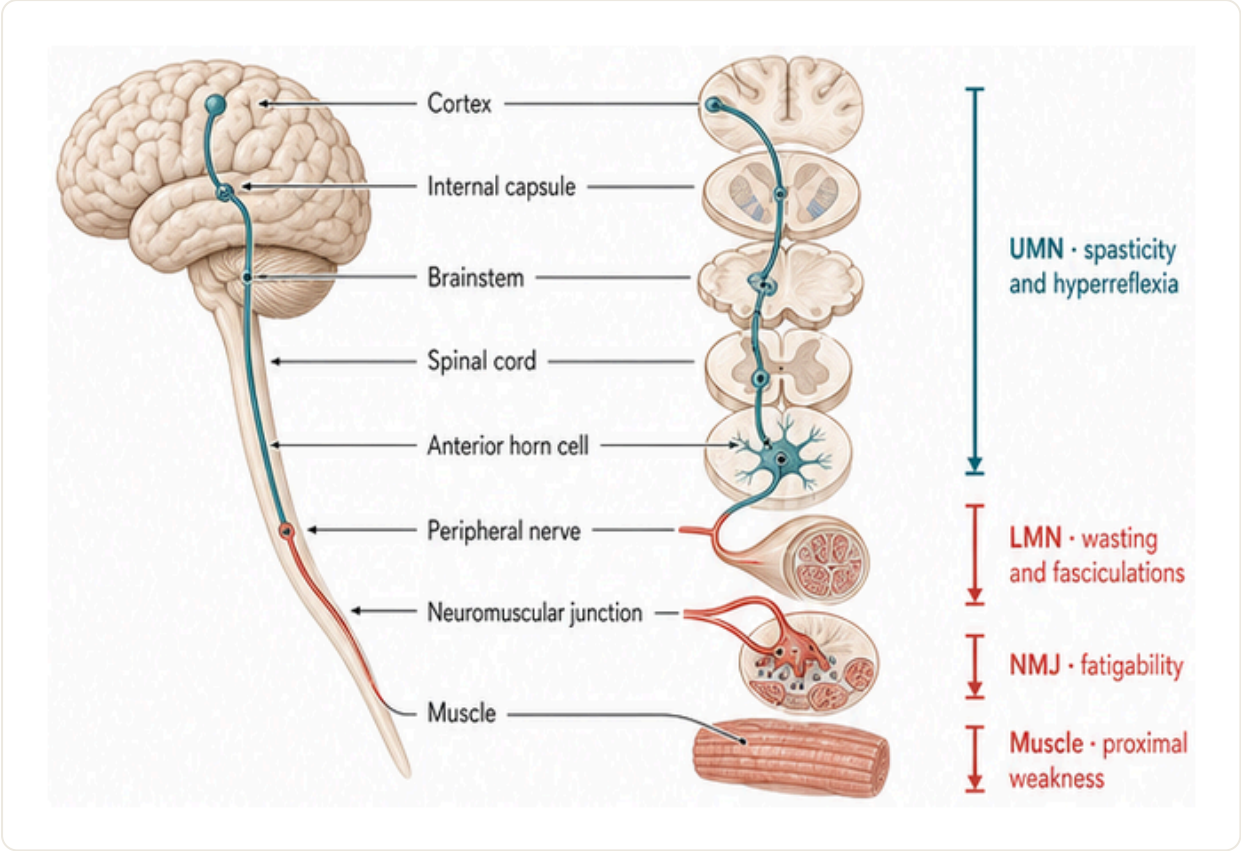


Fig 1.19 Localising a motor lesion along the neuraxis: upper-motor-neuron signs arise above the anterior horn cell, lower-motor-neuron signs below it, with neuromuscular-junction and muscle patterns completing the sequence.

The exam frame. Localisation questions are answered in the order set out by the standard clinical scheme (StatPearls, NBK493159): first *what* is the lesion (pattern of weakness, upper versus lower motor neuron, sensory involvement), then *where* it sits, then *why*. This block trains the middle question. Read every rung as a level; read every sign as evidence for one rung over its neighbours.

15.1 The principle: a sign localises to a level of the neuraxis

A single motor pathway runs from cortex to muscle, and a fault at each successive station produces a distinguishable picture. The corticospinal (upper motor neuron) fibres descend through corona radiata, posterior limb of the internal capsule, cerebral peduncle, pons and medulla, decussate at the pyramids, then synapse on the anterior horn (lower motor neuron), whose axon runs through root, plexus and peripheral nerve, crosses the neuromuscular junction and drives the muscle (NBK493159). Reading the ladder from the muscle upward gives a fixed sequence of levels, and the discriminating feature at each rung is what you interrogate on examination.

Muscle (myopathy)

Symmetrical, proximal, wasted weakness. Tone and reflexes preserved until late; no fasciculation, no sensory loss. Preserved deep tendon reflexes are what separate a myopathy from a neuropathy of similar weakness (NBK493159).

Neuromuscular junction

Fatiguable weakness that worsens with use (myasthenia gravis, point 3 of the scheme). Bulk, tone and reflexes normal; no sensory loss. Fatiguability is the discriminator.

Peripheral nerve

Lower motor neuron weakness plus sensory loss in the nerve's territory. A length-dependent polyneuropathy gives the glove-and-stocking pattern; a mononeuropathy respects one nerve's distribution.

Root / plexus

Lower motor neuron weakness confined to one myotome (radiculopathy) or to the muscles of a plexus trunk/cord, with matching dermatomal or multi-root sensory loss and a lost reflex arc.

Anterior horn

Pure lower motor neuron signs (wasting, fasciculation, hyporeflexia) with *no* sensory loss. Anterior-horn disease with coexisting upper motor neuron signs and no sensory level is the motor-neuron-disease signature (ALS: absent reflexes, extensor plantars, wasting and fasciculation together, NBK493159).

Spinal cord

Upper motor neuron signs below the lesion, often a segmental lower motor neuron level at the lesion, and, decisively, a **sensory level**: a horizontal cut-off on the trunk below which sensation is impaired. Thoracic myelopathy gives paraplegia, cervical myelopathy quadriplegia.

Brainstem

The hallmark is **crossed signs**: an ipsilateral cranial-nerve deficit with contralateral long-tract (motor or sensory) signs. A cranial nerve plus a long tract equals brainstem, and the cranial nerve names the level.

Subcortical (internal capsule, corona radiata)

Pure contralateral upper motor neuron hemiplegia, face-arm-leg together (dense lacunar picture), *without* cortical signs and without crossed cranial-nerve loss.

Cortical

Contralateral upper motor neuron signs *plus* a cortical sign that betrays the lobe: aphasia, neglect, a Gerstmann element, or a homonymous field defect. The added cortical deficit is what raises the lesion above the capsule.

Three sidedness rules ride on top of the ladder and settle most ambiguous stems. Cerebral upper motor neuron signs are **contralateral**; cerebellar signs are **ipsilateral** (the fault sits on the same side as the ataxic limb, NBK493159); and the brainstem is the only place where motor and cranial deficits split to opposite sides in the same patient.

15.2 Upper versus lower motor neuron: the five-row discriminator

Every rung of the ladder resolves first into one prior question, whether the lesion is above or below the anterior horn. Five signs settle it, and only two of them are truly decisive under pressure.

SIGN	UPPER MOTOR NEURON	LOWER MOTOR NEURON
Tone	Increased (spasticity, clasp-knife)	Decreased (flaccid)
Deep tendon reflexes	Brisk, exaggerated; clonus	Reduced or absent
Plantar response	**Extensor (Babinski positive)**	**Flexor (normal)**
Muscle bulk	Preserved (disuse atrophy only, late)	Early, marked wasting
Fasciculation	Absent	Present (anterior horn / root / nerve)

The upper-versus-lower motor neuron split; the plantar response is the single most reliable bedside discriminator and is shaded across both columns.

HOLD THIS

An extensor (upgoing) plantar is corticospinal until proven otherwise; fasciculation localises downward to anterior horn, root or nerve. The plantar rarely lies, so it settles the upper-versus-lower question first.

The plantar response is marked because it flips sign cleanly and rarely lies: an extensor (upgoing) plantar is corticospinal until proven otherwise, a flexor plantar is compatible with any level at or below the anterior horn. Fasciculation, by contrast, is a positive localiser downward: visible twitching of single motor units points to the anterior horn, root or nerve, never to a pure cortical lesion. Note the tongue, where lower motor neuron denervation produces true fibrillation visible to the naked eye, distinct from the fasciculation of limb muscles (NBK493159). One trap sits inside this table: in acute upper motor neuron injury (spinal shock, hyperacute stroke) tone and reflexes are transiently *reduced*, so a flaccid, areflexic limb in the first hours does not exclude a corticospinal lesion.

15.3 Brainstem and eye-movement localisers

The eyes are the most exact localising instrument in the head because horizontal and vertical gaze are wired through named, adjacent brainstem stations, so a specific gaze failure drops a pin at a specific level. Work outward from the fine-grain neuroanatomy topic (see the fine-grain topic for the MLF's course): here the point is the sign-to-locus mapping.

Internuclear ophthalmoplegia (INO) to the medial longitudinal fasciculus

The MLF is the heavily myelinated tract that yokes the sixth-nerve nucleus in the pons to the contralateral third-nerve nucleus for conjugate horizontal gaze. A lesion gives failure of *adduction* of the ipsilateral eye with abducting nystagmus of the other eye, convergence often spared. Bilateral INO in a young adult means demyelination (multiple sclerosis) until proven otherwise; unilateral INO in an older patient suggests a brainstem lacunar infarct (Virgo and Plant 2017).

Horizontal gaze centre (PPRF and abducens nucleus, pons)

The paramedian pontine reticular formation, working through the ipsilateral abducens nucleus, drives conjugate horizontal gaze *toward* its own side. A destructive pontine lesion therefore causes gaze deviation *away* from the lesion (the eyes look away from a pontine lesion, toward a hemispheric one). One-and-a-half syndrome combines a PPRF/abducens-nucleus lesion with the adjacent MLF.

Vertical gaze (riMLF and dorsal midbrain)

Upward and vertical gaze is organised in the rostral interstitial nucleus of the MLF and the dorsal midbrain tectum. A dorsal midbrain (pretectal) lesion gives **Parinaud syndrome**: upgaze palsy, light-near dissociation of the pupils, convergence-retraction nystagmus and lid retraction, classically from a pineal-region mass or hydrocephalus. Isolated vertical-gaze palsy also flags progressive supranuclear palsy.

Pupillary and pontine signs

A fixed dilated pupil with ptosis and a down-and-out eye is a compressive third-nerve palsy (posterior communicating aneurysm or uncal herniation, pupil-involving because parasympathetic fibres run superficially). Bilateral pinpoint but reactive pupils localise to the pons (haemorrhage disrupting descending sympathetic fibres). Horner syndrome (partial ptosis, miosis, anhidrosis) localises anywhere along a long sympathetic chain, brainstem to lung apex to carotid.

> **CLINICAL ANCHOR**
>
> Crossed signs are the brainstem's signature. A left pontine lesion gives left lower-motor-neuron facial weakness with right hemiplegia; a left midbrain lesion gives a left third-nerve palsy with right hemiparesis and an upper-motor-neuron right facial weakness, the constellation named **Weber syndrome** (NBK493159). Whenever a stem pairs an ipsilateral cranial-nerve palsy with contralateral limb signs, stop looking above the tentorium: the lesion is in the brainstem, and the palsied cranial nerve tells you which segment (III midbrain, VI and VII pons, IX to XII medulla).

15.3b Cortical localisers, recap

Once a cortical sign appears alongside contralateral weakness, the lesion is cortical and the sign names the lobe. These are treated fully in the lobes topic; the pointers below are the discriminators most likely to decide a single-best-answer stem.

Aphasia to the dominant perisylvian lobes

Non-fluent, effortful, agrammatic speech with preserved comprehension points to *Broca area* (dominant posteroinferior frontal, BA 44/45). Fluent, empty speech with impaired comprehension points to *Wernicke area* (dominant posterior superior temporal / temporoparietal). Fluent speech with intact comprehension but disproportionate repetition failure is conduction aphasia (arcuate fasciculus / supramarginal region).

Hemispatial neglect to the non-dominant parietal lobe

Inattention to the contralateral (usually left) half of space, with anosognosia, localises to the *right (non-dominant) inferior parietal* cortex.

Gerstmann syndrome to the dominant parietal lobe

The tetrad of agraphia, acalculia, finger agnosia and left-right disorientation localises to the *dominant angular gyrus* (Cleveland Clinic parietal syndromes).

Cortical blindness to the occipital lobes

Bilateral occipital damage causes cortical blindness with preserved pupillary reflexes; denial of the deficit is Anton syndrome. A unilateral occipital lesion gives a contralateral homonymous hemianopia, characteristically with macular sparing.

15.4 The master localisation table

This is the discrimination drill in one grid. The signs are deliberately interleaved across levels so that no two adjacent rows share a locus; read the middle column only after you have committed to an answer from the discriminating logic on the right.

SIGN	LOCALISES TO	DISCRIMINATING LOGIC
Fatiguable weakness, reflexes normal, no sensory loss	Neuromuscular junction	**Fatiguability with intact reflexes and bulk; nothing else on the ladder fatigues**
Glove-and-stocking sensory loss with distal LMN weakness	Peripheral nerve (polyneuropathy)	Length-dependent, symmetrical, crosses no single dermatome or myotome
Wasting + fasciculation, no sensory loss, upgoing plantars	Anterior horn (with corticospinal, i.e. MND)	**Mixed UMN and LMN with a clean sensory examination: only MND does this**
Sensory level on the trunk, spastic paraparesis below	Spinal cord (myelopathy)	A horizontal sensory cut-off exists nowhere but the cord
Ipsilateral loss of vibration/proprioception, contralateral loss of pain/temperature	Hemicord (Brown-Sequard)	**Dissociated, side-split sensory loss: dorsal columns uncrossed, spinothalamic crossed**
Ipsilateral cranial-nerve palsy + contralateral hemiparesis	Brainstem	Crossed signs occur only where cranial nuclei and long tracts are adjacent
Failure of adduction with abducting nystagmus of the other eye	MLF (INO)	Dissociated horizontal gaze, one eye only; convergence spared
Upgaze palsy + light-near dissociation + convergence-retraction nystagmus	Dorsal midbrain (Parinaud)	Vertical, not horizontal, gaze fails; pupils spare light-near
Dense face-arm-leg hemiplegia, no cortical sign, no crossed CN	Internal capsule (subcortical)	Everything weak equally, cortex silent: a small deep lesion hits packed fibres
Contralateral hemiparesis + aphasia or neglect	Cortex (dominant vs non-dominant)	**A cortical sign lifts the lesion above the capsule; language = dominant, neglect = non-dominant**

The master drill; the shaded cell in each interleaved row is the feature that forces the choice of that level over its neighbours on the ladder.

RULE **A cranial-nerve palsy plus a contralateral long-tract sign equals brainstem, and the cranial nerve names the level.** A sensory level means cord; a cortical sign lifts the lesion above the capsule.

MNEMONIC

"MoJo Never Really Anchors Cord, Brainstem, Subcortex, Cortex"

The rungs from muscle up: **Mo**tor unit (muscle), **Jo**int of nerve and muscle (neuromuscular junction), **N**erve (peripheral), **R**oot/plexus, **A**nterior horn, then **C**ord, **B**rainstem, **S**ubcortex, **C**ortex. Eight rungs, one order, run it every time from the sign upward.

15.5 False localisers: why one sign can mislead

The whole method assumes a sign points to its own generator. False localisers break that assumption: they are produced at a distance, usually by raised intracranial pressure or by mechanical distortion of the brainstem, and they are the classic way an examiner sets a trap. Treat any of the following as suspect and re-anchor to the rest of the picture before committing.

COMMON TRAP

Sixth-nerve palsy in raised intracranial pressure. The abducens has the longest intracranial course of any cranial nerve, so it is stretched by generalised pressure and may fail unilaterally or bilaterally without any pontine lesion. A lateral-rectus palsy with headache and papilloedema is a pressure sign, not a localising one (NBK493159).

Kernohan notch phenomenon. An expanding supratentorial mass can shove the midbrain against the opposite tentorial edge, crushing the contralateral cerebral peduncle. The result is hemiparesis *ipsilateral* to the mass, the wrong side, a false localiser that can point surgery at the wrong hemisphere if trusted.

Papilloedema. Bilateral disc swelling signals raised pressure but not *where*; it localises to "somewhere raising ICP," nothing finer. Unilateral disc swelling is not truly papilloedema and demands the Foster Kennedy pairing (ipsilateral optic atrophy from a frontal mass with contralateral papilloedema) or optic neuritis to be considered (Foster Kennedy described in NBK493159 and Pastora-Salvador 2011).

The general principle. A single sign is a hypothesis, not a diagnosis. Localise on the convergence of signs; when one sign refuses to fit the level the others point to, suspect a false localiser before you rebuild the whole map around it.

Neurophysiology

16 · Sleep physiology: stages and regulation

Sleep is an active, organised process, not the brain switching off. It alternates **non-REM** (four-fifths of the night, N1 to N3) with **REM** in roughly 90-minute cycles, four to six per night. Slow-wave sleep dominates the first third; REM lengthens toward morning.

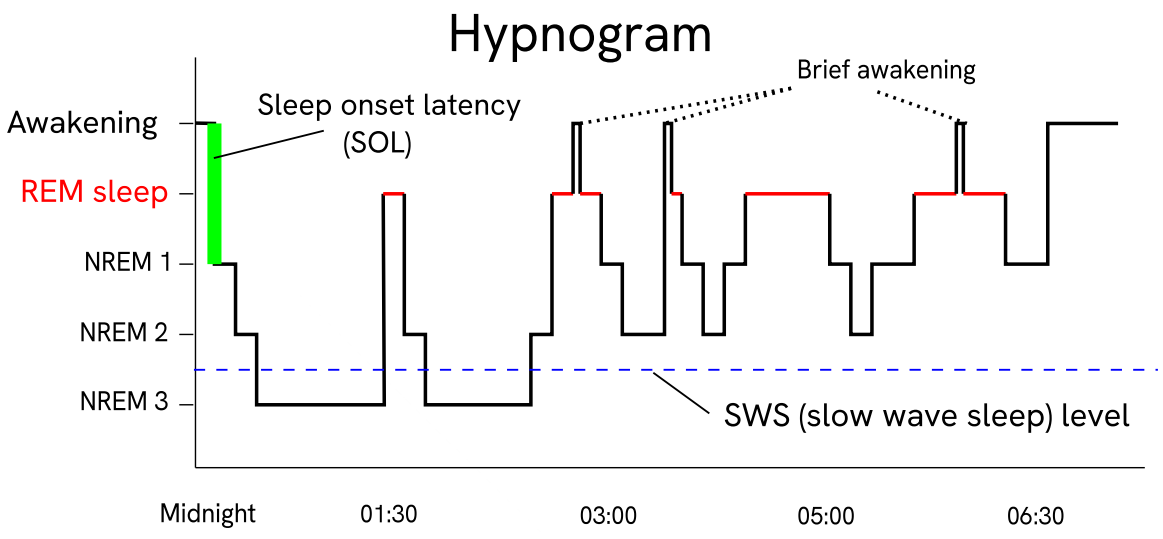


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Fig 1.20 A normal hypnogram. Slow-wave sleep (deep NREM) dominates the first cycles; REM periods lengthen toward morning. The older Rechtschaffen-Kales staging shown (1 to 4) maps to current AASM staging as N1, N2 and N3 (stages 3 and 4 combined). Borbely's two-process model frames it: a homeostatic sleep-pressure process (S) falls across the night while the circadian process (C) times its onset.

STAGE	EEG	SHARE OF NIGHT	FEATURES
N1	Low-voltage, theta; vertex sharp waves	~5%	Drowsy transition, hypnic jerks, easily woken
N2	**Sleep spindles + K-complexes**	~45 to 55%	True sleep onset; the bulk of the night
N3 (SWS)	Delta (high-amplitude, <4 Hz)	~15 to 20%	Deepest; growth hormone; sleepwalking, night terrors, enuresis (parasomnias)
REM	**Low-voltage, mixed; sawtooth waves; EEG resembles wake**	~20 to 25%	Dreaming, atonia, rapid eye movements; "paradoxical sleep"

Tab 1.3 · Sleep stages. Spindles/K-complexes (N2) and the wake-like EEG with atonia (REM) are the shaded discriminators.

~90 min	4-6	20-25%
NREM-REM CYCLE LENGTH	CYCLES PER NIGHT	OF ADULT NIGHT IS REM

TRAP A sleep-onset REM period is **normal in the neonate** but in an adult points to narcolepsy. Do not call neonatal sleep-onset REM pathological, or adult sleep-onset REM benign.

CLINICAL ANCHOR

Sleep architecture is a psychiatric biomarker. In **major depression**: reduced REM latency (REM appears too early after sleep onset), increased REM density, and reduced slow-wave sleep, though these REM changes are a state marker, not specific to depression. In **mania**: a markedly reduced need for sleep is a core diagnostic symptom and often the earliest relapse signal. The flip-flop switch[11] (sleep-promoting VLPO versus the ascending arousal system, stabilised by orexin) explains both the abruptness of state transitions and how DORAs and sedatives act.

Managing chronic insomnia the Weave way. Where a physiology topic carries a treatable disorder, we structure it as Locus, Focus, Modus, guidelines first.

Chronic insomnia	Guidelines: BAP 2019 · NICE · AASM 2021
LOCUS where	Outpatient in almost all cases. Inpatient only where insomnia is secondary to a disorder needing admission (acute mania, severe depression with risk).
FOCUS what · when	SHORT TERM Treat any driver (mood, anxiety, substances, pain, sleep apnoea); sleep hygiene and stimulus control; a short, time-limited hypnotic only if needed. MID TERM Cognitive behavioural therapy for insomnia (CBT-I) as the definitive first-line treatment; taper hypnotics. LONG TERM Maintain CBT-I gains; relapse prevention; review comorbidity; avoid chronic hypnotic dependence.
MODUS how	Psychological (CBT-I, first-line per BAP and AASM) · pharmacological (short-term Z-drugs or short-acting benzodiazepines; sedating antidepressants where comorbid depression; melatonin or melatonin agonists, especially in older adults; DORAs as a newer option) · treat the primary disorder.

INDIA CONTEXT

CBT-I, although first-line, is poorly available across much of India, so benzodiazepine and Z-drug prescribing is high and often unsupervised. Tele-MANAS (14416) and structured brief behavioural sleep interventions are practical ways to widen access; reserve hypnotics for short, defined courses. The clinical sleep-wake disorders (insomnia, narcolepsy, parasomnias, restless legs, circadian rhythm disorders) are worked in full on the Eating & sleep-wake disorders notes, and the neurology of sleep and sleep-disordered breathing on the Neurology foundations for psychiatrists notes; this topic keeps the underlying physiology.

16.1 Architecture in depth: stage proportions, the cycle, and ontogeny

Sleep is scored on polysomnography (the gold standard: EEG, electro-oculogram and submental electromyogram together) into the stages summarised in Tab 1.3, but the exam reward is in the numbers behind that table and how they move across a life. A young adult enters through N1 (1 to 5 min, roughly 5 percent of the night, the lightest stage with the lowest arousal threshold), settles into N2 (the workhorse stage, close to 45 to 55 percent), descends into N3 slow-wave sleep

(deepest, roughly 15 to 20 percent, highest arousal threshold), then ascends to the first REM period about 90 minutes after sleep onset. That first REM episode is brief (often around 10 min); successive NREM-REM cycles recur every 90 to 120 minutes, four to six times a night.

The intra-night gradient. Architecture is not uniform across the night, and the gradient itself is examinable. **Slow-wave sleep is front-loaded** into the first third (when homeostatic sleep pressure is highest), while **REM is back-loaded**, with episodes lengthening toward morning so that most REM falls in the second half of the night (driven by the circadian REM propensity peak near the core body-temperature nadir). This is exactly the hypnogram shape in Fig 1.20, and it explains two clinical facts: early-night awakenings interrupt deep sleep (hence confusional arousals and parasomnias of NREM), and late-morning lie-ins are REM-rich (hence vivid dreaming on waking).

Ontogeny. The lifespan trajectory is a perennial question. The neonate sleeps 16 to 18 hours and spends roughly half of it in REM (then termed *active sleep*; NREM is *quiet sleep*, with an *indeterminate* third category), and crucially enters sleep directly through REM (a sleep-onset REM pattern that would be pathological in an adult). REM proportion falls steeply through infancy toward the adult 20 to 25 percent by about age 3 to 5, as the wake-sleep cycle consolidates over the first six months of life. Slow-wave sleep peaks in childhood and then declines progressively: the **elderly show markedly reduced N3, reduced total sleep time, reduced sleep efficiency, more fragmentation and earlier circadian phase (phase advance)**, with relatively preserved REM percentage. A useful single sentence: REM percentage falls fastest in infancy, slow-wave sleep falls steadily across adulthood and old age.

AGE BAND	TOTAL SLEEP	REM SHARE	SLOW-WAVE SLEEP	CARDINAL FEATURE
Neonate	16 to 18 h	**~50% (active sleep)**	Not yet differentiated	Sleep-onset REM is normal
Child	10 to 12 h	~20 to 25%	**Maximal**	Deepest, most restorative N3
Young adult	7 to 9 h	~20 to 25%	~15 to 20%	Stable reference architecture
Elderly	Reduced, fragmented	Relatively preserved	**Markedly reduced**	Phase advance, low efficiency

Lifespan change in sleep architecture. The shaded cells are the discriminators examiners test: half the neonatal night is REM, N3 peaks in childhood and collapses in old age.

⚠ COMMON TRAP

A sleep-onset REM period (REM within 15 min of falling asleep) is **normal in the neonate** but in an adult points to **narcolepsy** (or to REM rebound after deprivation, or to severe depression). Do not call neonatal sleep-onset REM pathological, and do not call adult sleep-onset REM benign.

16.2 EEG signatures: spindles, K-complexes, sawtooth and PGO waves

Stage scoring rests on a handful of graphoelements, and the generator of each is a favourite viva probe. Build the picture by frequency band first: wake gives *alpha* (about 8 to 12 Hz, posterior, eyes closed) with *beta* (above about 12 Hz) on attention; N1 is the loss of alpha and the appearance of *theta* (4 to 7 Hz) low-voltage mixed-frequency activity with vertex sharp waves; N3 is high-amplitude *delta* (under about 4 Hz, conventionally scored when slow waves occupy at least 20 percent of the epoch).

Sleep spindles (the N2 marker)

Waxing-and-waning 11 to 16 Hz (typically 12 to 14 Hz) bursts lasting 0.5 to 3 s, recurring every 3 to 6 s. **Thalamocortical in origin**: generated by the GABAergic thalamic reticular nucleus pacing thalamocortical relay neurons. They gate sensory throughput (raising arousal threshold) and are implicated in memory consolidation; spindle density rises after new learning.

K-complexes (the other N2 marker)

A large biphasic transient, sharp negative deflection then a slower positive component, arising in the cortex. Can occur spontaneously or be evoked by a stimulus; thought to both protect sleep continuity and contribute to consolidation. Spindles and K-complexes together define true sleep onset.

Sawtooth waves (the REM marker)

Trains of sharply contoured, often serrated 2 to 6 Hz waves seen frontocentrally during REM, frequently heralding bursts of rapid eye movements. The surrounding EEG is low-voltage mixed-frequency and paradoxically wake-like.

PGO waves (the REM mechanism marker)

Ponto-geniculo-occipital waves: phasic field potentials that propagate from the pons (pedunculopontine and laterodorsal tegmentum) to the lateral geniculate nucleus and on to the occipital cortex. They are the cellular substrate of the phasic REM events (eye movements, twitches) and, in classic theory, the brainstem trigger underlying dream imagery. PGO waves are a textbook REM feature recorded directly in animals and inferred in humans.

MNEMONIC

Spindles SPIN in the Thalamus

SPIN ties the N2 sleep **spin**dle to its **thalamic** reticular-nucleus pacemaker; K-complex is **K**ortical (cortex). If you can place each graphoelement at its generator (spindle to thalamus, K-complex to cortex, sawtooth and PGO to pons), you have answered the commonest one-line question on this topic.

16.3 The two-process model in detail: Process S and Process C

Borbely's 1982 two-process model (reappraised by Borbely and colleagues in 2016) remains the framework that organises everything else here, and it is the model Fig 1.20 invokes. Two independent oscillators interact to time sleep.

- **Process S, homeostatic sleep pressure.** A debt that rises monotonically across waking and dissipates during sleep, indexed physiologically by EEG slow-wave activity (delta power), which is highest at sleep onset after a long day and decays exponentially across the night. The

leading molecular correlate is **adenosine**: as the brain metabolises ATP during waking, adenosine accumulates in the basal forebrain, inhibiting wake-promoting neurons and exciting sleep-promoting groups. Caffeine antagonises adenosine A1 and A2A receptors, which is precisely why it postpones sleep, and why a post-caffeine crash follows once accumulated adenosine is unmasked.

- **Process C, the circadian drive.** An roughly 24-hour wake-promoting (alerting) signal generated by the suprachiasmatic nucleus, independent of prior sleep. It rises through the day to oppose mounting Process S (keeping us alert despite a growing debt) and falls at night, opening the gate for sleep. Its evening dip and the secondary post-lunch trough are the two windows of greatest sleepiness.

Sleep occurs when the falling alerting drive of Process C no longer offsets the high sleep pressure of Process S; the timing, depth and structure of a night fall out of their interaction. The model elegantly predicts recovery sleep (after deprivation, S is elevated, so slow-wave activity rebounds) and explains why sleeping at the wrong circadian phase, as in jet lag or shift work, is short and unrefreshing even when the debt is large.

RULE **Process S is homeostatic sleep pressure (adenosine); Process C is the circadian alerting drive from the SCN.** Caffeine works by antagonising adenosine, postponing sleep.

16.4 The flip-flop switch: VLPO, orexin, adenosine and galanin

The two-process model says *when* we sleep; the flip-flop switch (Saper and colleagues) says *how* the brain commits cleanly to one state and avoids the dangerous middle ground. The switch is a pair of mutually inhibitory populations.

The sleep side

The **ventrolateral preoptic nucleus (VLPO)** of the anterior hypothalamus, whose neurons co-express the inhibitory transmitter *GABA* and the inhibitory neuropeptide *galanin*. The neighbouring median preoptic nucleus (MnPO) is GABAergic. VLPO neurons fire in sleep and project inhibition onto every major arousal nucleus.

The wake side

The ascending arousal system: noradrenergic locus coeruleus, serotonergic raphe, histaminergic tuberomammillary nucleus, cholinergic pedunculopontine and laterodorsal tegmentum, plus dopaminergic input. These nuclei in turn inhibit the VLPO.

Why it flips, not fades. Because each side inhibits the other, the circuit is a **self-reinforcing bistable switch**: when one side gains the slightest edge it suppresses the other and is itself disinhibited, so the system snaps fully into wake or sleep and resists intermediate, half-awake states (the property engineers call hysteresis). Process S and Process C bias the switch (rising adenosine and the circadian dip both tip it toward sleep), but the switch itself produces the sharpness of the transition.

Orexin as the stabiliser. **Orexin (hypocretin)** neurons, found exclusively in the posterior and lateral hypothalamus, do not sit on either side of the switch; they reinforce the wake side and

hold the switch stable, preventing inappropriate transitions into sleep or REM. This is the unifying lesion in **narcolepsy type 1**: selective loss of orexin neurons weakens the switch, which then drifts toward its boundary zone and produces the tetrad of excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations, with sleep-onset REM periods. The same boundary-zone instability, from VLPO cell loss this time, is thought to underlie the sleep fragmentation and daytime napping of **old age** and Alzheimer disease.

> **PEARL**
>
> Read the modern hypnotics straight off the switch. **Z-drugs and benzodiazepines** act on the sleep side (positive allosteric modulation of GABA-A, mimicking VLPO output). **Dual orexin receptor antagonists (DORAs)**, suvorexant, lemborexant and daridorexant, act on the wake side by blocking the orexin stabiliser, removing the brake on sleep rather than sedating the cortex. **Low-dose doxepin** targets the histaminergic tuberomammillary arm. Each drug class maps to one node of the flip-flop circuit.

16.5 Neurochemistry of sleep and wake, state by state

The cleanest way to hold the neurochemistry is by what each state turns on and off. **Wake** is driven by the full ascending arousal system firing together: noradrenaline (locus coeruleus), serotonin (raphe), histamine (tuberomammillary nucleus), acetylcholine (brainstem and basal forebrain), dopamine (ventral tegmental area) and orexin holding them stable. **NREM** is the arousal system stood down by GABAergic and galaninergic VLPO and MnPO output, with adenosine accumulating as the homeostatic signal. **REM** has a signature dissociation that examiners love.

SYSTEM	WAKE	NREM	REM
Acetylcholine	High	Low	**High (REM-on, drives the cortical activation and PGO waves)**
Noradrenaline / serotonin / histamine	High	Low	**Silent (these aminergic REM-off cells fall quiet)**
Dopamine	High	Tonic firing low	Phasic firing can rise (dreaming, salience)
GABA / galanin (VLPO)	Low	High	High

State-dependent neurochemistry. The shaded REM column is the discriminator: cholinergic cells fire while aminergic cells go silent, the reciprocal-interaction pattern that makes REM the cholinergically dominant, aminergically demuted state.

This *reciprocal-interaction* arrangement (cholinergic REM-on cells in the pons versus aminergic REM-off cells in locus coeruleus and raphe) explains several drug effects: antidepressants that boost serotonin and noradrenaline suppress REM and prolong REM latency, while cholinergic agonists shorten it; and abrupt withdrawal of REM-suppressing agents (alcohol, many antidepressants) causes REM rebound with vivid dreaming and nightmares.

16.6 Circadian control: the SCN, light entrainment and melatonin

Process C is anatomically the **suprachiasmatic nucleus (SCN)**, a paired nucleus in the anterior hypothalamus sitting above the optic chiasm at the base of the third ventricle, and it is the master clock. Its intrinsic period runs slightly longer than 24 hours and must be reset (entrained) daily, principally by light.

- **Entrainment pathway.** Light is detected not only by rods and cones but by intrinsically photosensitive retinal ganglion cells containing the photopigment *melanopsin*, which signal via the retinohypothalamic tract to the SCN. The SCN then relays through the subparaventricular zone and dorsomedial hypothalamus to wake- and sleep-promoting centres.
- **Melatonin output.** At night the SCN drives the pineal gland (via a multisynaptic sympathetic pathway) to secrete *melatonin*, the internal "darkness signal" that feeds back on SCN MT1 and MT2 receptors to consolidate sleep timing. Exogenous melatonin and the agonist ramelteon exploit this, and are especially useful in older adults and in circadian-rhythm disorders.
- **Molecular clock.** At the cellular level the rhythm is a transcription-translation feedback loop of clock genes (CLOCK and BMAL1 activating Period and Cryptochrome, whose products feed back to inhibit them), the discovery that earned the 2017 Nobel Prize. Polymorphisms here underlie familial advanced and delayed sleep-phase syndromes and are an active seam in mood-disorder chronobiology.

> ♡ CLINICAL ANCHOR
>
> Circadian-rhythm sleep-wake disorders are coded in ICD-11 (block 7A60 to 7A6Z) and DSM-5-TR, and the common types map onto everyday psychiatry: **delayed sleep-phase** (the classic adolescent and young-adult "night owl", easily mistaken for primary insomnia or amotivation), **advanced sleep-phase** (early-evening sleepiness and pre-dawn waking in older adults, mimicking depression), and **shift-work** and **jet-lag** types. Timed bright light and timed low-dose melatonin (light in the morning to advance, melatonin in the evening to advance) are the targeted treatments, not hypnotics.

16.7 Functions of sleep: memory consolidation and glymphatic clearance

Why we sleep is still not fully settled, but two functions carry the strongest evidence and the most exam weight.

Memory consolidation. Sleep does not merely protect memory passively; it actively reorganises it. The dominant framework is the *active systems consolidation* account: during slow-wave sleep, hippocampal memory traces are replayed and gradually redistributed to neocortex for long-term storage. The cellular choreography is a nesting of three rhythms, neocortical slow oscillations, thalamocortical spindles and hippocampal sharp-wave ripples, time-locked so that the hippocampus "teaches" the cortex (which is why spindle density predicts overnight retention and rises after learning). **Slow-wave sleep favours declarative (hippocampus-dependent) memory; REM sleep favours procedural, emotional and creative memory** and is implicated in down-

scaling the emotional charge of experiences ("overnight therapy"). Selectively depriving a stage degrades the corresponding memory, the experimental backbone of this claim.

Glymphatic clearance. The glymphatic system (Nedergaard and colleagues) is the brain's waste-clearance pathway: cerebrospinal fluid enters along periarterial spaces, exchanges with interstitial fluid via aquaporin-4 channels on astrocytic end-feet, and flushes metabolic waste, including *amyloid-beta* and *tau*, into perivenous drainage. Its defining feature is that it is **strongly upregulated during sleep, particularly slow-wave sleep**: the interstitial space expands and clearance rises sharply compared with the waking brain. This gives a mechanistic bridge between chronic sleep loss and neurodegeneration, and it is the rationale behind the current interest in protecting deep sleep as a modifiable dementia-risk factor, now alongside the anti-amyloid monoclonal antibodies (lecanemab, donanemab) in Alzheimer disease.

Other established functions worth a line each: **synaptic homeostasis** (Tononi and Cirelli: waking potentiates synapses, sleep, especially slow-wave sleep, renormalises synaptic strength to restore signal-to-noise and capacity); **energy conservation and metabolic restoration**; **growth-hormone secretion**, which peaks in early-night N3; and **immune regulation** (early-night NREM lowers HPA-axis and sympathetic tone and favours an inflammatory or pro-defence milieu, while sleep deprivation raises sympathetic output and inflammatory markers and lowers natural-killer-cell activity).

16.8 Sleep as a psychiatric biomarker: depression, mania, schizophrenia

The clinical-correlation core of this topic is that disordered architecture is woven into psychiatric illness, not merely a complication of it. The existing clinical anchor names the headline findings; here is the discriminating detail.

DISORDER	REM LATENCY	REM DENSITY	SLOW-WAVE SLEEP	EXAM-GRADE NUANCE
Major depression	**Reduced (REM comes too early)**	Increased	Reduced	Prolonged first REM period; shortened REM latency persists in remission and in unaffected high-risk relatives, so it is a trait-like vulnerability marker, not just state
Bipolar disorder	Reduced in mania and depression	Increased	Variable	**Reduced need for sleep** is a core manic criterion and often the earliest relapse signal; euthymic patients keep short REM latency with increased total REM
Schizophrenia	Reduced (inconsistent)	Higher (inconsistent)	Reduced	Reduced **sleep-spindle** density (thalamic reticular nucleus dysfunction) is the more replicated finding and links to impaired consolidation; failure to show REM rebound after deprivation

Sleep architecture across the major psychoses and mood disorders. The shaded cell is the single most tested fact on this topic: reduced REM latency in depression.

HOLD THIS

Depression shows reduced REM latency, increased REM density and reduced slow-wave sleep. Reduced REM latency is a sensitive but non-specific marker; in mania the giveaway is a reduced *need* for sleep.

⚠ COMMON TRAP

Reduced REM latency is **not specific to depression**: it also appears in mania, schizophrenia, narcolepsy and after REM deprivation. The viva answer is that it is a sensitive state-and-trait marker of depression but a poor discriminator; the manic distinction is the *reduced need* for sleep (the patient feels rested on three hours), which is a symptom, not a polysomnographic sign.

16.9 Sleep disorders overview: the ICSD-3 map and high-yield entities

Beyond insomnia (managed in the Locus-Focus-Modus block above), the field is organised by the International Classification of Sleep Disorders, third edition (ICSD-3), and cross-coded in ICD-11 (chapter 7, Sleep-wake disorders) and DSM-5-TR. Hold the map in six families, then anchor the entities exams favour.

Insomnia disorders

Covered above; CBT-I is definitive first-line (BAP 2019, AASM 2021).

Sleep-related breathing disorders

Obstructive sleep apnoea is the heavyweight: repetitive upper-airway collapse, apnoea-hypopnoea index on polysomnography, daytime sleepiness, and a strong bidirectional tie to depression, treatment-resistant mood disorder and cognitive impairment. CPAP is first-line.

Central disorders of hypersomnolence

Narcolepsy type 1 (orexin loss, cataplexy, CSF orexin low; modafinil for sleepiness, sodium oxybate for cataplexy), narcolepsy type 2, idiopathic hypersomnia and Kleine-Levin syndrome.

Circadian-rhythm sleep-wake disorders

Delayed and advanced sleep-phase, shift-work and jet-lag types (Section 10.6); treated with timed light and melatonin.

Parasomnias

NREM parasomnias arise from N3 in the first third of the night with amnesia for the event: sleepwalking, sleep terrors, confusional arousals (childhood-predominant, the existing N3 row). **REM parasomnias**: nightmare disorder and, critically, **REM sleep behaviour disorder (RBD)**, loss of REM atonia with dream enactment, found in roughly 0.5 percent of the elderly and a powerful prodrome of the synucleinopathies (Parkinson disease, dementia with Lewy bodies, multiple system atrophy).

Sleep-related movement disorders

Restless legs syndrome (an urge to move with circadian evening worsening, linked to brain-iron deficiency and dopaminergic dysfunction) and periodic limb movements of sleep.

> **INDIA CONTEXT**
>
> Polysomnography access remains concentrated in tertiary centres and metros, so much of Indian sleep practice is clinical and screening-led: validated tools such as the Epworth Sleepiness Scale, STOP-BANG for obstructive sleep apnoea risk, and the Insomnia Severity Index carry the diagnosis where a sleep lab is out of reach. Be alert to the high comorbidity of obstructive sleep apnoea with the metabolic syndrome in Indian patients, and to chronic short sleep among shift workers and resident doctors; treat the breathing disorder before escalating psychotropics for a "treatment-resistant" mood presentation.

17 · EEG: basics and waveforms

The EEG records summed post-synaptic potentials of cortical pyramidal neurons. Frequency falls and amplitude rises as the brain moves from alert to deep sleep, so the band tells you the state.

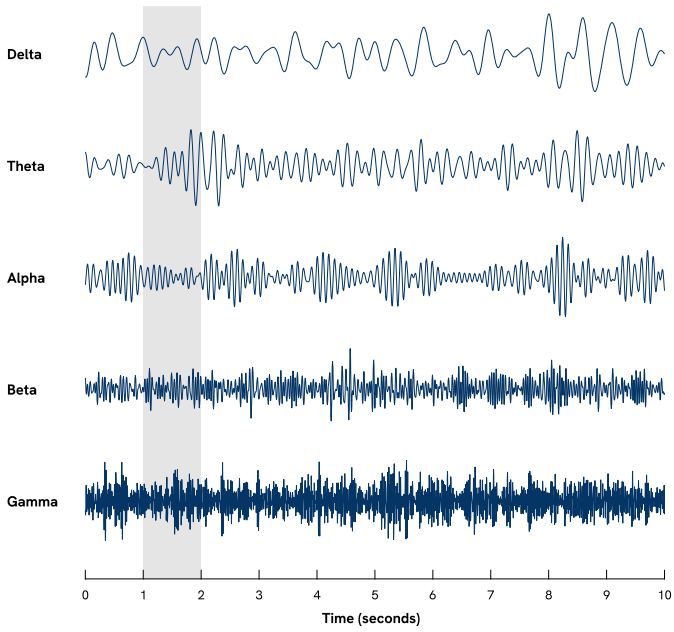


Image: Laurens R. Krol, CC0 / public domain, via Wikimedia Commons

Fig 1.21 The EEG frequency bands as real traces. As arousal falls, frequency drops and amplitude grows: gamma (>30 Hz, binding) and beta (13 to 30 Hz, alert, also raised by benzodiazepines) give way to alpha (8 to 13 Hz, relaxed eyes-closed, posterior dominant rhythm), then theta (4 to 8 Hz, drowsy and N1) and delta (<4 Hz, deep N3 sleep, or pathology if awake). Alpha is blocked by opening the eyes (alpha attenuation).

Clinical EEG in psychiatry. Most primary psychiatric illness has a normal EEG; the value of the test is to exclude organic mimics. **Delirium** shows diffuse background slowing (the degree tracks severity), a key bedside-to-EEG correlation. Epilepsy shows spikes and sharp waves. **Benzodiazepines and barbiturates** increase beta; many drugs lower the seizure threshold. EEG also guides and monitors ECT (seizure adequacy). **Creutzfeldt-Jakob disease** gives periodic sharp-wave complexes; hepatic encephalopathy gives triphasic waves.

EEG PATTERN	POINTS TO	WHY IT MATTERS
Diffuse background slowing	Delirium	Degree tracks severity; the one EEG sign that separates delirium from a primary psychiatric state
Periodic sharp-wave complexes (~1 Hz)	Sporadic Creutzfeldt-Jakob disease	Supports a rapidly progressive dementia with myoclonus
Triphasic waves	Hepatic and other metabolic encephalopathy	Flags a metabolic cause of the confusional state
Periodic complexes every 4 to 15 s	Subacute sclerosing panencephalitis	Classic with the regular myoclonic jerks; still seen in India
Increased beta activity	Benzodiazepines, barbiturates	A drug effect, not disease; do not over-read it

Tab 1.4 · The EEG patterns the exam pairs with a diagnosis. Delirium (shaded) is the highest-yield bedside-to-EEG correlation.

HOLD THIS

Primary psychiatric illness gives a normal EEG; a clearly abnormal EEG redirects you to an organic cause. Diffuse slowing that tracks severity is the sign that separates delirium from a psychiatric state.

17.1 Electrophysiological basis: what the scalp actually reads

The brief overview noted that the EEG is the summed activity of cortical pyramidal cells. The depth that exams probe is *which* potentials, in *which* cells, and why the signal is so small. The scalp electrode does not see action potentials; those are too brief and too asynchronous to summate. It sees the slow **excitatory and inhibitory postsynaptic potentials** (EPSPs and IPSPs) generated at the dendrites of large vertically oriented *pyramidal neurons* in cortical layers III and V (Physiopedia). An EPSP draws sodium into the apical dendrite, leaving the extracellular space around it negative; the cell body end stays relatively positive. This separation of charge along the long axis of the neuron creates an **open dipole field**, and because adjacent pyramidal cells are aligned in parallel like the bristles of a brush, their dipoles add rather than cancel.

Why the signal is weak and why synchrony matters. Roughly 10 cm^2 of cortex must fire **synchronously** before a deflection is visible at the scalp (Physiopedia). The skull, scalp and CSF attenuate and smear the field, so scalp EEG is a low-resolution, surface-weighted average; sulcal sources and deep generators (hippocampus, brainstem) are largely invisible to it. This is the principle of **volume conduction**: current spreads passively through the conductive head, so a potential generated in one region appears, reduced and time-locked, at distant electrodes. Volume conduction is the trap behind apparent "widespread" discharges and is why a single intracranial spike can show up across several scalp channels (Wennberg and Lozano 2003). It also explains montage logic: bipolar montages localise by phase reversal, referential montages by amplitude, both exploiting how a dipole projects across the array.

The 10-20 system. Electrode placement follows the **International 10-20 system**, named because electrodes sit at 10 percent and 20 percent of measured distances between the bony landmarks nasion, inion and the preauricular points. A standard adult montage uses 21 or more electrodes plus reference and ground (Physiopedia). Each site carries a letter for the lobe (Fp frontopolar, F frontal, C central, P parietal, T temporal, O occipital) and a number: **odd numbers lie over the left hemisphere, even numbers over the right**, with z (zero) marking the midline (Fz, Cz, Pz). The high-density 10-10 and 10-5 systems extend the same scheme for research and source localisation.

PEARL

EEG is fast (millisecond temporal resolution) but spatially blurred; functional MRI is the inverse (millimetre spatial resolution but seconds slow). The favourite single-best-answer discriminator: EEG records **postsynaptic potentials of pyramidal cells**, not action potentials, and needs **synchrony over about 10 cm^2** to be seen.

17.2 The frequency bands in full: amplitude, topography and state

The overview table gave the band ranges and the arousal gradient. The exam-relevant depth is the precise generator, topography and amplitude of each band, and the rule that lets you read state from the trace (Niedermeyer tradition, here confirmed against the StatPearls and PMC9749579 reviews). A clean way to hold it: as you go alert to deep sleep, frequency falls and amplitude rises, and there is an **anterior-to-posterior gradient** with faster rhythms frontally and slower rhythms posteriorly.

Delta (under 4 Hz, classically 0.5 to 4 Hz)

Highest amplitude, slowest band. Physiological in N3 deep sleep and infancy, frontocentral in adults. When present in an awake adult it is pathological, signalling diffuse (generalised slowing) or focal cortical dysfunction. Subtypes worth naming: **FIRDA** (frontal intermittent rhythmic delta activity) in adults and OIRDA (occipital, in children), both markers of encephalopathy or deep midline pathology.

Theta (4 to 7 Hz)

Drowsiness and N1 to N2 sleep, frontocentral, migrating posteriorly to replace alpha as the patient becomes drowsy. Frontal midline theta tracks cognitive control and working memory. **Focal theta in a fully awake patient indicates focal cerebral dysfunction.** A high theta-beta ratio is the classic quantitative-EEG signature linked to ADHD.

Alpha (8 to 12 Hz, posterior dominant rhythm)

The hallmark of relaxed wakefulness with eyes closed, maximal over the occipital region, generated by reciprocal thalamocortical (visual cortex to thalamus) loops. It is **blocked by eye-opening, attention or mental effort** (alpha attenuation or Berger effect). The PDR matures to about 8.5 Hz by age eight; slowing of the PDR is an early sign of diffuse cerebral dysfunction. The unreactive, non-attenuating variant is *alpha coma*, a poor-prognosis pattern after anoxic injury.

Beta (13 to 30 Hz)

Low amplitude, typically 10 to 20 microvolts, frontocentral, the dominant rhythm of the alert engaged brain. It rises in drowsiness and N1 then falls in N2 to N3. Crucially for psychiatry, sedative-hypnotics (benzodiazepines, barbiturates, chloral hydrate) augment beta; focal beta attenuation flags an overlying structural lesion or fluid collection.

Gamma (over 30 Hz, about 30 to 80 Hz)

Lowest amplitude, first recorded in monkey visual cortex. Linked to feature binding, sensory integration and conscious perception. Narrowband gamma declines with healthy ageing and in early Alzheimer disease; beta-gamma phase-amplitude coupling over sensorimotor cortex is a Parkinson disease signature relevant to deep brain stimulation.

BAND	FREQUENCY	DOMINANT STATE	TOPOGRAPHY	DISCRIMINATOR
Delta	under 4 Hz	N3, infancy; pathology if awake	Frontocentral	**Highest amplitude; FIRDA in adults**
Theta	4 to 7 Hz	Drowsy, N1 to N2	Frontocentral	**Focal theta awake = focal dysfunction**
Alpha	8 to 12 Hz	Relaxed, eyes closed	Occipital (PDR)	**Blocked by eye-opening**
Beta	13 to 30 Hz	Alert, engaged	Frontocentral	**Raised by benzodiazepines, barbiturates**
Gamma	over 30 Hz	Binding, perception	Widespread	**Lowest amplitude; falls in Alzheimer**

The five bands by amplitude, state and the single fact most likely to be tested for each. Reading direction: alert and posterior-blocking at the top, deep and high-amplitude at the bottom.

<4 Hz	4-7 Hz	8-12 Hz	13-30 Hz
DELTA (DEEP N3)	THETA (DROWSY, N1)	ALPHA (RELAXED, EYES CLOSED)	BETA (ALERT; RAISED BY BENZODIAZEPINES)

MNEMONIC

"Bad Boys Are Tired and Drowsy" by falling frequency

Beta and Gamma (Boys, fast, alert), then Alpha (Are, relaxed eyes-closed), then Theta (Tired, drowsy), then Delta (Drowsy, deep sleep). Frequency falls top to bottom; amplitude rises in the same direction.

17.3 Normal variants and sleep architecture: the patterns that fool you

A large slice of EEG mis-reading is calling a benign variant epileptiform. Knowing the named normal patterns is high yield because the exam tests exactly this discrimination. The two families are **sleep transients** and **benign awake or drowsy variants** (StatPearls, Normal EEG Waveforms).

- **Vertex sharp transients (V waves).** Monophasic to triphasic surface-negative sharp waves with phase reversal at the vertex (Cz), about 100 ms long, appearing in drowsiness and N1 to N2. Not epileptiform despite the sharp look.
- **Sleep spindles (sigma, 12 to 16 Hz).** The defining marker of N2 sleep, frontocentral, generated by thalamocortical (thalamic reticular nucleus) circuits, the same machinery that produces 3 Hz spike-wave. Slow spindles run 12 to 14 Hz, fast spindles 14 to 16 Hz. They are highly heritable and index sleep-dependent memory consolidation; reduced spindle density appears in ageing, Alzheimer disease and schizophrenia.

- **K complexes.** High-voltage polyphasic waves lasting over 0.5 s, frontally dominant, the other hallmark of N2, often followed by a spindle. Less sharply contoured than a true spike, which is the discriminator.
- **POSTS.** Positive occipital sharp transients of sleep, seen in roughly 50 to 80 percent of healthy people during NREM, occipital, lambda-like, most common in adolescents and young adults.
- **Benign variants of the awake or drowsy record.** *Wicket spikes* (the single most commonly over-read normal pattern), *benign epileptiform transients of sleep* (small sharp spikes, amplitude under 90 microvolts, duration over 90 ms, midtemporal, ages 30 to 60), *rhythmic midtemporal theta of drowsiness* (the old "psychomotor variant"), the *6 Hz phantom spike-wave* (amplitude under 40 microvolts, spike under 30 ms), 14- and 6-Hz positive spikes, and SREDA (subclinical rhythmic EEG discharges of adults). All are non-epileptogenic.

Sleep staging in one line. Wake shows posterior alpha; N1 shows theta with vertex waves and (early) POSTS; N2 is defined by spindles and K complexes; N3 (slow-wave sleep) is over 20 percent high-amplitude delta; REM shows a low-voltage mixed-frequency desynchronised trace resembling wakefulness with sawtooth waves and muscle atonia. Other named awake patterns include the *mu rhythm* (arciform 8 to 12 Hz over the central strip, attenuated by contralateral movement) and *lambda waves* (occipital positive sharp transients during visual scanning, gone on eye closure).

> ⚠ COMMON TRAP
> Wicket spikes, small sharp spikes (BETS) and 6 Hz phantom spike-wave are **benign** and must never be reported as epileptiform. Over-reading them generates a false epilepsy label, unnecessary antiseizure drugs and a needlessly restricted licence. Sharpness alone does not make a discharge epileptiform; context, field, after-going slow wave and disruption of background do.

17.4 Activation procedures: provoking the abnormal

Routine EEG has limited sensitivity, so technicians use standard **activation procedures** to coax out latent abnormalities. These are testable as a triad.

Hyperventilation

Three minutes of overbreathing induces hypocapnia and cerebral vasoconstriction, producing physiological diffuse slowing (build-up), more pronounced in children and with hypoglycaemia. Its diagnostic power is in **generalised epilepsy**: it readily activates the 3 Hz spike-wave of childhood absence epilepsy. Contraindicated in significant cardiopulmonary or cerebrovascular disease, recent stroke, sickle cell disease and moyamoya.

Intermittent photic stimulation

A strobe flickered across a range of frequencies. A normal response is the symmetric *photic driving* response (occipital rhythms time-locked to the flash). The abnormal response is the **photoparoxysmal (photoconvulsive) response**, generalised spike-wave triggered by the flash, the electrographic correlate of **photosensitive epilepsy**, characteristically juvenile myoclonic epilepsy.

Sleep and sleep deprivation

Drowsiness and sleep activate many epileptiform discharges, including benign focal epilepsy of childhood with centrotemporal spikes (which is unaffected by hyperventilation or photic stimulation but switched on by sleep) and the continuous spike-wave of EE-SWAS. Prior sleep deprivation increases the yield of interictal discharges and is a standard part of a repeat or prolonged study when a first routine EEG is normal but suspicion is high.

PEARL

Map activation to syndrome: hyperventilation pairs with **absence**, photic stimulation with **juvenile myoclonic epilepsy** (photosensitivity), sleep with **Rolandic epilepsy (BECTS)** and EE-SWAS. A single routine 30-minute EEG detects interictal discharges in only roughly 12 to 50 percent of adults with new-onset seizures, so a normal study never excludes epilepsy.

17.5 Epileptiform discharges: morphology and syndrome map

An **interictal epileptiform discharge** is a synchronous discharge from a focus of cortical neurons, classified by morphology into spikes, polyspikes and sharp waves (StatPearls, EEG Abnormal Waveforms). The duration thresholds are exam favourites: a **spike lasts 20 to 70 ms**, a **sharp wave 70 to 200 ms**, and a **polyspike** is two or more consecutive spikes within a total under 0.5 s. The after-going slow wave of a spike-wave complex is mediated by GABA-B currents, which is why drugs acting on inhibitory tone modulate the discharge.

PATTERN	FREQUENCY OR MORPHOLOGY	POINTS TO	DISCRIMINATOR
3 Hz spike-and-wave	3.5 to 4 Hz at onset, slows to 2.5 to 3 Hz; frontal maximum	Childhood absence epilepsy	**Normal background; activated by hyperventilation, blocked by eye-opening**
Polyspike-and-wave (fast spike-wave)	3.5 to 5 Hz, generalised frontocentral	Juvenile myoclonic epilepsy, myoclonic epilepsies	**Photic stimulation activates; precedes tonic-clonic seizures**
Slow spike-and-wave	1 to 2.5 Hz, generalised	Lennox-Gastaut syndrome	**Slow background; may evolve from hypsarrhythmia**
Centrotemporal (Rolandic) spikes	Horizontal dipole, centrotemporal negative	BECTS	**Unchanged by hyperventilation or photic; activated by sleep**
Hypsarrhythmia	Chaotic high-voltage delta with multifocal spikes	Infantile epileptic spasms (West syndrome)	**Disorganised, asynchronous high-amplitude chaos**
LPDs (formerly PLEDs)	Repetitive lateralised periodic discharges	Acute focal lesion; classically herpes simplex encephalitis (temporal)	**Periodicity over one hemisphere; also CJD, stroke, tumour**
GPDs / periodic sharp-wave complexes	Generalised, about 1 Hz periodic	Sporadic Creutzfeldt-Jakob disease, anoxia	**Generalised periodicity; supports rapidly progressive dementia with myoclonus**

Epileptiform morphology to syndrome, with the one feature that nails each. The 3 Hz versus slow spike-wave versus periodic discharge distinction is the spine of every EEG single-best-answer.

RULE **3 Hz spike-wave is childhood absence; slow (1-2.5 Hz) spike-wave is Lennox-Gastaut; ~1 Hz periodic complexes are sporadic CJD.** The frequency of the discharge names the syndrome.

TRAP Calling triphasic waves pathognomonic of hepatic encephalopathy. They are a **non-specific** marker of any metabolic encephalopathy (uraemia, anoxia, drug effects).

CLINICAL ANCHOR

Temporal LPDs in an acutely confused, febrile, dysphasic patient point to herpes simplex encephalitis: start aciclovir empirically before confirmation, because the EEG and the clinical picture together cannot wait for PCR. This is the highest-stakes EEG-to-action link a psychiatrist on call will meet in an organic-confusion workup.

17.6 EEG in psychiatric and organic disease: extending the picture

The overview table already lists diffuse slowing in delirium, periodic complexes in CJD and triphasic waves in metabolic encephalopathy. The conceptual point to hold beyond that table is a single sorting rule: **primary psychiatric illness almost always gives a normal or non-specific EEG; a clearly abnormal EEG should redirect you toward an organic cause.** The clinical value of the test in psychiatry is therefore mostly exclusionary, plus a few specific positive signs.

- **Delirium versus dementia.** Diffuse slowing appears early in delirium and its degree tracks severity, whereas it appears late in most dementias. This is the EEG sign that separates an acute confusional state from a primary psychiatric presentation, and from early dementia, at the bedside.
- **Triphasic waves.** First described by Foley (1950), once thought pathognomonic of hepatic encephalopathy but now recognised as non-specific to any metabolic encephalopathy (uraemia, anoxia, and drug effects from cefepime, lithium, baclofen and ifosfamide). High-amplitude (over 70 microvolts), bifrontal, synchronous, three-phase waves beginning with a negative deflection, present only with reduced consciousness. They are now classified as a subset of generalised periodic discharges arising from thalamocortical disruption.
- **Dementias.** Sporadic CJD gives generalised periodic sharp-wave complexes at roughly 1 Hz supporting a rapidly progressive dementia with myoclonus. Alzheimer disease shows progressive background slowing and loss of fast activity; subclinical epileptiform discharges, especially left temporal, are now linked to faster cognitive decline. Frontotemporal dementia characteristically spares the EEG until late, a useful contrast.
- **Functional and primary psychiatric states.** Schizophrenia, mood and anxiety disorders have no diagnostic EEG, though group-level findings (reduced alpha, increased slow and fast activity, reduced P50 sensory gating, mismatch-negativity and P300 changes) are research markers, not bedside tests. A normal EEG never excludes a psychiatric diagnosis and never confirms one.

- **Where EEG earns its place in psychiatry.** New-onset psychosis or mood change with atypical features, episodic or stereotyped behavioural disturbance suggesting temporal-lobe or non-convulsive status, suspected autoimmune (anti-NMDA-receptor) encephalitis with the "extreme delta brush" pattern, first presentation of catatonia, and any cognitive decline that is rapid or has focal signs.

> ⚠ COMMON TRAP
> Triphasic waves are **not** pathognomonic of hepatic encephalopathy. Calling them so is a classic single-best-answer error; the correct stem answer is "non-specific marker of metabolic encephalopathy". Equally, do not attribute a clearly abnormal slowing or epileptiform EEG to a primary psychiatric illness without first excluding an organic cause.

17.7 EEG and psychotropics: how drugs read on the trace

Psychotropic effects on the EEG are testable and clinically relevant for seizure-threshold counselling. The unifying frame: sedatives shift the spectrum toward fast (beta) activity while some agents add slowing or paroxysmal features, and several agents lower the seizure threshold.

Benzodiazepines and barbiturates

Increase beta amplitude and quantity (also chloral hydrate). Useful corollary: a fast, beta-rich record in an obtunded patient suggests sedative effect rather than structural pathology.

Antipsychotics

Most slow the background and increase epileptiform potential dose-dependently. **Clozapine** is the prototype: marked, dose-related EEG slowing and the highest seizure risk of the class (roughly up to several percent at high dose), warranting EEG if myoclonus or new confusion appears. Low-potency phenothiazines (chlorpromazine) also lower the threshold; high-potency agents (haloperidol) and several second-generation drugs are comparatively safer.

Antidepressants

Bupropion has the clearest dose-related seizure risk (highest with the immediate-release formulation and in eating-disorder or withdrawal states); tricyclics, especially clomipramine and maprotiline, lower the threshold and are dangerous in overdose. SSRIs and SNRIs are comparatively low risk.

Mood stabilisers and others

Lithium can produce diffuse slowing and, at toxicity, triphasic-like waves and even non-convulsive features. Anticonvulsant mood stabilisers (valproate, carbamazepine, lamotrigine) raise the threshold. Stimulants used at therapeutic dose do not meaningfully lower the threshold in most patients.

> ♡ CLINICAL ANCHOR
> A patient on high-dose clozapine who develops jerks, a fluctuating sensorium or a frank seizure needs an EEG, a clozapine level and a dose review, often with valproate cover. Pairing the EEG slowing with the clinical picture turns an abstract "clozapine lowers seizure threshold" fact into a management decision.

17.8 Quantitative EEG and evoked potentials

Quantitative EEG (qEEG) applies spectral analysis (the fast Fourier transform) to digitised EEG to quantify absolute and relative power in each band, coherence between regions and topographic maps. Its evidence-based uses are narrow: it supports localisation in epilepsy and detection of subtle slowing in encephalopathy, and the **theta-beta ratio** has an FDA-cleared role as an adjunct (never a stand-alone test) in ADHD assessment. Claims that qEEG or EEG-guided neurofeedback can diagnose or treat most psychiatric disorders remain unproven and are an examiners favourite "overclaim" to reject.

Evoked and event-related potentials. Averaging the EEG time-locked to repeated stimuli cancels background activity and reveals small, fixed-latency responses. *Evoked potentials* are exogenous and stimulus-bound: visual (VEP, the P100 used in optic neuritis and multiple sclerosis), brainstem auditory (BAEP, for acoustic neuroma and brainstem integrity, also a marker of fast EEG-range activity), and somatosensory (SSEP, for spinal-cord and coma prognosis). *Event-related potentials* are endogenous and cognition-dependent: the **P300** (a positive wave around 300 ms to an oddball target, reduced in amplitude and delayed in latency in schizophrenia and in dementia), the **mismatch negativity** (a pre-attentive auditory-deviance response, attenuated in schizophrenia and a candidate NMDA-receptor biomarker), and the P50 (sensory gating, deficient in schizophrenia). These bridge the EEG to cognitive neuroscience and recur in exams as the "which potential maps to which deficit" question.

POTENTIAL	TYPE	LATENCY OR MARKER	CLINICAL LINK
VEP (P100)	Evoked, visual	about 100 ms	**Optic neuritis, multiple sclerosis**
BAEP	Evoked, auditory	Waves I to V	**Acoustic neuroma, brainstem and coma**
P300	Event-related (endogenous)	about 300 ms	**Reduced amplitude, delayed in schizophrenia and dementia**
Mismatch negativity	Event-related (pre-attentive)	about 150 to 250 ms	**Attenuated in schizophrenia; NMDA marker**
P50	Event-related (gating)	about 50 ms	**Sensory-gating deficit in schizophrenia**

Evoked versus event-related potentials and their disease links. The split to remember: exogenous and stimulus-locked (VEP, BAEP, SSEP) versus endogenous and cognition-locked (P300, MMN, P50).

17.9 EEG monitoring in ECT

The overview noted that EEG guides and monitors ECT; the depth examiners want is *what a good seizure looks like* on the trace and why it matters. Most modern ECT machines display a one- or two-channel EEG continuously, and seizure adequacy is judged from the ictal EEG, not from the visible motor convulsion (which is masked by the muscle relaxant in modified ECT).

The ictal sequence. A well-formed ECT seizure evolves through recognisable phases: an initial recruiting (epileptic-recruiting) rhythm of low-amplitude fast activity, a build to high-amplitude rhythmic **polyspike** activity, then organised **spike-and-wave (slow-wave) activity** that grows in amplitude and slows in frequency, and finally an abrupt **postictal suppression** where the trace flattens. Markers of an adequate, therapeutic seizure include good **midictal amplitude and regularity**, clear **postictal suppression**, and adequate **duration** (the CTP titration endpoint is a 20 to 25 second motor or EEG seizure; seizures under 15 seconds arise close to threshold and are often considered abortive). Postictal suppression and high ictal amplitude correlate better with efficacy than raw duration.

Why it matters clinically. A poorly formed or very brief seizure, or one without postictal suppression, suggests a sub-therapeutic stimulus and prompts re-stimulation or an increase in charge at the next session; missed or "abortive" seizures, and prolonged seizures over about 2 to 3 minutes needing termination, are both detected on the EEG. Suprathreshold dosing relative to the seizure threshold, especially in right unilateral ECT, drives efficacy, and the EEG is how that threshold and the quality of each seizure are tracked across a course.

INDIA CONTEXT

ECT is widely used across Indian government and teaching hospitals, and modern (modified, anaesthetised, EEG-monitored) ECT is the standard of care; the Mental Healthcare Act 2017 prohibits unmodified (direct) ECT and bars ECT in minors without Mental Health Review Board sanction. For exams, know that seizure adequacy is judged from the **ictal EEG**, that EEG monitoring is part of guideline-concordant practice, and that consent and MHRB provisions are part of any management answer on ECT in India.

18 · Neural basis of memory: hippocampal circuits and LTP

Memory divides into **declarative (explicit)**, served by the medial temporal lobe and hippocampus, and **non-declarative (implicit)**, served by the striatum, cerebellum and amygdala. The cellular currency of declarative memory is **long-term potentiation (LTP)**, a lasting strengthening of synapses that fire together, the physiological reading of Hebb's rule.

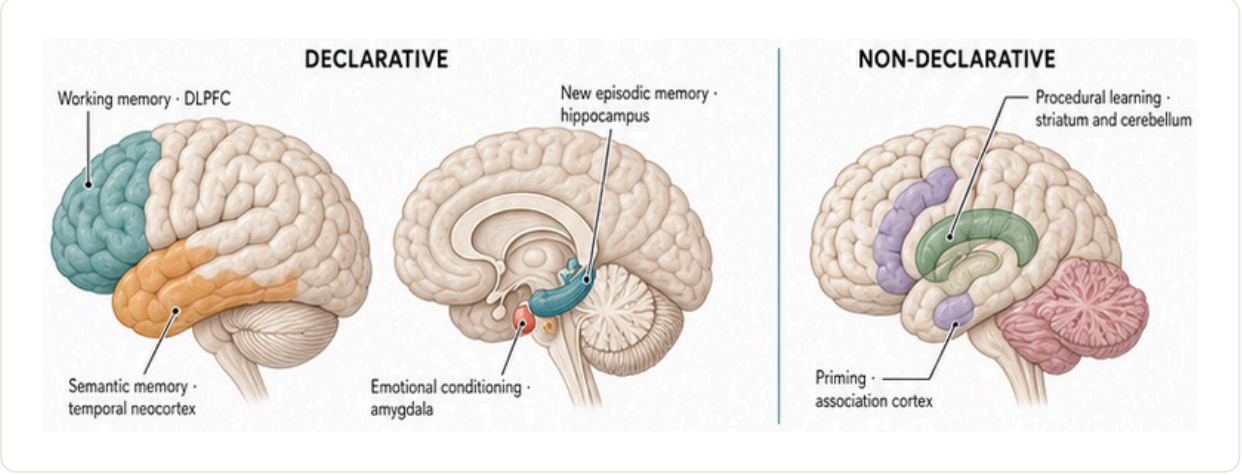


Fig 1.22 Memory systems and their principal neural substrates. Declarative memory depends on medial temporal and association cortex; non-declarative learning recruits striatum, cerebellum, amygdala and priming networks.

HOLD THIS

Declarative memory runs through the medial temporal lobe and hippocampus; long-term potentiation is its cellular currency. Non-declarative (procedural, priming, conditioning) survives medial-temporal damage.

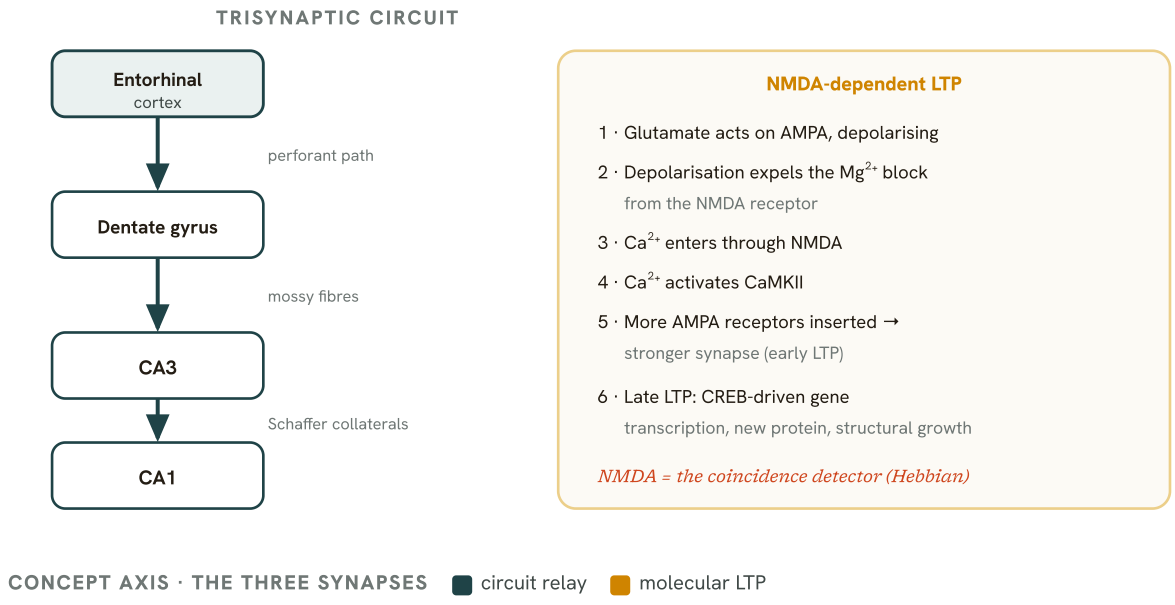


Fig 1.23 The hippocampal trisynaptic circuit (entorhinal to dentate to CA3 to CA1) and the NMDA-dependent mechanism of LTP, the synaptic basis of declarative memory.

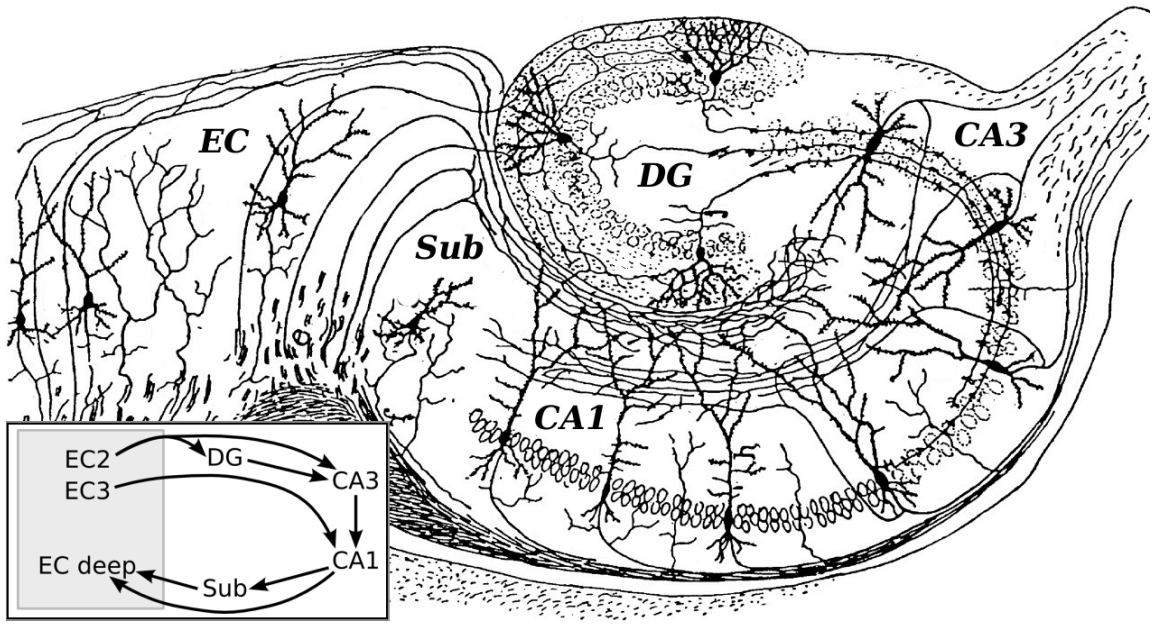


Image: Santiago Ramon y Cajal (1911), public domain, via Wikimedia Commons

Fig 1.24 Cajal's own Golgi-stain drawing of the hippocampus. The dentate gyrus, CA3 and CA1 fields of the schematic in Fig 1.23, as he first resolved them by hand.

Bliss & Lømo (1973) LANDMARK · DISCOVERY OF LTP

Design. Stimulation of the perforant path in the rabbit hippocampus (dentate gyrus). **Finding.** Brief high-frequency stimulation produced a long-lasting increase in synaptic efficacy. **Why it matters.** The first demonstration of activity-dependent synaptic strengthening, the cellular model of learning and memory and the anchor of every plasticity answer (topic 19). The paper describes the phenomenon; the NMDA-receptor mechanism was worked out in the 1980s.

⚠ COMMON TRAP

Do not write "all hippocampal LTP is NMDA-dependent". CA1 (Schaffer-collateral) LTP is the classic NMDA-dependent, postsynaptic form. The **mossy-fibre synapse (dentate to CA3)** is the textbook exception: its LTP is presynaptic and NMDA-receptor-*independent*. Examiners use this to separate the candidate who memorised from the one who understood.

18.1 The full memory taxonomy and working memory

The half-page above split memory into declarative and non-declarative; this is the tree the examiner wants drawn in full. **Declarative (explicit)** memory is consciously accessible and divides into *episodic* memory (events you have lived through, the wedding, the road traffic accident) and *semantic* memory (context-free facts and word meanings). **Non-declarative (implicit)** memory is expressed through performance, never through conscious recall, and has four limbs: **procedural** skills and habits (striatum and cerebellum), **priming** (neocortex), classical **conditioning** (amygdala for emotional, cerebellum for skeletal-motor responses), and **non-associative** learning (habituation and sensitisation, reflex pathways). The clinical hinge is that the medial temporal lobe is dedicated to declarative memory, which is precisely why an amnesic patient can still learn a motor skill they have no memory of practising (Almaraz-Espinoza and Grider, StatPearls).

Time axis. Cutting the same material a second way: *sensory* memory (sub-second iconic and echoic traces), *short-term* or working memory (seconds, capacity-limited), and *long-term* memory (effectively unlimited, durable). The hippocampus consolidates labile short-term traces into distributed cortical long-term stores; the trace is laid down in the hippocampus but ultimately **stored throughout the neocortex**, not in the hippocampus itself.

Working memory (Baddeley and Hitch model)

The active, manipulable workspace, not a passive store. A *central executive* (attentional controller, dorsolateral prefrontal cortex) directs three slave systems: the *phonological loop* (verbal and acoustic material, the "inner voice and inner ear"), the *visuospatial sketchpad* (visual and spatial imagery), and the later-added *episodic buffer* (binds information across the subsystems and links to long-term memory). High-yield: working memory is the cognitive domain most consistently impaired in schizophrenia and a core ADHD deficit, and it maps onto dorsolateral prefrontal function (Baddeley 1992).

MNEMONIC

"PETS Can't Hide Procedures"

Priming, **E**pisodic and **S**emantic (the declarative pair sits with episodic), conditioning, and **Procedures**: the non-declarative limbs are **P**riming, **C**onditioning, **P**rocedural, and non-associative. Reserve "explicit = episodic plus semantic; implicit = the rest" as the one line you write first.

18.2 The trisynaptic circuit, expanded

Fig 1.23 names the three relays; here is the architecture the examiner builds questions on. The hippocampal formation receives a **highly processed multimodal stream**: association cortex feeds the parahippocampal and perirhinal cortices, which converge on the **entorhinal cortex**, the single great gateway into and out of the hippocampus. From there the canonical loop runs:

- **Synapse 1, perforant path.** Entorhinal layer II neurons project to the granule cells of the *dentate gyrus*. The dentate performs **pattern separation**, decorrelating similar inputs into distinct representations, and is the site of adult neurogenesis (topic 19).
- **Synapse 2, mossy fibres.** Dentate granule-cell axons (the mossy fibres) synapse on the proximal dendrites of *CA3* pyramidal cells via large detonator-type terminals. CA3 has dense recurrent collaterals, the substrate for **pattern completion** and autoassociative recall (one cue retrieves the whole memory).
- **Synapse 3, Schaffer collaterals.** CA3 axons project to the apical dendrites of *CA1* pyramidal cells. CA1 is the principal output stage and the classic site of NMDA-dependent LTP.

CA1 then projects to the **subiculum**, the major output structure, which returns the processed signal to the deep layers of entorhinal cortex and onward to neocortex, and contributes the bulk of the fimbria-fornix output to the mammillary bodies and anterior thalamus (the Papez circuit, topic 3). Note the vulnerability gradient: **CA1 is the most ischaemia-sensitive sector** (Sommer sector), selectively lost after hypoxic-ischaemic injury and cardiac arrest, whereas CA3 and the dentate are relatively resistant.

SUBFIELD	RECEIVES FROM	COMPUTATION	EXAM HOOK
Dentate gyrus	Entorhinal (perforant path)	**Pattern separation**	Adult neurogenesis site
CA3	Dentate (mossy fibres)	**Pattern completion (recurrent net)**	NMDA-independent mossy-fibre LTP
CA1	CA3 (Schaffer collaterals)	Output, comparator	**Most ischaemia-vulnerable (Sommer sector)**
Subiculum	CA1	Main output relay	Origin of fornix output to mammillary bodies

The four hippocampal stages, each with its signature computation and its single most testable fact. Dentate separates, CA3 completes, CA1 reads out and is the one that dies in hypoxia.

18.3 LTP induction: NMDA as coincidence detector

The figure inset gives the six-step cartoon; this is the mechanism in the detail an MD viva demands. At rest the **NMDA receptor** channel is plugged by an **extracellular Mg^{2+} ion** (zinc contributes a second block), so glutamate binding alone does nothing. Two conditions must be met simultaneously for the channel to conduct (StatPearls, Physiology NMDA Receptor):

- **Ligand.** Two molecules of glutamate must bind, *and* a co-agonist must occupy the glycine site: **glycine at extrasynaptic receptors, D-serine within the synapse.** This obligate co-agonist requirement is a favourite single-best-answer discriminator.
- **Voltage.** The postsynaptic membrane must already be depolarised, classically by glutamate acting on co-localised AMPA receptors, to expel the Mg^{2+} block. Only then does the channel open and admit **Ca^{2+}**.

Because the receptor opens only when presynaptic transmitter release (glutamate) coincides with postsynaptic depolarisation, the NMDA receptor is the molecular reading of Hebb's rule: a **coincidence detector.** The same source frames a graded triad worth memorising. A *small* Ca^{2+} rise transiently recruits a few AMPA receptors (short-term potentiation, lasting hours). A *large* Ca^{2+} rise engages transcription factors and lasting growth (LTP, lasting years). An *overwhelming, prolonged* Ca^{2+} load is lethal to the cell, the basis of **excitotoxicity** in stroke, epilepsy and traumatic brain injury. Calcium dose, not a different receptor, separates learning from cell death.

RULE **The NMDA receptor is the coincidence detector: it opens only when glutamate binding meets postsynaptic depolarisation that expels the Mg block.** Calcium dose then decides potentiation, depression or excitotoxic death.

TRAP Writing that all hippocampal LTP is NMDA-dependent. The **mossy-fibre (dentate-to-CA3)** synapse is the classic exception: its LTP is presynaptic and NMDA-independent.

CLINICAL ANCHOR

Every clinically important NMDA drug maps onto this scheme. **Memantine**, an uncompetitive (open-channel) antagonist, dampens chronic low-grade excitotoxic Ca^{2+} flux in Alzheimer disease while sparing physiological signalling. **Ketamine and phencyclidine** are channel blockers; ketamine's rapid antidepressant effect runs through NMDA blockade on inhibitory interneurons, a glutamate surge, then AMPA and mTOR-driven synaptogenesis (the bridge to topic 19). **Magnesium** is the endogenous block itself, which is why hypomagnesaemia lowers the seizure threshold and magnesium sulphate is neuroprotective in eclampsia. Anti-NMDA-receptor (anti-GluN1) encephalitis presents with psychosis, seizures and dyskinesias and is a must-exclude organic mimic of first-episode psychosis.

18.4 LTP expression: early versus late phase

The defining textbook division is by protein synthesis. **Early-phase LTP (E-LTP)** is **independent of new protein synthesis and gene transcription**. The Ca^{2+} that entered through NMDA receptors activates **CaMKII** (Ca^{2+}/calmodulin-dependent protein kinase II) and PKC, which become autonomously, persistently active by autophosphorylation, a molecular switch.

These kinases then do two things: they *phosphorylate existing AMPA receptors* to raise their single-channel conductance, and they *traffic additional AMPA receptors* from a non-synaptic pool into the postsynaptic membrane. A stronger AMPA response to the same glutamate is the physical expression of the strengthened synapse. This is also how **silent synapses** (those bearing only NMDA receptors) are "unsilenced" by AMPA insertion (Lynch; Wikipedia, Long-term potentiation).

Late-phase LTP (L-LTP) is the natural extension that converts a labile change into a durable one, and it **requires gene transcription and protein synthesis**. The signal reaches the nucleus largely via the **ERK/MAPK** cascade onto which CaMKII, PKC and the cAMP/PKA pathway converge, activating the transcription factor **CREB** (cAMP response element binding protein). New gene products drive *structural remodelling*: more dendritic spines, larger spine heads, enhanced AMPA-receptor synthesis, and even presynaptic changes (more synaptotagmin and vesicles). Maintenance over the longest timescales has been linked to the constitutively active atypical kinase **PKMζ**, although transgenic knockouts that retain normal LTP keep this contested.

FEATURE	EARLY LTP (E-LTP)	LATE LTP (L-LTP)
Protein synthesis	**Not required**	**Required**
Gene transcription	No	Yes (CREB-driven)
Key molecules	CaMKII, PKC, AMPA trafficking	ERK/MAPK, PKA, CREB, PKMζ
Mechanism of strengthening	Phosphorylate and insert AMPA receptors	New proteins, spine growth, structural change
Duration	Minutes to 1 to 2 hours	Hours to days, weeks, months

The single most examined contrast in synaptic plasticity. The one-word answer to "what divides early from late LTP" is protein synthesis; the one-word answer to "the transcription factor" is CREB.

PEARL

NMDA receptors *induce* LTP; AMPA receptors *express* it. Block NMDA and you prevent new learning but leave established memories intact; the AMPA change is what the synapse "remembers". This induction-versus-expression split explains why an NMDA antagonist disrupts acquisition without erasing the past.

18.5 The four cardinal properties of LTP and the non-Hebbian exception

NMDA-dependent LTP shows four properties the examiner expects listed (Wikipedia, Long-term potentiation):

Input specificity

LTP is confined to the stimulated synapse and does not spread to neighbouring inactive synapses on the same cell. This is the cellular basis of memory selectivity, reconciled with cell-wide protein synthesis by the *synaptic tagging and capture* hypothesis (Frey and Morris 1997): a tagged synapse captures plasticity-related proteins shipped from the soma.

Cooperativity

A single weak input cannot reach the threshold for LTP; many weak inputs firing together can summate enough postsynaptic depolarisation to cross it. There is an intensity threshold.

Associativity

A weak input that would fail alone is potentiated if it fires together with a strong input onto the same cell. This is the synaptic analogue of classical conditioning, pairing a weak cue with a strong one.

Persistence

The change lasts from minutes to many months, the feature that separates LTP from transient plasticity.

Reinforcing the trap already flagged above: most hippocampal LTP is **Hebbian** (needs coincident pre- and postsynaptic activity, NMDA-dependent, postsynaptic, as at CA1). The **mossy-fibre synapse onto CA3 is non-Hebbian**: its LTP is presynaptic, depends on a presynaptic cAMP/PKA rise and increased glutamate release, and is **NMDA-receptor independent**. A rarer *anti-Hebbian* LTP requires presynaptic firing with postsynaptic hyperpolarisation. When a stem asks for "the exception to NMDA-dependent LTP", the answer is the mossy-fibre (dentate to CA3) synapse.

18.6 Long-term depression and the bidirectional synapse

Plasticity is bidirectional: the same machinery that strengthens a synapse can weaken it. **Long-term depression (LTD)** is the persistent weakening of synaptic strength and the functional opposite of LTP. The decisive variable is again the **amplitude and timing of the postsynaptic Ca^{2+} signal**: a brief, high-amplitude Ca^{2+} rise (from strong high-frequency stimulation) favours LTP and activates kinases, whereas a modest, sustained Ca^{2+} rise (from prolonged low-frequency stimulation) favours LTD and preferentially activates **protein phosphatases**, notably calcineurin (PP2B) and PP1. Where LTP phosphorylates and inserts AMPA receptors, LTD dephosphorylates and **internalises (endocytoses) AMPA receptors**, shrinking the response.

Two LTD forms recur in exams. Hippocampal and neocortical LTD is largely NMDA-receptor-dependent; **cerebellar LTD** at the parallel-fibre to Purkinje-cell synapse is the classic *mGluR-dependent* form and is the cellular substrate of motor learning (topic on cerebellum). Functionally, LTD is not just forgetting: it clears redundant synaptic weight, sharpens pattern separation, and together with LTP gives the network a dynamic range. *Metaplasticity* (the plasticity of plasticity, the prior-activity-dependent shifting of the LTP/LTD threshold, the BCM sliding threshold) and *depotentiation* (active reversal of recent LTP) are the higher-order terms to recognise.

18.7 Engram, systems consolidation and reconsolidation

An **engram** is the physical memory trace: the specific, sparse population of neurons whose coordinated LTP encodes a particular memory, now directly demonstrable by optogenetic tagging and reactivation. Two consolidation processes operate on different timescales:

- **Synaptic (cellular) consolidation.** The hours-long stabilisation of a new trace through E-LTP to L-LTP, the protein-synthesis-dependent fixing described above. It is local to the synapse.
- **Systems consolidation.** Over days to years the memory's dependence shifts **from the hippocampus to distributed neocortex**; the hippocampus initially indexes and replays the

trace (notably during sleep, topic on sleep) and the cortex gradually becomes the independent store. This time-graded transfer explains **Ribot's law**: in retrograde amnesia recent memories (still hippocampus-dependent) are lost while remote, cortically consolidated memories are spared.

Reconsolidation. A consolidated memory is not permanently fixed. When **retrieved, it returns to a labile state** and must be re-stabilised by a fresh round of protein synthesis; during this window it can be updated, strengthened or weakened. This is a high-yield bridge to psychiatry: it is the proposed mechanism behind *memory-reactivation plus propranolol* protocols and reconsolidation-based exposure in PTSD, and it reframes psychotherapy as the controlled rewriting of a reactivated trace.

18.8 Clinical correlation: the amnesias

The depth of this topic is its clinical mapping, disorder by disorder. First the two directions of amnesia:

Anterograde amnesia

Inability to form *new* declarative memories after the insult. The hippocampus and medial temporal lobe are required for laying down new traces, so bilateral damage abolishes new learning while leaving old memories and procedural learning intact.

Retrograde amnesia

Loss of memories formed *before* the insult, characteristically time-graded per Ribot's law (recent worse than remote), reflecting loss of the still hippocampus-dependent traces.

CONDITION	LESION / MECHANISM	MEMORY SIGNATURE
Patient H.M.	Bilateral medial temporal lobectomy (hippocampi removed for epilepsy)	**Profound anterograde amnesia, working memory and procedural learning preserved; the founding case proving the hippocampus is necessary for declarative consolidation**
Korsakoff syndrome	Thiamine (B1) deficiency, classically chronic alcohol use; damage to mammillary bodies and dorsomedial thalamus (and prefrontal cortex)	**Anterograde and retrograde amnesia with confabulation; preceded by Wernicke encephalopathy (ophthalmoplegia, ataxia, confusion)**
Alzheimer disease	Entorhinal and hippocampal neurofibrillary tangles and amyloid; degeneration begins in medial temporal lobe	Early **episodic** anterograde loss; semantic affected more than episodic over time; procedural memory relatively spared early
Vascular / PD / Lewy body dementia	Strategic infarcts; subcortical and Lewy-body pathology	Memory pattern depends on territory; procedural and remote memory often spared early relative to declarative

CONDITION	LESION / MECHANISM	MEMORY SIGNATURE
Transient global amnesia	Transient hippocampal (CA1) dysfunction, often diffusion-restricting	Abrupt, isolated, self-limited (under 24 h) anterograde amnesia with repetitive questioning, full recovery
Dissociative (psychogenic) amnesia	No structural lesion; psychological, stress-related (ICD-11 6B61; DSM-5-TR Dissociative Amnesia)	**Typically retrograde loss of autobiographical and often personal-identity information with *preserved new learning*, the mirror image of organic amnesia**

The amnesia comparison the long-case and viva return to. The organic-versus-dissociative discriminator is the direction: organic amnesias spare old and block new (anterograde); dissociative amnesia blocks old autobiographical material yet preserves new learning.

HOLD THIS

Organic amnesia blocks new learning and spares the old (anterograde); dissociative amnesia loses old autobiographical material yet preserves new learning. H.M. is hippocampal, Korsakoff is diencephalic.

INDIA CONTEXT

Wernicke-Korsakoff is under-recognised and under-treated on Indian wards. With the country's high burden of alcohol use disorder, any malnourished or alcohol-dependent patient with confusion warrants **parenteral thiamine before glucose** (a glucose load without thiamine can precipitate Wernicke encephalopathy). Confabulation in a recovering drinker is Korsakoff until proven otherwise. Anti-NMDA-receptor encephalitis is an increasingly diagnosed young-adult mimic of acute psychosis and should be screened for in atypical first episodes with seizures, autonomic instability or movement disorder.

COMMON TRAP

Do not pin Korsakoff amnesia on the hippocampus. The lesions are **diencephalic**: the mammillary bodies and the anterior and dorsomedial thalamic nuclei (the Papez and extended limbic circuit). H.M.'s amnesia is hippocampal; Korsakoff's is diencephalic. Both produce a dense anterograde amnesia, but the structures, and the answer, differ.

19 · Synaptic transmission and neuroplasticity

Transmission in six steps. An action potential reaches the terminal, opens voltage-gated Ca^{2+} channels, Ca^{2+} triggers vesicle fusion and neurotransmitter release, the transmitter crosses the cleft and binds post-synaptic receptors (ionotropic, fast, ligand-gated channels; or metabotropic, slower, G-protein-coupled), and the signal is terminated by reuptake (transporters), enzymatic degradation or diffusion. Most psychotropics act on one of these nodes.

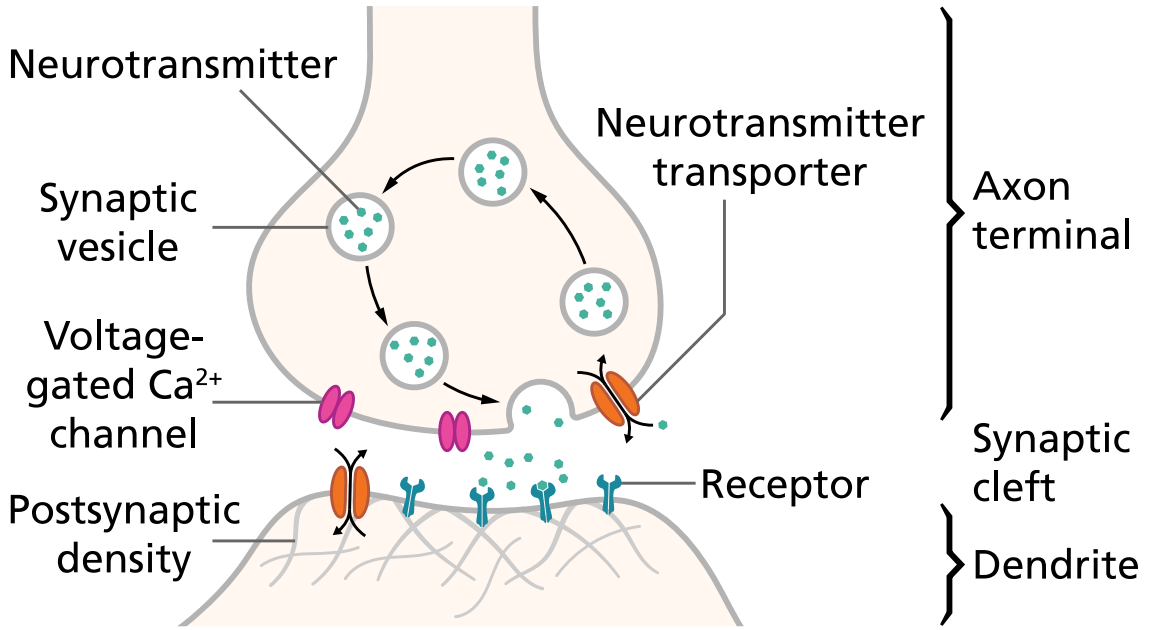


Image: Thomas Splettstoesser (scistyle.com), CC BY-SA 4.0, via Wikimedia Commons

Fig 1.25 The chemical synapse. An action potential opens voltage-gated Ca^{2+} channels, vesicles fuse and release transmitter into the cleft, which binds post-synaptic receptors before transporters and enzymes clear it. Almost every psychotropic acts at one of these nodes, which is why this single picture sits behind most of pharmacology.

Neuroplasticity is the brain's capacity to remodel. Forms to know: synaptic (LTP and its opposite, long-term depression, LTD), structural (dendritic spine and synapse turnover), and adult **neurogenesis**, confined mainly to the dentate gyrus of the hippocampus and the subventricular zone.

KEY POINT: THE NEUROTROPHIC HYPOTHESIS

Chronic stress and depression reduce **BDNF** (brain-derived neurotrophic factor) and hippocampal neurogenesis; antidepressants, exercise and ECT raise serum BDNF and restore it,[10] on a timescale that fits the delayed onset of antidepressant effect. **Ketamine** acts faster by a related route: NMDA-related disinhibition drives a glutamate surge, AMPA and mTOR signalling and rapid synaptogenesis. This is the single most testable bridge between molecular plasticity and clinical psychiatry.

HOLD THIS

Chronic stress lowers BDNF; antidepressants, exercise and ECT raise it, on a timescale matching the therapeutic lag. The monoamine and neurotrophic hypotheses are upstream and downstream of one pathway, not rivals.

19.1 Chemical transmission, dissected step by step

The summary in the opening paragraph collapses an entire molecular sequence into one sentence. Examiners reward the candidate who can unpack it node by node, because every node is a drug target. The human brain runs roughly **86 billion neurons** (Caire 2023), each carrying anywhere from a few to hundreds of thousands of synaptic contacts, and the chemical synapse is the dominant connection type in the mammalian CNS. Three numbers anchor the whole topic

and are worth memorising: the cleft is less than **50 nm** wide, transmitter crosses it in microseconds, yet the full *synaptic delay* (presynaptic current to postsynaptic response) is **0.5 to 1.0 ms**, the delay being dominated not by diffusion but by the calcium-triggered fusion step.

1. Action potential invades the terminal

Depolarisation propagates down the axon and reaches the presynaptic bouton, depolarising its membrane.

2. Voltage-gated Ca^{2+} channels open

P/Q-type and N-type channels clustered at the **active zone** open; Ca^{2+} floods in down a steep electrochemical gradient, producing a brief, highly localised calcium microdomain immediately beneath the docked vesicles.

3. Ca^{2+} triggers fusion via the SNARE machinery

This is the rate-limiting, delay-generating step. See 13.2.

4. Transmitter crosses the cleft and binds receptors

Ionotropic (fast, ligand-gated channels) or metabotropic (slow, G-protein-coupled). See 13.3.

5. Postsynaptic integration

EPSPs and IPSPs sum spatially and temporally at the axon hillock; the neuron fires or does not.

6. Signal termination

Reuptake, enzymatic degradation or diffusion. See 13.4.

Quantal release. Transmitter is not released as a continuous stream but in discrete packets, each corresponding to the contents of a single vesicle: the **quantum**. Katz's quantal hypothesis (foundational, from the neuromuscular junction) holds that the miniature endplate potential (the "mini") is the postsynaptic response to one spontaneously fusing vesicle, and that an evoked response is an integer multiple of that unit. At central glutamatergic synapses the same logic applies, though probability of release per active zone is low (Lisman 2007). Small-molecule transmitters (glutamate, GABA, acetylcholine, monoamines) are packaged in *small clear-core vesicles*; neuropeptides travel in large dense-core vesicles and, importantly, cannot be recovered by reuptake, so they must be degraded.

> ♡ CLINICAL ANCHOR
>
> The calcium-trigger step is hijacked by two classic toxidromes. **Lambert-Eaton myasthenic syndrome** is an autoantibody attack on presynaptic *P/Q-type voltage-gated calcium channels*, so insufficient calcium enters and acetylcholine release fails (weakness that improves with repetitive activity as calcium accumulates). **Botulinum toxin** cleaves SNARE proteins (see 13.2) and abolishes release entirely. Both teach the same lesson: no calcium-driven fusion, no transmission, however healthy the postsynaptic receptor.

19.2 The SNARE complex and the vesicle cycle

Membrane fusion is catalysed by the **SNARE complex** (soluble N-ethylmaleimide-sensitive factor attachment protein receptors). The three core proteins are **syntaxin-1** and **SNAP-25** on the target (presynaptic plasma) membrane, the t-SNAREs, and **synaptobrevin-2** (also called VAMP) on the vesicle membrane, the v-SNARE. As these coil together into a tight four-helix

bundle they zipper the two membranes into contact (Sudhof 2013). The calcium sensor that converts a calcium signal into fusion is *synaptotagmin-1*; when calcium binds its C2 domains it triggers the final fusion-pore opening, which is why the calcium-to-fusion conversion, not diffusion, sets the synaptic delay.

TOXIN	MOLECULAR TARGET	CLINICAL PICTURE
Botulinum toxin (A,C,E)	**Cleaves SNAP-25 / syntaxin**	Flaccid paralysis; therapeutic in dystonia, spasticity, cosmetic use
Botulinum toxin (B,D,F,G)	**Cleaves synaptobrevin (VAMP)**	Flaccid paralysis
Tetanus toxin	**Cleaves synaptobrevin in inhibitory interneurons**	Spastic paralysis (blocks GABA/glycine release)

Why the same enzymatic family (clostridial proteases all targeting SNAREs) produces opposite clinical syndromes: botulinum disables excitatory neuromuscular release (flaccid), tetanus disables spinal inhibitory release (spastic). A favourite single-best-answer discriminator.

RULE **Both botulinum and tetanus cleave SNAREs, but at opposite synapses: botulinum blocks excitatory neuromuscular release (flaccid), tetanus blocks spinal inhibitory release (spastic).**

TRAP Saying acetylcholine is cleared by reuptake. It is terminated by **enzymatic degradation** (acetylcholinesterase); only the choline is recaptured. The monoamines and amino acids use reuptake.

After fusion the vesicle membrane is recovered and refilled. The classic *clathrin-mediated endocytosis* pathway, alongside faster kiss-and-run modes, retrieves vesicle components; transmitter is reloaded by vesicular transporters (VGLUT for glutamate, VMAT for monoamines, VGAT for GABA) using the proton gradient generated by a vesicular H^+-ATPase. **Reserpine** irreversibly blocks VMAT, depleting monoamines, the historical observation that seeded the monoamine hypothesis of depression.

MNEMONIC

"SNARE catches Sy-SNAP-Sy"

The three core SNAREs: **Sy**ntaxin-1, **SNAP**-25, **Sy**naptobrevin-2. Two on the target membrane (syntaxin, SNAP-25), one on the vesicle (synaptobrevin). The calcium sensor sitting on top is synapto**tagmin** (tag = the one that "tags" calcium).

19.3 Electrical synapses and gap junctions

A minority of CNS connections are **electrical synapses**: the pre- and postsynaptic membranes sit far closer than in a chemical synapse and are bridged by channels built from **connexin** proteins (six connexins forming a connexon, two apposed connexons forming a gap-junction channel). Ions and small molecules pass directly, so transmission is near-instantaneous, bidirectional and immune to the 0.5 to 1.0 ms chemical delay (Caire 2023). They dominate where speed and synchrony matter: escape reflexes, and rhythmic, synchronised firing of inhibitory

interneuron networks, which is one substrate of cortical gamma oscillations relevant to the dysconnectivity models of schizophrenia.

FEATURE	CHEMICAL SYNAPSE	ELECTRICAL SYNAPSE
Bridge	Neurotransmitter across <50 nm cleft	**Connexin gap junction, direct ionic flow**
Delay	**0.5 to 1.0 ms**	Essentially none
Direction	Unidirectional	Usually bidirectional
Plasticity / amplification	High; can amplify and modulate	Low; largely passive
Main role	Computation, learning, drug target	Synchrony, speed

The five discriminators that let you place any described synapse into the correct class. Note that "almost all psychotropics act here" applies only to the chemical column.

19.4 Receptor superfamilies: ionotropic versus metabotropic

Once transmitter binds, the postsynaptic neuron responds through one of two receptor logics.

- **Ionotropic (ligand-gated ion channels).** The transmitter binding site and the ion pore are in the same protein, so binding opens the channel **directly**. Response is fast (a few milliseconds) and brief. Families: nicotinic acetylcholine receptors, ionotropic glutamate receptors (*AMPA, NMDA, kainate*), GABA-A and glycine receptors (Cl^- channels, inhibitory), and 5-HT3 (the only ionotropic serotonin receptor, exploited by ondansetron).
- **Metabotropic (G-protein-coupled receptors).** Binding activates a G-protein that drives a **second-messenger cascade** (cAMP, IP3, DAG), eventually phosphorylating channels or altering gene transcription. Response is slow (seconds to minutes) and long-lasting. Families: all dopamine (D1 to D5), all adrenergic, most serotonin (5-HT1, 5-HT2 and others), muscarinic acetylcholine, GABA-B, and metabotropic glutamate (mGluR) receptors.

> **PEARL**
>
> For every neurotransmitter, know which receptors are ionotropic versus metabotropic, because this predicts the speed and reversibility of a drug's action. Glutamate and acetylcholine are the two transmitters that have **both** kinds: glutamate (AMPA/NMDA ionotropic; mGluR metabotropic) and acetylcholine (nicotinic ionotropic; muscarinic metabotropic). GABA likewise splits (GABA-A ionotropic; GABA-B metabotropic). The monoamines dopamine and noradrenaline are **purely metabotropic**; serotonin is metabotropic *except* 5-HT3.

19.5 Signal termination, the third pharmacological node

The signal must be switched off, and the three mechanisms map onto three drug classes.

Reuptake

Plasma-membrane transporters recover small-molecule transmitter into the presynaptic neuron or into glia. This is recyclable and energetically cheap. Only small-molecule transmitters are recovered; neuropeptides cannot be (Caire 2023). Glutamate is taken up largely by *glia*, converted to glutamine by glutamine synthetase, and shuttled back (the glutamate-glutamine cycle), a design that limits

glutamate excitotoxicity. Transporter blockade is the mechanism of SSRIs (SERT), SNRIs (SERT plus NET), the noradrenaline transporter blocker atomoxetine, and cocaine (DAT).

Enzymatic degradation

Monoamine oxidase (MAO): MAO-A preferentially deaminates serotonin, noradrenaline and adrenaline; both isoforms metabolise dopamine and tyramine; MAO-B also handles phenethylamine. MAO-A inhibition underlies antidepressant action and the tyramine "cheese reaction"; selective MAO-B inhibition (selegiline, rasagiline) treats Parkinson disease. **COMT** degrades catecholamines and is inhibited by entacapone in Parkinson therapy. **Acetylcholinesterase** hydrolyses acetylcholine in the cleft and is the target of donepezil, rivastigmine and galantamine in Alzheimer dementia.

Diffusion

Transmitter simply diffuses away from the cleft into nearby capillaries, lowering concentration. The slowest and least specific route, and not a meaningful drug target.

> ⚠ COMMON TRAP
>
> Acetylcholine is terminated by **enzymatic degradation, not reuptake**. There is no plasma-membrane "acetylcholine transporter" pulling intact ACh back; instead acetylcholinesterase splits it to choline plus acetate, and only the *choline* is recaptured by a choline transporter for resynthesis. Writing "ACh is cleared by reuptake" loses the mark. By contrast the monoamines and amino acids (5-HT, NA, DA, glutamate, GABA, glycine) are cleared primarily by reuptake.

19.6 Forms of neuroplasticity

Neuroplasticity is the capacity of the nervous system to change its structure, function or connections in response to intrinsic or extrinsic stimuli (Puderbaugh 2023). The term traces to William James (1890), with "neural plasticity" credited to Konorski (1948) and popularised by Hebb (1949), whose rule, "cells that fire together wire together," remains the conceptual spine. It is convenient to separate the levels at which the brain remodels.

- **Synaptic plasticity.** Experience-dependent change in the strength of existing connections. The canonical exemplar is **long-term potentiation (LTP)**, first shown by Bliss and Lomo (1973) in rabbit hippocampus: brief high-frequency stimulation of presynaptic fibres produced a lasting increase in the postsynaptic response. The mirror process is **long-term depression (LTD)**. Mechanistically, classic CA1 LTP is NMDA-receptor-dependent, with calcium entry driving AMPA-receptor insertion (see the existing CA1 / mossy-fibre trap in this document).
- **Spike-timing-dependent plasticity (STDP).** A refinement of Hebb: whether a synapse strengthens or weakens depends on the millisecond *order* of pre- and postsynaptic spikes. Pre-before-post potentiates; post-before-pre depresses.
- **Structural plasticity.** Physical remodelling: dendritic spine growth and pruning, axonal sprouting, synaptogenesis. After injury this unfolds in three epochs, the first 48 hours (cell death, recruitment of secondary networks), the following weeks (shift from inhibitory to excitatory tone, new connections), and weeks to months (axonal sprouting and reorganisation) (Puderbaugh 2023).

- **Adult neurogenesis.** Generation of new neurons in the adult brain. The two candidate human sites are the subgranular zone of the hippocampal dentate gyrus and the subventricular zone of the lateral ventricles. Against Cajal's "harsh decree" of no new adult neurons, Altman found neurogenesis in adult rats; in humans the evidence remains **contested** (Puderbaugh 2023), which is the examiner-safe position to state.
- **Metaplasticity and homeostatic plasticity.** "Plasticity of plasticity": prior activity sets the threshold for future LTP or LTD (metaplasticity), while homeostatic mechanisms (for example synaptic scaling) keep overall network activity within bounds so that runaway potentiation does not saturate the circuit.

⚠ COMMON TRAP

Plasticity is not always benign. **Maladaptive plasticity** is the same machinery producing pathology: phantom limb pain and use-dependent focal dystonia (writer's cramp) both involve aberrant remapping of primary sensory or motor cortex. Do not equate "plastic" with "good".

19.7 Neurotrophins and the neurotrophic hypothesis of depression

Neurotrophins are secreted growth factors that govern neuronal survival, differentiation and synaptic plasticity: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophins 3 and 4/5. In psychiatry, **BDNF acting at its TrkB receptor** is the central player. TrkB is a receptor tyrosine kinase; BDNF binding activates downstream cascades (including the mTOR pathway) that drive dendritic-spine formation and the synthesis of synaptic proteins, the molecular substrate of LTP.

The **neurotrophic hypothesis of depression** proposes that chronic stress and elevated glucocorticoids lower hippocampal and prefrontal BDNF, contributing to the dendritic atrophy and reduced hippocampal volume seen in depression, while effective treatment restores BDNF and synaptic connectivity. The model is attractive because it unifies several observations: stress lowers BDNF and is depressogenic; conventional antidepressants raise BDNF, but only after weeks, paralleling their delayed clinical onset; exercise, environmental enrichment and several neuromodulators (notably dopamine) raise BDNF and promote plasticity (Puderbaugh 2023). A common functional polymorphism, the BDNF Val66Met variant, alters activity-dependent BDNF secretion and is widely studied as a moderator of plasticity and treatment response.

💡 PEARL

The neurotrophic hypothesis is the most examinable explanation for the **therapeutic lag** of antidepressants. Monoamine reuptake is blocked within hours, yet mood lifts over two to four weeks; the gap is filled by the slower downstream rise in BDNF and the synaptic remodelling it drives. Frame the monoamine and neurotrophic hypotheses as upstream and downstream of the same pathway, not as rivals.

19.8 Ketamine and rapid plasticity

Ketamine reframed depression from a slow neurotrophic disorder to one in which connectivity can be restored within hours. It is a non-competitive **NMDA-receptor antagonist**, yet its antidepressant action is best explained downstream of the receptor: a burst of glutamate release activates AMPA receptors, triggering BDNF release and rapid **mTOR-dependent synaptogenesis** in the prefrontal cortex, reversing stress-induced spine loss within hours. This is the same BDNF-TrkB-mTOR axis as conventional antidepressants, but engaged in a single dose rather than over weeks.

Clinically, **esketamine** (the S-enantiomer, intranasal) is regulatory-approved for treatment-resistant depression and for depression with acute suicidal ideation, administered under monitored conditions because of dissociation, transient blood-pressure rise and abuse potential. Through 2026 the field has moved toward refining who benefits and how to sustain response, alongside interest in agents that engage rapid plasticity without the dissociative and abuse liabilities. This subtopic is also where neuroplasticity stops being abstract for the exam: it is the mechanistic bridge between basic synaptic science and a modern, life-saving intervention.

RULE **Ketamine is an NMDA antagonist, but its antidepressant action is downstream: a glutamate surge drives AMPA, BDNF and mTOR-dependent synaptogenesis within hours.**

Bliss and Lomo (1973) LANDMARK

Design. Electrophysiology in anaesthetised rabbit hippocampus; brief high-frequency tetanic stimulation of the perforant path to dentate granule cells. **Finding.** A long-lasting increase in synaptic efficacy outlasting the stimulus, named long-term potentiation. **Why it matters.** Gave synaptic plasticity its defining experimental model and the cellular candidate for memory; every later plasticity concept, including the ketamine story, descends from it.

19.9 Clinical relevance across disorders

Pulling the threads together, the synapse is where psychiatric pathology and pharmacology meet. The points below map each node to the disorders examiners pair with it.

- **Depression.** Monoamine reuptake (SSRI/SNRI mechanism) and the downstream neurotrophic axis (BDNF-TrkB-mTOR) explaining therapeutic lag; ketamine and esketamine as the rapid-plasticity exemplar.
- **Schizophrenia.** Dopamine (metabotropic) at the synapse is the antipsychotic target; the NMDA-hypofunction model and gap-junction-coupled interneuron synchrony connect glutamate and gamma-oscillation dysconnectivity to symptoms.
- **Alzheimer dementia.** Acetylcholinesterase inhibition (donepezil and others) prolongs cholinergic signalling; memantine, an NMDA antagonist, counters glutamate excitotoxicity, the same receptor ketamine blocks.
- **Parkinson disease.** Termination enzymes as targets, MAO-B inhibitors (selegiline, rasagiline) and COMT inhibitors (entacapone), prolong dopaminergic signalling.

- **Anxiety, insomnia, epilepsy.** GABA-A (ionotropic) potentiation by benzodiazepines and related agents; GABA accounts for roughly 40% of the brain's inhibitory processing (Caire 2023).
- **Movement and pain syndromes.** Maladaptive structural plasticity in dystonia and phantom limb pain; therapeutic SNARE disruption by botulinum toxin in dystonia and spasticity.

INDIA CONTEXT

SSRIs, SNRIs, acetylcholinesterase inhibitors and the dopaminergic adjuncts above are all on the WHO and Indian essential-medicine landscape and are routinely available, so the synaptic mechanisms here are not academic trivia but the everyday rationale for ward prescribing. Esketamine and intravenous ketamine for treatment-resistant depression remain specialist, access-limited and used under monitored protocols in Indian practice, a realistic caveat worth stating rather than implying routine availability.

20 · Evoked potentials and event-related potentials

Averaging the EEG time-locked to a stimulus extracts tiny, reproducible voltage deflections. Early (exogenous) components index sensory pathways; later (endogenous) components index cognition and are the ones psychiatry cares about.

COMPONENT	LATENCY	PARADIGM / MEANING	PSYCHIATRIC FINDING
P300 (P3b)	~300 ms (250-400)	Oddball task; attention and context updating	Reduced amplitude and prolonged latency in schizophrenia; also dementia, alcohol
Mismatch negativity (MMN)	~100-250 ms	Pre-attentive change detection; NMDA-dependent	Robustly reduced in schizophrenia; a leading biomarker / endophenotype
P50	~50 ms	Paired-click sensory gating	Impaired gating in schizophrenia (and relatives)
N400	~400 ms	Semantic incongruity	Altered in thought disorder / schizophrenia
CNV	Slow, pre-stimulus	Expectancy / anticipation	Altered in anxiety, attention disorders

Tab 1.5 · Key event-related potentials. P300 and MMN (shaded) are the two the exam returns to.

HOLD THIS

Exogenous potentials test wiring; endogenous potentials test computation. The two psychiatry lives by are the NMDA-dependent MMN and the context-updating P300, both reduced in schizophrenia and both present in unaffected relatives.

20.1 Principle: signal averaging and the exogenous-endogenous divide

An evoked potential is buried in the ongoing EEG at a signal-to-noise ratio so poor that a single trial shows nothing. The trick is **signal averaging**: the same stimulus is delivered tens to hundreds of times, the EEG epochs are aligned to stimulus onset, and the segments are summed and divided. Activity that is genuinely *time-locked* (phase-locked) to the stimulus adds coherently and survives; the random background EEG, being unrelated to stimulus timing, averages towards zero. Because uncorrelated noise falls as the square root of the number of trials, doubling the count does not halve the noise, which is why robust components need many repetitions.

The naming convention. Components are labelled by polarity and latency: P for a positive-going deflection, N for negative, followed by the approximate peak latency in milliseconds (P300, N400) or simply the ordinal position (N1, P2). Polarity at the scalp is a convention only and depends on the reference and the orientation of the underlying cortical generator, so a "negativity" is not pathological by name alone.

Exogenous (sensory) components

Early, short-latency waves (roughly the first 100 ms) whose amplitude and latency track the **physical properties** of the stimulus (intensity, modality, rate) and the integrity of the sensory pathway. They are obligatory: they appear whether or not the subject attends. These are the clinical neurophysiologist's tools (VEP, BAEP, SSEP).

Endogenous (cognitive) components

Later waves (beyond about 200 ms) that depend on the **psychological context**, the subject's task, attention, expectancy and the meaning of the stimulus, not on its physical form. These are the event-related potentials (ERPs) that psychiatry uses as cognitive and endophenotype markers.

> PEARL
>
> The single dividing question the examiner wants: does the component change if the stimulus stays identical but the subject's task or attention changes? If yes, it is endogenous (P300, N400). If it tracks only stimulus physics, it is exogenous (BAEP waves). Latency alone does not classify a wave; dependence on context does.

20.2 Sensory evoked potentials: VEP, BAEP, SSEP

These three exogenous potentials test the afferent sensory pathways and are the neurologist's bedside electrophysiology. Psychiatry meets them mainly as differentials (demyelination, brainstem lesions, functional or non-organic complaints) and in intensive-care or anaesthetic monitoring.

POTENTIAL	STIMULUS	PATHWAY TESTED	KEY CLINICAL USE
VEP	Pattern-reversal checkerboard (or flash)	Retina to occipital (calcarine) cortex via optic nerve and radiation	Optic neuritis and multiple sclerosis: delayed **P100** latency with preserved waveform signals demyelination of the optic nerve
BAEP / BAER	Repetitive clicks	Cochlea to inferior colliculus along the auditory brainstem	Acoustic neuroma, brainstem lesions, brainstem death, neonatal and infant hearing screening
SSEP	Electrical pulse to a peripheral nerve (median, posterior tibial)	Dorsal column to medial lemniscus to thalamus to primary sensory cortex	Spinal cord and dorsal-column integrity; intraoperative monitoring; prognostication after hypoxic coma

The three sensory evoked potentials, the pathway each interrogates, and the clinical question each answers.

The BAEP deserves a memory hook because the wave-to-generator mapping is examinable. Classically **five to seven peaks** occur within 10 ms of the click; the durable teaching is that wave *I* arises from the distal eighth nerve, wave *II* from the cochlear nucleus, wave *III* from the superior olivary complex, wave *IV* from the lateral lemniscus, and wave *V* (the most robust, used for hearing thresholds) from the inferior colliculus. The VEP P100 is the most reliable single index of optic-nerve conduction in suspected multiple sclerosis.

MNEMONIC

ECOLI (BAEP waves I to V)

Eighth nerve (I), **C**ochlear nucleus (II), **O**livary complex, superior (III), **L**ateral lemniscus (IV), **I**nferior colliculus (V). Reading rostrally up the brainstem as the number rises.

20.3 The P300 in full: P3a and P3b

The P300 is the workhorse cognitive ERP and the existing Tab 1.5 lists its headline. The depth the exam rewards is that "P300" is not one wave but two functionally separable subcomponents, dissociated by Squires and colleagues.

P3b

The classic parietocentral positivity, maximal over the parietal midline, elicited when an attended, task-relevant *target* appears in an oddball stream. It indexes **context updating** of working memory and the conscious allocation of attention to a meaningful, expected-but-rare event. This is the wave meant when "P300" is used unqualified.

P3a

An earlier, frontocentral positivity (often termed the "novelty P3") elicited by an **unexpected, distracting novel** stimulus that the subject was not instructed to attend. It indexes the automatic,

bottom-up **orienting response** and involuntary capture of attention, and depends on a frontal-hippocampal network rather than the temporoparietal generators of the P3b.

Mechanistically the P3b is best understood through the **context-updating model** (Donchin and Coles 1988): when an incoming stimulus mismatches the current internal model of the environment, working memory is revised, and the P300 indexes that revision. Amplitude scales with how improbable and how task-relevant the stimulus is; latency indexes the speed of stimulus evaluation and classification, largely independent of motor response time, which is why P300 latency is a cleaner cognitive-speed measure than reaction time. The generators are distributed (temporoparietal junction, prefrontal cortex, hippocampus and a locus-coeruleus noradrenergic contribution to the orienting variant), so the P300 is a network signal, not a single nucleus.

20.4 Mismatch negativity and the predictive-coding frame

The mismatch negativity (MMN) is the ERP psychiatry now cares about most, because it joins a robust clinical deficit to a clean molecular mechanism. It is the negative deflection (peaking roughly 100 to 250 ms frontocentrally) generated whenever the auditory system detects a deviant sound against a background of repeated standards, in the oddball paradigm. Its defining property is that it is **pre-attentive**: it is recorded while the subject reads or watches a silent video and attends elsewhere, so it indexes an automatic, memory-based comparison rather than effortful attention (Michie et al. 2002). It reflects a short-lived sensory (echoic) memory trace and the brain's automatic detection of a violation of that trace.

The mechanism is the examinable core. MMN generation is **NMDA-receptor dependent**: NMDA antagonists such as ketamine and phencyclidine reduce MMN in healthy volunteers, reproducing the schizophrenia deficit and tying the marker to the glutamatergic-hypofunction model of psychosis. In the predictive-coding account, repeated standards build a prediction; a deviant generates a **prediction error** that propagates up the cortical hierarchy, and the MMN is the scalp signature of that error signal. Work in the roving-stimulus paradigm localises the relevant pathology to **supragranular (superficial) cortical layers** of the superior temporal cortex, where impaired NMDA-dependent plasticity weakens the encoding and propagation of prediction errors to higher modules, an account that explains why MMN deficits correlate with broader cognitive impairment in schizophrenia.

RULE **Mismatch negativity is pre-attentive and NMDA-receptor dependent.** Ketamine reproduces the schizophrenia deficit in healthy volunteers, tying the marker to the glutamate-hypofunction model.

TRAP Conflating the two gating stories. **P50** is paired-click sensory gating (alpha-7 nicotinic); **MMN and P300** are oddball deviance-detection and context-updating (NMDA). Different paradigm, receptor and wave.

Roving-paradigm confirmatory study (Schizophr. Res. group) LANDMARK

Design. MMN "memory-trace effect" (response growing with the number of standard repetitions) compared across schizophrenia, bipolar disorder, probable Alzheimer's disease and controls. **Finding.** Attenuation of the MMN memory-trace effect and its correlation with memory impairment was present **only in the schizophrenia group**, not in bipolar or Alzheimer's. **Why it matters.** It argues MMN is a relatively *specific* marker of the supragranular NMDA-plasticity pathology of schizophrenia, and a sensitive index of the early prodromal phase, well suited to testing cognition-enhancing agents.

20.5 N400, P50 gating, CNV, error-related negativity and N170

Beyond the two flagship waves, a handful of ERPs recur in viva and theory because each maps to a different cognitive operation and a different disorder.

- **N400.** A centroparietal negativity around 400 ms elicited by **semantic incongruity** (the classic "He spread the warm bread with socks" violation). It indexes the effort of integrating a word into its semantic context: amplitude rises when a word is unexpected or hard to integrate. In schizophrenia with formal thought disorder the normal modulation is altered (reduced context benefit, abnormal semantic priming), making N400 a probe of disordered language and loosened associations.
- **P50 sensory gating.** Measured with the **paired-click paradigm**: two identical clicks 500 ms apart. In health the P50 response to the second click is markedly suppressed (the S2/S1 ratio is low), reflecting inhibitory **gating** of redundant input. Schizophrenia patients, and many of their unaffected relatives, fail to suppress the second response (high S2/S1 ratio). The deficit is linked to the **alpha-7 nicotinic receptor** and the *CHRNA7* locus, part of why patients smoke heavily (transient nicotinic normalisation of gating).
- **Contingent negative variation (CNV).** A slow negative shift that develops *between* a warning stimulus and an imperative stimulus that calls for a response. It indexes **expectancy, anticipation and response preparation** and is sensitive to attention and arousal; it is altered in anxiety and in attention disorders.
- **Error-related negativity (ERN/Ne).** A sharp frontocentral negativity peaking within about 100 ms **after an erroneous response**, generated in the **anterior cingulate cortex**, indexing performance monitoring and error detection. The ERN is **enhanced** in obsessive-compulsive disorder and anxiety (over-active error monitoring) and tends to be **blunted** in conditions of impulsivity and externalising pathology, making it a transdiagnostic marker of the monitoring system.
- **N170.** An occipitotemporal negativity around 170 ms that is **face-selective**, generated near the fusiform and superior temporal face areas. It indexes the structural encoding of faces and is attenuated or delayed in **autism spectrum disorder** and in schizophrenia, dovetailing with social-cognition deficits.

COMPONENT	OPERATION INDEXED	GENERATOR EMPHASIS	SIGNATURE DISORDER LINK
N400	Semantic integration	**Temporal language cortex**	Thought disorder in schizophrenia
P50 gating	Inhibitory sensory gating	**Hippocampal-CA3, nicotinic**	Schizophrenia and relatives (CHRNA7)
ERN	Error / performance monitoring	**Anterior cingulate cortex**	OCD and anxiety (enhanced)
N170	Face structural encoding	**Fusiform face area**	Autism, schizophrenia (attenuated)

Mapping each cognitive ERP to its operation, its main generator, and the disorder it flags, the comparison the viva tests.

⚠ COMMON TRAP

Do not conflate the two schizophrenia "gating" stories. **P50** is sensory gating in the paired-click paradigm (alpha-7 nicotinic, S2/S1 ratio). **MMN and P300** are deviance-detection and context-updating in the oddball paradigm (NMDA-dependent). Different paradigm, different receptor, different wave. Examiners deliberately swap them.

20.6 Clinical and endophenotype use across disorders

The reason ERPs occupy a basic-sciences paper at all is that they behave as candidate **endophenotypes**: heritable, trait-like, state-independent intermediate markers that sit between genes and the clinical syndrome and are detectable in unaffected relatives. The two strongest in psychiatry are the schizophrenia pair, MMN and P300.

Schizophrenia, P300. The reproducible finding is **reduced P300 amplitude and prolonged P300 latency**, first reported by Roth and Cannon (1972) and confirmed across decades. Crucially the amplitude reduction is also seen in **siblings and offspring** of probands, supporting endophenotype status (Frangou et al. 1997; Turetsky et al. 2000). A nuance worth carrying: amplitude reduction may be partly state-sensitive and can improve with antipsychotic treatment, whereas latency is more trait-like.

Schizophrenia, MMN. MMN amplitude is **robustly reduced**, the reduction is present in recent-onset patients, in clinically unaffected family members and in children at high risk, and reduced MMN in clinical-high-risk individuals **predicts conversion to psychosis**, which is why it is among the most promising prodromal biomarkers and a target-engagement readout for NMDA-modulating drugs. A teaching subtlety from family studies: in some cohorts MMN amplitude separates patients from controls and even relatives from controls, yet does not always show strong measurable *familial influence* within a single family design (Sevik et al. 2011), a reminder that "abnormal in relatives" and "demonstrably heritable in this sample" are not the same claim.

Schizophrenia, P50. Failure of P50 suppression in the paired-click paradigm is found in patients and roughly half of first-degree relatives, tied to *CHRNA7*, making it a third candidate endophenotype anchored to nicotinic-cholinergic gating.

Dementia, P300. P300 latency **prolongs with normal ageing** and prolongs further in dementia, broadly tracking cognitive decline. It is sensitive but not specific (it lengthens in many causes of slowed processing), so it is an adjunctive cognitive-speed index rather than a diagnostic test, and it cannot reliably separate dementia subtypes on its own.

Alcohol-dependence risk, P300. A landmark behaviour-genetics finding: reduced P300 amplitude is seen not only in alcohol-dependent individuals but in their **young, alcohol-naive sons** who are at high familial risk (the Begleiter and Porjesz work). This positions reduced P300 as a marker of an inherited **disinhibitory or externalising** diathesis that precedes and predicts later substance use, rather than a consequence of drinking. It is one of the cleanest demonstrations in psychiatry that an ERP can be a trait vulnerability marker.

HOLD THIS

Reduced P300 amplitude appears in the unaffected relatives of both schizophrenia and alcohol-risk pedigrees, marking an inherited disinhibitory diathesis. That "abnormal in relatives" is what makes it an endophenotype, not a symptom.

CLINICAL ANCHOR

If a stem asks for the ERP that is reduced in unaffected relatives across *both* schizophrenia and alcohol-risk pedigrees, the answer is the **P300 amplitude**, the prototype shared endophenotype of disinhibition. If it asks for the NMDA-dependent, pre-attentive marker that predicts conversion in the psychosis prodrome, the answer is the **MMN**.

PEARL

One sentence that ties the topic together: **exogenous potentials test wiring, endogenous potentials test computation**, and the two endogenous waves psychiatry lives by are the NMDA-dependent MMN (deviance and prediction error) and the context-updating P300 (attention and salience), both reduced in schizophrenia and both present in unaffected relatives, which is exactly what makes them endophenotypes rather than mere symptoms.

21 · Neuroinflammation and cytokines in psychiatry

The immune system is now a mainstream actor in psychiatric pathophysiology. Microglia (the brain's resident macrophages) and astrocytes release pro-inflammatory cytokines, and a measurable low-grade inflammatory state accompanies a subset of mood, psychotic and neurodegenerative disorders.

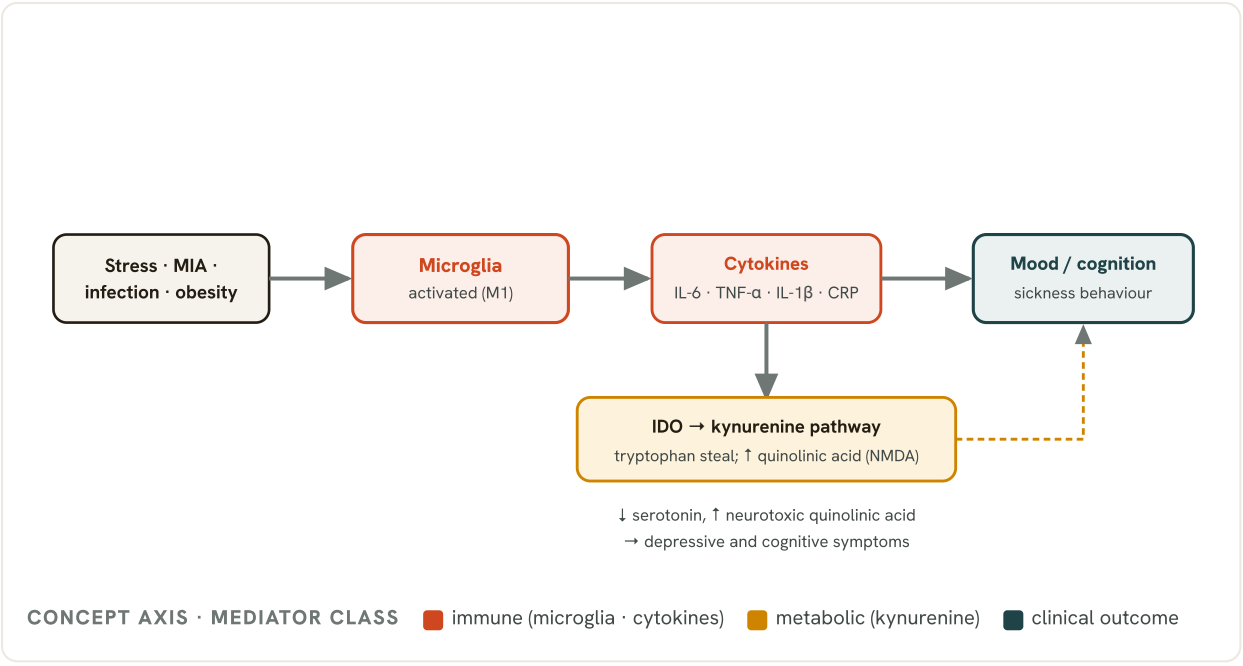


Fig 1.26 The inflammatory route to mood symptoms: peripheral and central immune activation drives cytokine release, which shunts tryptophan down the kynurenine pathway (less serotonin, more neurotoxic quinolinic acid) and produces sickness behaviour.

- **Depression.** Meta-analysis shows consistently elevated IL-6 and TNF-α[9] (with raised CRP); IL-1β findings are less consistent. This grounds the "cytokine hypothesis" and the overlap of inflammation with treatment resistance. Interferon-α therapy can induce depression, a natural experiment.
- **Schizophrenia and autism.** Maternal immune activation in pregnancy raises offspring risk; microglial and complement (C4) abnormalities are implicated in aberrant synaptic pruning.
- **Neurodegeneration.** Microglial priming and chronic neuroinflammation contribute to Alzheimer's and other dementias.
- **Treatment.** Anti-inflammatory augmentation (e.g. celecoxib, minocycline) improves depressive symptoms in pooled trials, but those trials are at high risk of bias,[12] so it is not yet routine; the field is moving toward inflammation-stratified trials.

HOLD THIS

IL-6 and TNF-alpha are the consistently raised cytokines in depression; IL-1-beta is variable. Inflammation shunts tryptophan down the kynurenine pathway, lowering serotonin and raising neurotoxic quinolinic acid.

21.1 Cellular players: microglia, astrocytes and the blood-brain barrier

The intro and Fig 1.26 give the headline circuit; what the exam rewards is knowing *which cell does what*, because the same cytokine produces opposite metabolites depending on which glial compartment it acts in. Three cellular players carry the story: microglia, astrocytes, and the neurovascular unit that gates traffic between blood and brain.

Microglia. The brain's resident macrophages, yolk-sac-derived and self-renewing, sit in a **ramified surveillant** state with fine processes that continuously extend and retract, clearing

apoptotic debris, pruning synapses and sampling the parenchyma. On a pathological stimulus (stress, infection, damage-associated molecular patterns) they retract processes, assume an amoeboid morphology and *polarise*. The classically activated **M1** phenotype releases pro-inflammatory IL-1beta, IL-6 and TNF-alpha plus reactive oxygen species and drives neurotoxicity; the alternatively activated **M2** phenotype secretes anti-inflammatory IL-10 and TGF-beta and promotes repair and resolution. The M1/M2 dichotomy is a teaching simplification (real states form a spectrum), but it is the version exams test. The therapeutic aim emerging in the literature is not to silence microglia (they are needed for pruning and circuit maintenance) but to shift the balance back toward the protective M2-like, homeostatic pole.

Astrocytes. The most numerous glia, they maintain the BBB, buffer extracellular potassium and clear synaptic glutamate through the EAAT transporters. Crucially for the kynurenine story, **astrocytes lack the enzyme kynurenine-3-monooxygenase (KMO)**, so they cannot make the neurotoxic branch; instead they convert kynurenine to the neuroprotective **kynurenic acid** via kynurenine aminotransferase (KAT). Microglia, which possess KMO, drive the opposite, neurotoxic branch toward quinolinic acid. This compartmentation (covered in detail in 15.3) is the single most testable mechanistic fact in this topic.

Blood-brain barrier and the neurovascular unit. M1 cytokines and reactive oxygen species disrupt tight junctions and adhesion molecules, making the BBB leaky, which amplifies neuroinflammation by admitting peripheral cytokines, lipopolysaccharide and immune cells. Endothelial cells constitutively produce kynurenic acid and pericytes produce picolinic acid; both ramp up kynurenine production under IFN-gamma and TNF-alpha. The barrier is also selective: only tryptophan, kynurenine and 3-hydroxykynurenine cross it readily (via the large neutral amino acid transporter), so the brain's neurotoxic load depends heavily on peripheral flux, a point developed in 15.3.

> **PEARL**
>
> "Surveillant, not resting." Microglia in the healthy brain are not idle: their processes are the most motile structures in the CNS, sampling the parenchyma constantly. Calling the baseline state "resting" is outdated; the exam-safe term is ramified or surveillant.

21.2 The cytokine model of depression: Maes, the macrophage theory and the inflammatory biomarkers

The existing bullet on depression names IL-6, TNF-alpha and CRP; here is the model behind those numbers and the names attached to it. The **macrophage theory of depression** (Smith 1991) proposed that excessive macrophage-derived monokines, chiefly IL-1, drive depressive symptoms. Maes and colleagues built this into the *inflammatory and neurodegenerative (cytokine) hypothesis*: depression is accompanied by a measurable activation of the inflammatory response system, with raised pro-inflammatory cytokines, acute-phase proteins and a lowered tryptophan availability. The model reframes a subset of depression as a low-grade, chronic inflammatory state rather than a purely monoaminergic deficit.

Consistently raised

IL-6 and TNF-alpha are the most reproducible findings across meta-analyses, accompanied by elevated C-reactive protein (CRP). These are the two cytokines to name first in any answer.

Less consistent

IL-1beta findings are mixed; do not overstate them. The honest exam line is "IL-6 and TNF-alpha consistently, IL-1beta variably".

Anti-inflammatory side

IL-4, IL-10 and TGF-beta oppose the pathway; IL-4 actively inhibits IDO induction.

The model explains several clinical observations that the monoamine theory cannot. Inflammation correlates with treatment resistance: high baseline CRP predicts poorer SSRI response and may predict better response to agents acting on glutamate or inflammation. A bidirectional loop ("stress to HPA axis to microglia to neuroinflammation to depression") links chronic stress, glucocorticoid priming of microglia and sustained NF-kappaB signalling, with the gut microbiome and lipopolysaccharide translocation feeding the peripheral arm. Mendelian randomisation now supports causality rather than mere correlation: each standard-deviation rise in kynurenine corresponds to roughly 1.4-fold higher odds of depression (Zong 2024), and IDO blockade prevents inflammation-induced depressive behaviour in animals, implying that kynurenine metabolite generation is a necessary step, not an epiphenomenon.

CYTOKINE	CLASS	DIRECTION IN DEPRESSION	EXAM NOTE
IL-6	Pro-inflammatory	**Consistently raised**	Anti-IL-6 (tocilizumab) helps depressive symptoms in inflammatory disease
TNF-alpha	Pro-inflammatory	**Consistently raised**	Infliximab helps only the high-CRP subgroup
IL-1beta	Pro-inflammatory	Variably raised	Central to macrophage theory; data less robust
CRP	Acute-phase protein	Raised	hs-CRP >5 mg/L marks the inflamed subtype
IL-10 / TGF-beta	Anti-inflammatory	Relatively reduced	M2 microglial output; resolution signals

The cytokine signature of depression: IL-6 and TNF-alpha are the reproducible pair, CRP the practical clinic marker, and the inflamed subtype (hs-CRP >5) is the one that responds to anti-inflammatory augmentation.

21.3 The kynurenine and IDO pathway in detail: the tryptophan steal and the quinolinic-versus-kynurenic balance

This is the mechanistic heart of the topic and the most heavily examinable sub-section. Under normal conditions more than 90 percent of dietary tryptophan is degraded down the kynurenine pathway rather than toward serotonin or melatonin. Inflammation pushes that flux harder and biases it toward neurotoxic end-products.

Step one, the diversion. Pro-inflammatory cytokines (IFN-gamma is the strongest inducer, with IFN-alpha, IL-1, IL-6, IL-18 and TNF-alpha contributing; IL-4 inhibits) up-regulate **indoleamine**

2,3-dioxygenase (IDO), the rate-limiting first enzyme, which converts tryptophan to kynurenine. The hepatic isoform *tryptophan 2,3-dioxygenase (TDO)* does the same job and is induced by IFN-gamma, cortisol and glucagon, linking the stress axis to the pathway. Because tryptophan is the precursor of serotonin, diverting it depletes serotonin synthesis: this is the **tryptophan steal**. The peripheral kynurenine-to-tryptophan (K/T) ratio is the standard biomarker of IDO activity, and more than 60 percent of the brain's kynurenine is imported from the circulation across the BBB, so a high peripheral K/T ratio drives central neurotoxicity.

Step two, the branch point. Kynurenine sits at a fork, and which way it goes is decided by which cell type takes it up.

- **Neuroprotective branch (astrocytes).** KAT converts kynurenine to **kynurenic acid (KYNA)**, an antagonist at the NMDA receptor glycine site and at the alpha-7 nicotinic acetylcholine receptor, with anti-excitotoxic and anti-inflammatory effects. Astrocytes lack KMO, so this is the branch they are confined to. Critically, KAT is *not* induced by inflammation, so inflammation shifts the balance away from KYNA.
- **Neurotoxic branch (microglia).** KMO (induced by inflammation) converts kynurenine to 3-hydroxykynurenine (3-HK, a pro-oxidant generating superoxide and hydrogen peroxide), then kynureninase and 3-hydroxyanthranilate dioxygenase lead to **quinolinic acid (QUIN)**. QUIN is an NMDA-receptor agonist; it also increases neuronal glutamate release and decreases astrocytic glutamate uptake, so it both opens the channel and raises the agonist, a double excitotoxic hit. The final step, quinolinate phosphoribosyltransferase (QPRT), salvages QUIN into NAD+, but its capacity is limited and rate-limiting, so QUIN accumulates when flux is high.

Step three, the gatekeeper. The unstable intermediate ACMS (half-life about 20 minutes) either rearranges spontaneously to QUIN or is decarboxylated by **ACMSD** (amino-beta-carboxymuconate-semialdehyde-decarboxylase) to neuroprotective picolinic acid. Low ACMSD activity therefore lets QUIN accumulate (see 15.4 for the suicide link).

The clinical signal is captured in ratios rather than absolute levels: a low **KYNA/QUIN ratio** (too little protection, too much excitotoxin) is the deranged pattern in major depression. KYNA/QUIN inversely correlates with anhedonia and with reduced hippocampal and amygdalar volumes (Savitz 2015), KYNA alone discriminates MDD with about 82.5 percent accuracy, and melancholic depression is marked by an elevated KYN/TRP ratio. This convergence of the inflammation hypothesis and the glutamate hypothesis on a single pathway is why ketamine (an NMDA antagonist) is conceptually the mirror image of QUIN.

FEATURE	KYNURENIC ACID (KYNA)	QUINOLINIC ACID (QUIN)
Made by	**Astrocytes (KAT; lack KMO)**	**Microglia (KMO present)**
NMDA receptor	Antagonist (glycine site)	Agonist
Other receptor	Alpha-7 nicotinic antagonist	Raises glutamate; blocks its uptake
Net effect	Neuroprotective, anti-excitotoxic	Excitotoxic, neurotoxic
Induced by inflammation?	No (KAT not induced)	Yes (IDO and KMO induced)

The two faces of the kynurenine fork. The discriminator (shaded) is cellular: astrocytes lack KMO and are stuck on the protective KYNA branch, while microglia carry KMO and drive the toxic QUIN branch, so inflammation tips the whole system toward excitotoxicity.

TRAP Reversing the receptor actions. Quinolinic acid is the NMDA **agonist** (toxic, from microglia); kynurenic acid is the NMDA **antagonist** (protective, from astrocytes). The microglial product attacks.

MNEMONIC

"A-PROTECTS, M-ATTACKS"

Astrocytes make the **P**rotective metabolite (kynurenic acid, NMDA antagonist). **M**icroglia make the **A**ttacking metabolite (quinolinic acid, NMDA agonist). The cell decides the chemistry.

COMMON TRAP

Do not reverse the receptor actions. Quinolinic acid is the NMDA *agonist* (toxic); kynurenic acid is the NMDA *antagonist* (protective). A frequent error is to assume the "acid" with the longer name must be the protective one. It is the reverse: the microglial product attacks.

21.4 Sickness behaviour, interferon-alpha-induced depression and the suicidality link

Sickness behaviour. When the peripheral immune system is activated, cytokine signals reach the brain (via vagal afferents, leaky circumventricular organs and active transport) and produce a stereotyped, adaptive syndrome: lethargy, anhedonia, anorexia, social withdrawal, hyperalgesia, sleep change and reduced motivation. Dantzer's work established this as the bridge between immune activation and mood: sickness behaviour is the normal, time-limited version, and depression may be its maladaptive, sustained form when cytokine signalling persists and the kynurenine pathway is engaged. The overlap with the neurovegetative symptoms of a depressive episode is obvious and examinable.

Interferon-alpha as a natural experiment. The existing section flags IFN-alpha therapy as a model; the detail is that 15 to 40 percent of patients treated with IFN-alpha (historically for hepatitis C or melanoma) develop a depressive syndrome, with rising KYN/TRP ratios tracking symptom emergence (Capuron, Lotrich). This is the cleanest human demonstration that giving a cytokine causes depression. Tellingly, Capuron found that the early neurovegetative symptoms

responded poorly to an SSRI (paroxetine), consistent with a mechanism downstream of, or parallel to, serotonin: the kynurenine and glutamate route rather than a simple serotonin deficit.

Suicidality and the ACMSD gatekeeper. Inflammation is over-represented in suicidal patients independent of diagnosis: CSF IL-6 is raised roughly threefold in recent attempters, and CSF QUIN is raised about threefold. Erhardt and colleagues showed that suicide attempters have reduced picolinic acid and a reduced **PIC/QUIN ratio** in both CSF ($P<0.001$) and blood, sustained for up to two years after the attempt, and that the minor C allele of the ACMSD SNP *rs2121337* is more common in attempters and associated with higher CSF QUIN. The interpretation: reduced ACMSD activity fails to shunt ACMS toward protective picolinic acid, so it defaults to neurotoxic QUIN. This dovetails with the rapid anti-suicidal effect of ketamine, an NMDA antagonist that opposes exactly the QUIN-driven NMDA agonism implicated here.

> **CLINICAL ANCHOR**
>
> If asked to connect inflammation, glutamate and suicide in one line: inflammation drives microglial quinolinic acid (an NMDA agonist), the kynurenine pathway is the common target, and ketamine (an NMDA antagonist) reverses the agonism, which is why a single infusion can rapidly reduce suicidal ideation.

21.5 Maternal immune activation: a developmental route to schizophrenia and autism

The existing bullet names maternal immune activation (MIA) in one phrase; the mechanism and its evidence base deserve unpacking because it is the classic "two-hit" developmental model and a recurrent exam theme. The premise: a maternal immune response during pregnancy, rather than any specific pathogen, raises the offspring's lifetime risk of schizophrenia and autism spectrum disorder. The mediator is the maternal cytokine milieu, with **IL-6** identified as the pivotal signal (Smith and Patterson): blocking maternal IL-6 prevents the offspring phenotype in animal models, and injecting IL-6 alone can reproduce it. IL-17A from maternal T-helper-17 cells is a downstream effector acting on the fetal cortex.

- **Epidemiology.** Ecological and cohort data link prenatal infection (the 1957 influenza pandemic studies, maternal rubella, raised maternal inflammatory markers) to elevated schizophrenia risk, supporting the neurodevelopmental hypothesis of schizophrenia.
- **Modelling.** Poly(I:C) (a viral-mimic) and lipopolysaccharide (a bacterial-mimic) given to pregnant rodents produce offspring with sensorimotor gating deficits (reduced prepulse inhibition), social and cognitive abnormalities, and altered dopaminergic and glutamatergic signalling.
- **Two-hit framing.** MIA is the first hit that primes microglia and perturbs circuit formation; a second postnatal hit (adolescent stress, cannabis, further infection) is needed to precipitate illness. This explains the long latency to a disorder seeded in utero.

PEARL

The exam point is that MIA risk is driven by the maternal immune *response*, not by a particular germ. IL-6 is the cytokine to name; poly(I:C) and LPS are the two standard modelling agents; reduced prepulse inhibition is the readout that maps onto the human sensory-gating deficit.

21.6 Complement C4 and aberrant synaptic pruning in schizophrenia

The existing bullet pairs C4 with aberrant pruning in a single clause; this is one of the landmark molecular findings of the decade and worth a dedicated card. The schizophrenia genome-wide association signal at the major histocompatibility complex on chromosome 6 is the strongest in the disorder, and Sekar and colleagues (2016) resolved that signal to structural variation in the **complement component 4 (C4)** gene. Alleles that drive higher expression of C4A confer greater schizophrenia risk.

The mechanism ties immunology to the developmental over-pruning hypothesis. In normal development, complement proteins (C1q, C3, and upstream of them C4) tag weak or redundant synapses for elimination by microglia, which engulf the marked synapses, a complement-dependent sculpting of postnatal circuits (Schafer 2012; Stevens). Excess C4A activity is proposed to over-tag synapses, so microglia prune *too aggressively* during adolescence, the developmental window when prefrontal synaptic density physiologically declines and when schizophrenia typically emerges. The result is the reduced dendritic spine density and grey-matter loss observed in the illness. This unifies three previously separate observations: the MHC genetic signal, the loss of synapses on post-mortem and neuroimaging, and the adolescent onset.

HOLD THIS

Excess complement C4A drives microglia to over-prune synapses in adolescence, the leading molecular model of schizophrenia. The problem is too much pruning, not too little.

Sekar et al. (2016) LANDMARK

Design. Fine-mapping of the schizophrenia GWAS association at the MHC locus, integrating structural variation in the complement C4 gene with post-mortem brain expression. **Finding.** The MHC signal arises largely from C4 structural alleles; higher C4A expression predicts greater schizophrenia risk, and C4 mediates synaptic pruning. **Why it matters.** First mechanistic bridge from a top genetic-risk locus to a cellular process (microglial, complement-dependent synapse elimination), validating the synaptic over-pruning model of schizophrenia.

COMMON TRAP

In schizophrenia the problem is *too much* pruning, not too little. Excess C4A leads microglia to eliminate too many synapses in adolescence, reducing spine density. Do not write that synapses are under-pruned.

21.7 Clinical translation: anti-inflammatory augmentation, its evidence and its limits (current to 2026)

The existing section ends by noting that anti-inflammatory augmentation helps in pooled trials but is not routine. Here is the structured evidence and why the field has moved to stratified designs. This is the one part of the topic with a genuine treatment dimension, so it is framed by target population and modality rather than as neuroanatomy.

FOCUS: who and what. The benefit of anti-inflammatory augmentation concentrates in the **inflamed subtype** of depression (raised baseline CRP), and the symptoms most responsive are the neurovegetative and anhedonic cluster that overlaps with sickness behaviour. Unselected populations show little or no benefit, which is the central limitation.

NSAIDs / COX-2 inhibitors

Celecoxib augmentation improves depressive symptoms in pooled short-term (6 to 12 week) trials without a major adverse-event signal (Kohler 2014). Effect sizes are modest and trials are heterogeneous.

Cytokine-targeted biologics

Anti-IL-6 (tocilizumab, sirukumab) produces statistically significant improvement in depressive symptoms in inflammatory-disease populations, correlated with baseline severity (Kappelmann 2018). The TNF-alpha antagonist infliximab was *not* superior to placebo overall but improved the high-inflammation subgroup (hs-CRP >5 mg/L), while placebo did better in the low-inflammation group (Raison 2013): the foundational proof-of-concept for inflammation-stratified treatment.

Microglia-modulating and antioxidant agents

Minocycline augmentation helped treatment-resistant depression with low-grade inflammation (Husain 2017); N-acetylcysteine has adjunctive antidepressant signal partly via reduced microglial activation and oxidative stress (Berk 2014). Conventional SSRIs themselves nudge microglia from M1 toward M2 in preclinical work.

The limits. The pooled positive trials are at high risk of bias, effects are small, and broad anti-inflammatory strategies have failed where tested hardest: in Alzheimer's disease the INTREPAD naproxen-prevention trial did not slow presymptomatic progression and raised adverse events, and earlier rofecoxib, celecoxib and etanercept trials in AD were negative. The lesson is that broad immunosuppression is both ineffective and risky (microglia are needed for normal pruning, and systemic suppression invites infection), whereas *targeted, stratified* approaches, selecting inflamed patients and acting on discrete nodes (specific cytokines, KMO inhibition, P2X7 antagonism, microglia-specific modulation), are the rational direction. No drug is yet approved specifically to target microglia or the kynurenine pathway in depression.

> **INDIA CONTEXT**
>
> Minocycline and N-acetylcysteine are cheap, widely available and already on Indian formularies, which makes them the realistic candidates if inflammation-stratified augmentation enters practice here; the costly biologics (infliximab, tocilizumab) are unlikely to be used for depression in routine Indian settings. CRP is an inexpensive, accessible stratification marker, which fits a resource-aware "test before you augment" approach.

CLINICAL ANCHOR

Exam-safe summary line: anti-inflammatory augmentation is promising but not standard of care; benefit is restricted to the high-CRP, treatment-resistant subgroup, the evidence base is biased and modest, and current guidelines do not recommend it as routine. The future is biomarker-stratified, not blanket, anti-inflammatory treatment.

Apply and consolidate

22 · Localize then manage: four vignettes

This is the transfer block. Everything earlier in these notes named a structure and gave it a function; here the reader runs the loop backwards, from a bedside picture to a locus and then to a first management move. Each vignette deliberately sits in a different lobe so that the discriminating feature, not the overall "brain-damaged" gestalt, is what carries the answer. The management arcs are kept light: this is a basic-science chapter, so each one points forward to the clinical material where the pathway is taught in full.

Read each case first and commit to a locus before you read the "Localise" line. The exam skill being drilled is **lesion-symptom mapping**: matching the single feature that could not be produced by any other lobe to the region that must be involved.

HOLD THIS

Localise on the one feature no other lobe could produce, not on the overall "brain-damaged" gestalt. The discriminator carries the mark.

22.1 Vignette 1: the tactless businessman (orbitofrontal)

CLINICAL ANCHOR

A 46-year-old businessman is brought by his wife eight months after a road-traffic head injury with frontal impact. He has kept his job title but makes crude jokes in meetings, propositions junior staff, and has emptied a joint savings account on impulsive purchases he cannot justify. Memory, language, calculation and gait are intact on testing; he is oriented and scores normally on bedside cognition. He minimises the whole account and finds his wife's concern amusing.

Localise. Preserved memory, language and orientation exclude a dominant-temporal or diffuse process; the deficit is confined to social conduct, impulse control and reward-based judgement with intact "hard" cognition. That dissociation is the signature of the **orbitofrontal cortex (OFC)**, whose ventral surface is the classic site of contusion in frontal-impact trauma. OFC lesions produce a disinhibition syndrome (impulsivity, tactlessness, hypersexuality, financial recklessness, emotional lability) historically labelled the "pseudopsychopathic" or frontal-lobe personality, with anosognosia for the change (Berlin 2004). The intact calculation and orientation actively argue against a parietal or global amnestic locus.

Post-traumatic orbitofrontal disinhibition (personality change due to traumatic brain injury)	Guidelines: see the Stroke, TBI, delirium & focal brain syndromes notes TBI neuropsychiatry
LOCUS where	Outpatient with a capable informant, escalating to structured rehabilitation. Inpatient only if behaviour endangers self, dependants or finances.
FOCUS what · when	**SHORT TERM** Establish safety: financial safeguards (spending controls, a trusted co-signatory), capacity assessment, workplace and driving review. **MID TERM** Behavioural and environmental structure; treat target symptoms (irritability, impulsivity) pharmacologically only where they drive risk. **LONG TERM** Neuropsychological rehabilitation, psychoeducation for the family about anosognosia, staged occupational re-entry.
MODUS how	Behavioural and environmental interventions first-line; caregiver support and safety planning throughout; SSRIs for disinhibition and agitation have modest evidence in analogous frontal-behavioural syndromes. Detailed protocol on the Stroke, TBI, delirium & focal brain syndromes notes.

22.2 Vignette 2: the ignored left plate (right MCA, non-dominant parietal)

CLINICAL ANCHOR

A 72-year-old right-handed man, three days after an acute event, eats only the right half of every meal and leaves the left half untouched. He shaves the right side of his face, bumps his wheelchair into left-sided doorframes, and when his weak left arm is lifted into his view he calmly insists it is not his and that nothing is wrong with it. Speech is fluent and comprehension intact.

Localise. Fluent, comprehending speech places the dominant (usually left) hemisphere out of the frame. Ignoring left-sided space (hemispatial neglect) together with denial of the left-sided weakness (anosognosia) localises to the **non-dominant, right inferior parietal lobe**, in the territory of the right middle cerebral artery (MCA). Neglect and denial of ownership of the contralateral limb are the classic right-hemisphere network signs (Parton 2004); a mirror-image lesion on the left would instead have produced aphasia or Gerstmann-type deficits rather than silent inattention.

FEATURE	LEFT (DOMINANT) PARIETAL	RIGHT (NON-DOMINANT) PARIETAL
Language	Aphasia, alexia	Preserved
Named tetrad	Gerstmann (agraphia, acalculia, finger agnosia, left-right disorientation)	Dressing and constructional apraxia
Awareness of deficit	Usually retained	**Neglect and anosognosia for the deficit**

The single discriminator that fixes this case to the right parietal lobe is unawareness of the deficit, not the motor weakness itself.

Right MCA territory ischaemic stroke with neglect and anosognosia	Guidelines: see the Stroke, TBI, delirium & focal brain syndromes notes stroke and vascular neuropsychiatry
LOCUS where	Acute stroke unit inpatient, then inpatient or community neuro-rehabilitation.
FOCUS what · when	**SHORT TERM** Enter the hyperacute stroke pathway (imaging, reperfusion decision by the stroke team), swallow screen, aspiration and pressure-area precautions on the neglected side. **MID TERM** Neglect-directed rehabilitation (visual scanning training, cueing to the left, prism adaptation), secondary prevention (antiplatelet, risk-factor and cardioembolic-source workup). **LONG TERM** Functional and occupational rehabilitation; anosognosia limits engagement and needs carer-mediated compensation.
MODUS how	Stroke-team-led acute care plus multidisciplinary rehabilitation (physiotherapy, occupational therapy, neuropsychology). Vascular pathway detailed on the Stroke, TBI, delirium & focal brain syndromes notes.

22.3 Vignette 3: the placid, hyperoral survivor (bilateral temporal)

CLINICAL ANCHOR

A 24-year-old man recovering from confirmed herpes simplex encephalitis is now medically stable but transformed. He is strikingly placid and unafraid, puts non-food objects into his mouth, touches and examines everything within reach, and makes indiscriminate sexual advances. He cannot retain any new information from one hour to the next and does not recognise that anything is wrong.

Localise. Herpes simplex encephalitis has a marked predilection for the medial temporal and orbitofrontal cortex, and here the picture is **bilateral temporal**. Two syndromes coexist. The placidity, hyperorality, hypermetamorphosis (compulsion to touch and examine) and hypersexuality are the human **Kluver-Bucy syndrome**, which follows bilateral destruction of the amygdala, uncus and adjacent temporal cortex. The dense inability to form new memories is **anterograde amnesia** from bilateral medial-temporal and hippocampal damage; bilateral involvement is what makes the amnesia global and severe rather than material-specific.

PEARL

Unilateral temporal lesions give material-specific memory loss (verbal on the dominant side, non-verbal on the non-dominant side). Only bilateral medial-temporal damage produces the dense, global amnesia seen here, and Kluver-Bucy features likewise require bilateral amygdalar involvement.

Post-HSV-encephalitis Kluver-Bucy syndrome with amnestic disorder	Guidelines: see the Stroke, TBI, delirium & focal brain syndromes notes CNS-infection neuropsychiatry; the Psychopharmacology II: emergencies, resistance, monitoring & interactions notes amnestic syndromes
LOCUS where	Acute inpatient (neurology or medicine) for the encephalitis, then supervised inpatient or high-support residential rehabilitation.
FOCUS what · when	SHORT TERM Treat the cause: complete the acyclovir course, monitor for relapse and seizures. Ensure a supervised, hazard-reduced environment given hyperorality (choking or ingestion risk) and disinhibition. MID TERM Behavioural management of hyperorality and hypersexuality; structured routine and external memory aids for the amnesia. LONG TERM Cognitive rehabilitation, safeguarding and capacity review, family psychoeducation about the permanence of dense amnesia.
MODUS how	Antiviral treatment of the underlying encephalitis first; environmental safety and behavioural interventions for the Kluver-Bucy features; compensatory memory strategies. Covered on the Stroke, TBI, delirium & focal brain syndromes notes and the Psychopharmacology II: emergencies, resistance, monitoring & interactions notes.

22.4 Vignette 4: blind but insisting she can see (occipito-parietal, watershed)

CLINICAL ANCHOR

A 58-year-old woman resuscitated from a cardiac arrest, once alert, cannot navigate her room and collides with furniture, yet insists her vision is normal and confabulates descriptions of objects placed in front of her. When asked to pick up a cup she looks at, her hand reaches wide of it; she can attend to only one object at a time and cannot grasp the whole scene. Pupillary reflexes and the anterior visual pathway are intact.

Localise. Intact pupils with a normal anterior pathway make the blindness cortical, not ocular. The lesion is **bilateral occipito-parietal**, in the posterior watershed (border-zone) territory that is selectively vulnerable to the global hypotension of a cardiac arrest. Two syndromes stack. Denial of cortical blindness with confabulation is **Anton syndrome** (visual anosognosia in the setting of bilateral occipital damage; Aldrich 1987). Misreaching for objects under vision (optic ataxia), inability to voluntarily shift gaze, and inability to perceive more than one object at a time (simultanagnosia) are the triad of **Balint syndrome**, from bilateral parieto-occipital dorsal-stream damage.

COMMON TRAP

Do not chase an ophthalmological cause because the patient "says she can see". In Anton syndrome the eyes and anterior pathway are normal; the denial is the neurological sign. Confirm cortical blindness rather than accepting the patient's report.

Hypoxic-ischaemic posterior watershed injury: Anton plus Balint syndrome	Guidelines: see the Stroke, TBI, delirium & focal brain syndromes notes hypoxic-ischaemic and vascular neuropsychiatry
LOCUS where	Inpatient (post-arrest and stroke care), then neuro-rehabilitation.
FOCUS what · when	**SHORT TERM** Confirm cortical blindness (normal eye exam, imaging of the occipito-parietal cortex); vascular and cardiac workup to identify and treat the arrest cause; environmental safety for a patient who denies the deficit. **MID TERM** Secondary prevention of further ischaemia; visual and functional rehabilitation, recognising that outcome depends on cause, severity and duration. **LONG TERM** Compensatory rehabilitation and carer support; confabulated denial makes insight-based counselling of limited value alone.
MODUS how	Treat the vascular or hypoxic cause, then multidisciplinary rehabilitation; recovery is possible when a reversible cause (for example cortical hypoperfusion) is corrected. Vascular pathway on the Stroke, TBI, delirium & focal brain syndromes notes.

23 · Consolidate: mnemonic total, retrieval and synthesis

This closing block is not new content; it is a **consolidation device**. The material has moved from where structures sit, through how they signal, to what breaks and how we treat what breaks, and the marks in the exam go to the candidate who can reproduce that arc without the page in front of them. **Study by producing, not by re-reading.** The evidence on durable learning is unambiguous: spaced *active recall* (self-testing from memory) and forced retrieval outperform repeated passive review for long-term retention, the effect Roediger and Karpicke (2006) named the testing effect. The three subtopics below give you the tools to run that loop: one master mnemonic that chains the smaller mnemonics into a single spine, a set of answer-free retrieval prompts, and a one-page synthesis map to redraw from memory.

Use them in that order. Recite the mnemonic spine to check the scaffold is intact, then close the notes and work the retrieval prompts aloud, then take a blank sheet and rebuild the whole circuit. If a limb of the map will not come, that is the prediction error telling you exactly which topic to reopen, which is the point of the exercise.

23.1 Master mnemonic total: chaining the chapter into one spine

Each topic already carries its own mnemonic. The problem at revision is not recalling any single one but retrieving the right one under time pressure and in the correct order. The device below is a *mnemonic of mnemonics*: a six-link spine that indexes the structural and physiological cores, so that recalling the spine pulls each sub-mnemonic up with it. Walk it top to bottom the way the brain is built, cortex and its loops first, then the ascending modulators, then the electrical readout.

MNEMONIC

"LOBES Feed PAPEZ, Basal GO-STOP-BRAKE, Monoamines RUN, EEG Bad Boys Are Tired Drowsy"

LOBES unpacks the four cerebral lobes and their signature lesion: *L*imbic-medial-temporal (memory and emotion), *O*ccipital (vision, cortical blindness and Anton syndrome), *B* for the *B*ig two association jobs of the parietal (right neglect, left Gerstmann) and the *E* for the *E*xecutive and social frontal, with *S* reminding you the temporal lobe delivers *S*ound, speech comprehension (Wernicke) and, medially, the *S*eahorse (hippocampus). Read as: four lobes, one dominant deficit each.

Feed PAPEZ chains straight into the limbic loop mnemonic already on the page, "HF-MAT-CE-H": *H*ippocampal *F*ormation, then *M*ammillary bodies via the fornix, *A*nterior *T*halamic nucleus via the mammillothalamic tract, *C*ingulate, *E*ntorhinal cortex, back to the *H*ippocampus. The prefrontal companion sits beside it as the three frontal syndromes: *D*orsolateral (dysexecutive, pseudodepressed), *O*rbitofrontal-ventromedial (disinhibited, pseudopsychopathic, Phineas Gage), *M*edial-cingulate (apathetic, abulic, akinetic mutism). Hold them as "DOM": one PFC zone, one syndrome.

Basal GO-STOP-BRAKE encodes the three basal-ganglia pathways by their net effect on movement: the *GO* direct pathway (D1, disinhibits thalamus, releases movement), the *STOP* indirect pathway (D2, raises GPi/SNr output, suppresses movement), and the *BRAKE* hyperdirect pathway (cortex to STN, fast, dopamine-independent, the reactive stop-signal). GO-STOP-BRAKE is the entire loop in three words.

Monoamines RUN fixes the "one nucleus, one transmitter" rule for the ascending modulatory systems: *R* the *R*aphe nuclei make serotonin, the *U* stands for the *U*pper-pontine-and-midbrain trio you must place, and *N* for *N*oradrenaline from the locus coeruleus. Expanded, the set to recite is: raphe to serotonin, locus coeruleus to noradrenaline, substantia nigra pars compacta and ventral tegmental area to dopamine (nigrostriatal versus mesolimbic-mesocortical), tuberomammillary nucleus to histamine, and the basal-forebrain and pedunculopontine-laterodorsal-tegmental cholinergic groups to acetylcholine. Each nucleus, one transmitter, one arousal or behavioural job.

EEG Bad Boys Are Tired Drowsy reuses the waveform mnemonic in falling frequency and rising amplitude: *B*eta and *Boys* for gamma (fast, alert, engaged; beta raised by benzodiazepines), *A*lpha (relaxed eyes-closed, occipital, blocked by eye-opening), *T*heta (drowsy, N1), *D*elta (deep N3, or pathology if awake). Frequency falls down the list; amplitude rises.

The table restates the spine so you can quiz yourself on any single link. Cover the right two columns and recall the sub-mnemonic and its content from the cue word alone.

SPINE LINK	SUB-MNEMONIC	WHAT IT UNLOCKS
LOBES	Four lobes, one deficit each	**Lobe to signature syndrome (occipital to Anton, parietal to neglect/Gerstmann, frontal to executive/social, temporal to Wernicke/memory)**
PAPEZ	HF-MAT-CE-H	The closed limbic memory loop, hippocampus back to hippocampus
PFC (DOM)	Dorsolateral, Orbitofrontal, Medial	**Three frontal syndromes: dysexecutive, disinhibited, apathetic**
Basal ganglia	GO-STOP-BRAKE	Direct (D1), indirect (D2), hyperdirect (STN) pathways by net effect
Monoamines	One nucleus, one transmitter (RUN)	**Raphe-5HT, LC-NA, SNc/VTA-DA, TMN-histamine, basal forebrain/PPT-LDT-ACh**
EEG	Bad Boys Are Tired Drowsy	Gamma-beta-alpha-theta-delta by falling frequency, rising amplitude

The six-link master spine, each row a cue word pointing to a topic mnemonic; recall the middle and right columns from the left cue alone.

23.2 Active-recall prompts: cover the page and answer aloud

These are retrieval questions, not a summary. Deliberately answer-free, they force you to generate the answer from memory, which is where the testing effect does its work; reading a model answer here would defeat the device. Cover everything below the label, answer each aloud in a full sentence, then reopen the relevant topic only for the ones you could not complete.

RETRIEVAL PRACTICE, COVER THE ANSWERS

1. Trace the Papez circuit synapse by synapse from hippocampus back to hippocampus, and name the one lesion site classically destroyed in thiamine deficiency.
2. Name the three prefrontal syndromes, the zone each maps to, and the single discriminating feature that separates the disinhibited picture from the apathetic one.
3. Trace the direct pathway as three sign changes and state why the net result is disinhibition of the thalamus.
4. Contrast the indirect and hyperdirect pathways: which is dopamine-independent, and what behavioural role does the hyperdirect route serve?
5. Give the four lobes and, for each, the one lesion syndrome the exam pairs with it.
6. For each monoamine transmitter, name its nucleus of origin and one arousal or behavioural function; which nucleus is active in both wake and REM?
7. List the five EEG bands from fastest to slowest with their frequency ranges, and state which band eye-opening blocks and which is raised by benzodiazepines.
8. Which thalamic nuclei relay to the primary visual, auditory and somatosensory cortices, and which nucleus completes the Papez loop?
9. Name the three large-scale networks, the anticorrelation between two of them, and the hub the salience network uses to switch between them.
10. Describe the HPA-axis stress cascade from hypothalamus to cortisol, and name the feedback structure that normally restrains it.
11. State the arterial territory of an anterior, middle and posterior cerebral artery stroke, and the classic deficit of each.
12. Define the cerebellar cognitive-affective syndrome and name its four components (Schmahmann 1998).
13. Distinguish long-term potentiation from long-term depression at the CA3-to-CA1 synapse: which receptor is the coincidence detector, and what is the sign of the postsynaptic calcium signal in each?
14. Give the generator, latency and clinical use of one sensory evoked potential and one event-related potential (for example the P300).
15. Name three named EEG patterns and the single diagnosis each points to.
16. State which brain structures the reticular activating system uses to set arousal, and name the sleep-promoting nucleus that opposes it.

If more than a third of these will not come cleanly, do not push through the list a second time the same day; space the next attempt, because retrieval spaced across days is what builds durable memory (Roediger and Karpicke 2006).

23.3 Synthesis map: the one page to redraw from memory

The final consolidation step is to build a single **synthesis map** that runs the whole chapter along one axis: **structure to sign to syndrome**. On a blank sheet, redraw from memory a page that places the cortical loops at the centre (the Papez ring closing through the anterior thalamus, the three prefrontal zones fanning forward, the cortico-striato-thalamo-cortical loop hanging below

with its GO-STOP-BRAKE arrows), then feeds in the ascending modulators from the brainstem (raphe, locus coeruleus, substantia nigra and ventral tegmental area, tuberomammillary and cholinergic groups, each labelled with its one transmitter), then reads the whole thing out as the EEG at the top and the vascular territories as a border, and finally annotates each node with the deficit that appears when it is lesioned. Redraw it once from memory, then check it against the figures in these notes and fill only the gaps; the act of reconstructing the map, not admiring a finished one, is what fixes the arc from anatomy to physiology to clinical sign. The figure below is the skeleton to rebuild: read each row left to right as a structure, the sign its lesion produces, and the named syndrome that results, across every system covered.

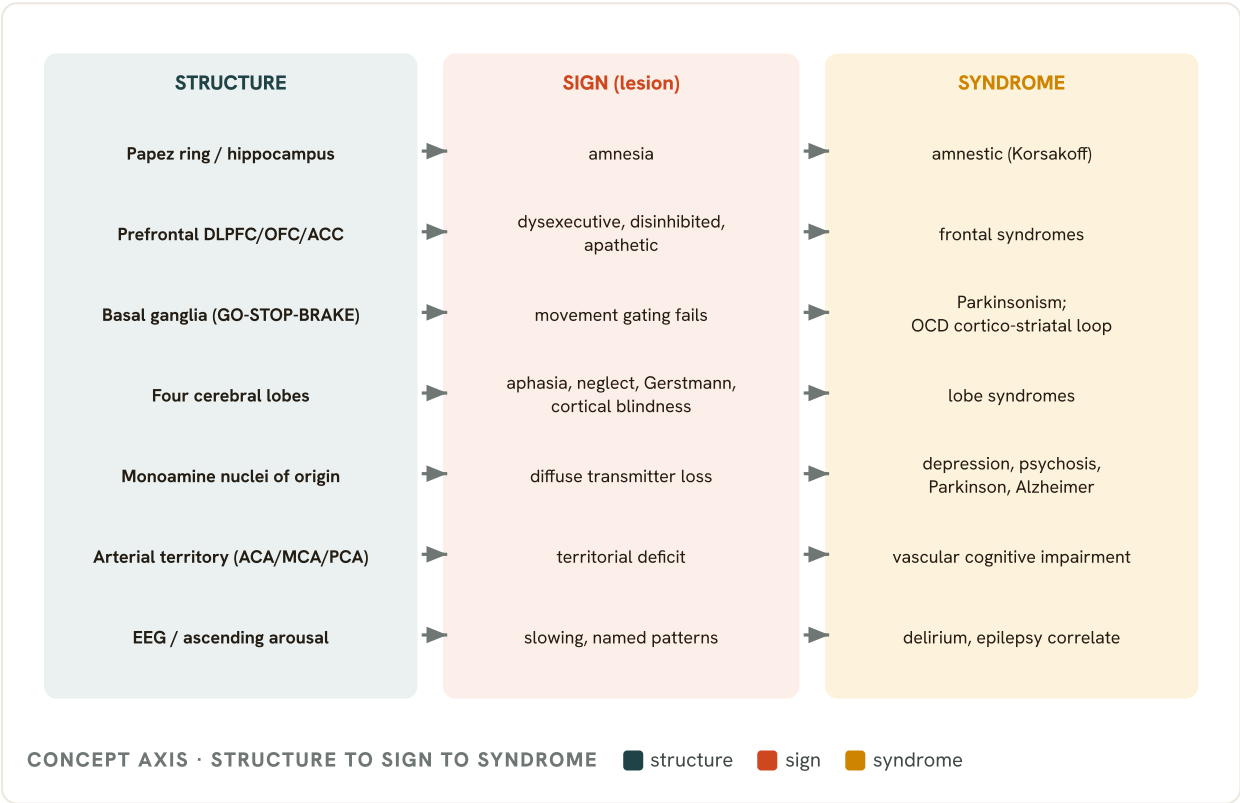


Fig 1.27 The whole-chapter synthesis map. Every system reduces to one line: a structure, the sign its lesion produces, and the named syndrome. Cover the right two columns and rebuild them from the structure alone; the rows you cannot complete are the topics to reopen.

Previously asked

Real long-essay (25-mark) and short-note (10-mark) questions from this territory, ordered by board.

LONG ESSAYS (25 MARKS)

Q Describe the limbic system and discuss its role in psychiatric disorders. MUHS 2011, 2012, 2013, 2016

Q Describe the neuroanatomy of the basal ganglia and discuss its role in psychiatric disorders. MUHS 2014, 2015

Q Circadian sleep-wake rhythm (within an organic-disorders essay). MUHS 2012, 2015

SHORT NOTES (10 MARKS)

- Q Prefrontal cortex · Dorsolateral prefrontal cortex · Frontal lobe. MUHS 2012, 2014, 2017
- Q Hypothalamus: connections and functions. MUHS 2017
- Q Anatomy, physiology and functions of the cerebellum. MUHS 2013
- Q Normal waves in EEG. MUHS 2011, 2012, 2013
- Q Long-term potentiation · Synaptic plasticity · Neuronal plasticity. MUHS 2011, 2014, 2015
- Q Working memory · Implicit memory. MUHS 2012, 2013

Quick review

The whole picture in one table

LIMBIC SYSTEM	Papez loop (hippocampus to fornix to mammillary to anterior thalamus to cingulate to entorhinal); amygdala = emotion, accumbens = reward. Hippocampal volume loss in schizophrenia and depression; amygdala in PTSD and anxiety.
PREFRONTAL CORTEX	DLPFC dysexecutive · OFC/VMPFC disinhibited (Gage) · medial/ACC apathetic. DLPFC = hypofrontality in schizophrenia and the rTMS target.
BASAL GANGLIA	Direct (D1) GO, indirect (D2) STOP, hyperdirect (STN) fast brake; output GPi/SNr clamps thalamus. CSTC loops, OFC loop = OCD.
THALAMUS & HYPOTHALAMUS	MD nucleus to PFC (schizophrenia); SCN clock, PVN drives HPA, VMH satiety / LH hunger. The 5 F's.
NETWORKS & AROUSAL	Triple network: DMN (self) / salience (switch, aberrant salience in psychosis) / CEN (task). ARAS sets arousal; orexin stabilises wake (DORAs).
SLEEP	NREM N1-N3 + REM, ~90 min cycles; N2 spindles/K-complexes; SWS early, REM late. Depression = short REM latency, low SWS. CBT-I first-line for insomnia.
EEG	Delta <4 (deep sleep), theta 4-8, alpha 8-13 (relaxed, eyes closed), beta 13-30 (alert, benzos), gamma >30. Delirium = diffuse slowing.
MEMORY & PLASTICITY	Declarative (MTL/hippocampus, H.M.) vs non-declarative; trisynaptic circuit; NMDA-dependent LTP (Bliss & Lømo); BDNF neurotrophic hypothesis; ketamine via mTOR.
ERPS	P300 ~300 ms reduced in schizophrenia; MMN (NMDA, pre-attentive) robustly reduced, a candidate endophenotype.
NEUROINFLAMMATION	Microglia and cytokines (IL-6, TNF-α, CRP) elevated in a depression subset; kynurenine shunt; maternal immune activation raises schizophrenia/autism risk.

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PART II

II

Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology

The chemical brain the paper tests: the transmitter systems, the hormonal axes, how we image it, and the pharmacology that follows.

01 Neurochemistry

02 Neuroendocrinology

03 Neuroimaging

04 Basic psychopharmacology

05 Apply and consolidate

Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology

Five sections · 23 topics · one complete notes document

the Functional Neuroanatomy & Neurophysiology notes built the wiring. This material builds what runs through it: the handful of neurotransmitter systems the brain actually uses, the three hormonal axes that set its tone, the imaging that lets us see the machinery, and the pharmacology that lets us move it. **Read systems, not molecules.** Almost every answer in this territory rewards the candidate who names the receptor, the pathway and the clinical read-out together, rather than reciting a synthesis chain. These notes run in the order a drug does its work: which chemical, at which receptor, through which second messenger, changing which circuit, producing which clinical effect.

HOW TO USE THESE NOTES

Every figure declares one clinical axis and codes it in colour and shape, with a small legend. The colours are consistent throughout: **petrol** marks structure, the receptor and the relay or executive role, **coral** marks danger, pathology or an excess or deficit state, and **marigold** highlights the drive, reward or facilitatory element. Learn the key once and every diagram reads faster.

Neurochemistry

1 · Orientation: the chemical brain from molecule to syndrome

Before the detail, the frame. the Functional Neuroanatomy & Neurophysiology notes mapped *where* the brain sits and *how* its structures wire together. Today is the layer on top: *how the wiring signals*, and how a molecule, once you follow it far enough, becomes a syndrome and then a drug target. This whole chapter runs on one move, repeated throughout: **trace the molecule to the syndrome to the drug**. A transmitter is made, released, meets a receptor, and reads out through a second messenger; a hormone axis sets the background tone; imaging is how the machinery is seen; and pharmacokinetics-pharmacodynamics is how a drug is pushed into that circuit. Hold that chain and every topic below has a place to land.

The brain does not use hundreds of signals. It runs on a small, examinable set: the **monoamines** (dopamine, serotonin, noradrenaline, and their cousins adrenaline and histamine), the fast amino acids (**glutamate** excitatory, **GABA** and glycine inhibitory), **acetylcholine**, and the slow, modulatory **neuropeptides** (including the endogenous opioids). Newer entrants, the gasotransmitters and the lipid-derived endocannabinoids, break the classical rules and are examined precisely because they do. Every one of these is read out downstream through second messengers and neurotrophic signalling, and three neuroendocrine axes (the HPA stress axis, the HPT and HPG hormonal axes, and the circadian clock) set the hormonal weather in which they all operate. That is the whole territory.

HOLD THIS

Answer with the receptor, the pathway and the clinical read-out together, never a bare synthesis chain. Almost every mark in this territory rewards trace-the-molecule-to-syndrome-to-drug over reciting a biosynthesis pathway.

1.1 The four sub-areas, bound in one frame

This chapter is four connected territories, not four silos. Learn them as a single sentence: *the chemistry does the signalling, the endocrine axes set the tone, imaging shows the machinery, and pharmacology is how we move it*. Each later topic slots under one of these four.

Neurochemistry

The transmitter systems (monoamines, amino acids, acetylcholine, neuropeptides, and the novel gaso- and lipid transmitters), their receptors, and the intracellular second-messenger and neurotrophic cascades they trigger. This is the engine of the chapter.

Neuroendocrinology

The three axes that set the hormonal background: the hypothalamic-pituitary-adrenal (HPA) stress axis, the thyroid and gonadal axes (HPT and HPG), and the circadian and pineal-melatonin clock. The interface where transmitter and hormone meet.

Neuroimaging

How the machinery is seen: structural (CT, MRI), functional (fMRI, PET, SPECT), and the molecular readouts (receptor and transporter occupancy, spectroscopy) that make a transmitter hypothesis testable in a living patient.

Basic psychopharmacology

Pharmacokinetics (how the drug moves: absorption, distribution, metabolism, excretion) and pharmacodynamics (what the drug does at the receptor: agonist, antagonist, partial agonist, inverse agonist). This is how the whole system is deliberately pushed.

1.2 Classification of neurotransmitters: the same list read on five different axes

Examiners ask you to *classify the neurotransmitters*, and the discriminating answer is that there is no single classification: the same set of molecules is sorted differently depending on the question you ask of it. Kaplan and Sadock frame the historical arc that produces this (Kaplan & Sadock 2024): the first transmitters found were small chemicals (acetylcholine, then the biogenic amines), then amino acids and peptides were recognised, then in the 1990s a lipid-derived signal (the endocannabinoids) and even a gas (nitric oxide) qualified, each bending the old definition. So instead of one list, hold five axes. Read the table across each row as one lens on the same molecules.

CLASSIFYING AXIS	CATEGORIES	MEMBERS AND THE DISCRIMINATOR THAT DEFINES EACH
(a) Chemical structure / class	Small-molecule vs neuropeptide vs gasotransmitter vs lipid messenger	**Small-molecule splits into monoamine (dopamine, serotonin, noradrenaline, adrenaline, histamine), amino-acid (glutamate, GABA, glycine) and acetylcholine; then neuropeptides (endorphins, substance P, CRH, oxytocin), gasotransmitters (NO, CO, H2S) and lipid endocannabinoids (anandamide, 2-AG)**
(b) Functional effect	Excitatory vs inhibitory vs modulatory	**Glutamate is the main excitatory workhorse; GABA and glycine are the main inhibitory brakes; the monoamines are chiefly *modulatory*, tuning gain rather than driving firing directly**
(c) Signalling and speed	Ionotropic vs metabotropic	**Ionotropic = a ligand-gated ion channel, fast (milliseconds): NMDA/AMPA, GABA-A, nicotinic, 5-HT3. Metabotropic = a G-protein-coupled receptor, slow (seconds and up) via a second messenger: all monoamine receptors, muscarinic, GABA-B, mGluR**
(d) Synthesis and storage	Classical vesicular vs non-classical made-on-demand	**Classical transmitters are pre-synthesised, packaged in vesicles and released by exocytosis; the gasotransmitters and endocannabinoids are *made on demand* and released *retrogradely* from the post-synaptic cell back onto the pre-synaptic terminal, with no vesicle and, for gases, no membrane receptor**
(e) Dale's principle and co-transmission	One-transmitter model vs co-transmission	**Dale's principle (one neuron, one transmitter) is an oversimplification; most neurons *co-transmit*, typically a fast small-molecule transmitter plus a slow modulatory neuropeptide released from the same terminal (for example noradrenaline with NPY)**

The high-yield insight is that axes (c) and (d) cut across axis (a): acetylcholine, glutamate, GABA and serotonin each act at *both* ionotropic and metabotropic receptors, so "fast or slow" is a property of the receptor, not the transmitter. The made-

on-demand, retrograde, non-vesicular pattern of the gases and endocannabinoids is the single most examined "exception" in the classification.

RULE **Fast-or-slow is a property of the receptor, not the transmitter.** ACh, glutamate, GABA and serotonin each act at both an ionotropic and a metabotropic receptor.

1.3 The made-on-demand exceptions: gasotransmitters and endocannabinoids

Why they matter. These two families break every rule a classical transmitter obeys, which is exactly why a Paper-1 stem singles them out. The **gasotransmitters** are nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H2S). Take NO as the model (Kaplan & Sadock 2024): it is not stored in vesicles but synthesised on demand by nitric oxide synthase from the amino acid arginine (yielding citrulline as a byproduct); being a small gas it diffuses freely across membranes rather than binding a surface receptor, acting directly on an intracellular target (soluble guanylyl cyclase, raising cyclic GMP); it has no reuptake mechanism and a half-life of only a few seconds. Functionally NO is tied to long-term potentiation and memory (it is generated post-synaptically after NMDA-receptor calcium entry and signals retrogradely), and its peripheral cGMP pathway is the target of the phosphodiesterase-5 inhibitors sildenafil and tadalafil. CO, made by heme oxygenase, activates the same guanylyl cyclase pathway more weakly.

The **endocannabinoids**, anandamide and 2-arachidonoylglycerol (2-AG), are the lipid-messenger class: derived from membrane lipids, synthesised on demand in the post-synaptic neuron, and released *retrogradely* onto pre-synaptic CB1 receptors to dampen further transmitter release (a feedback brake). Delta-9-THC is a partial agonist at CB1; rimonabant is a CB1 inverse agonist. Note the parallel with the gases: no vesicle, made when needed, and signalling backwards across the synapse.

COMMON TRAP

Do not call nitric oxide an "inhibitory" or "excitatory" transmitter in the amino-acid sense, and do not say it binds a membrane receptor. NO has no cell-surface receptor and no reuptake; it diffuses in and acts on an intracellular enzyme. Equally, the endocannabinoids are *retrograde* messengers (post-synaptic to pre-synaptic), the reverse of the classical direction, and they are not stored in vesicles.

1.4 The map in one schema: transmitter to receptor family to clinical signature

Before these notes fan out into one system per topic, bind each transmitter to its receptor family and the one clinical role that makes it examinable. This pearl is the spine to redraw from memory; every later topic pays it back in detail.

THE MAP, IN ONE SCHEMA

Dopamine (metabotropic D1 to D5): the psychosis-and-reward transmitter; four pathways, the mesolimbic drives positive symptoms. **Serotonin** (metabotropic, plus the one ionotropic 5-HT3): mood, anxiety, and the SSRI target; 5-HT3 is the emesis and gut receptor. **Noradrenaline** (metabotropic alpha and beta): arousal, attention and the stress response. **Glutamate** (ionotropic NMDA/AMPA/kainate, plus metabotropic mGluR): the main excitatory drive; NMDA hypofunction is the modern schizophrenia and ketamine story, and its overactivity is excitotoxicity. **GABA** (ionotropic GABA-A, metabotropic GABA-B): the main inhibitory brake and the benzodiazepine, barbiturate, alcohol and neurosteroid site. **Acetylcholine** (ionotropic nicotinic, metabotropic muscarinic): memory and the cholinergic hypothesis of Alzheimer disease. **Neuropeptides** (metabotropic): slow modulators, co-released with the classics; the opioid peptides run analgesia and reward. **Gases and endocannabinoids:** the made-on-demand, retrograde exceptions.

1.5 The master mnemonic, seeded now

The consolidation block at the end pays this schema back as a whole synthesis map. Seed the master mnemonic now so the material builds toward it: **"Some Modulators Are Nicely Guiding Growth And Neuroendocrine Physiology."** Unpacked, it walks the systems in order: **S**ignalling (the transmitter systems), **M**onoamines, **A**mino acids, **N**europeptides and **G**ases, then the second-messenger and neurotrophic **G**rowth signalling, **A**xes (HPA, HPT-HPG, circadian) as the **N**euroendocrine tone, and finally **P**harmacology (kinetics and dynamics) as how the whole thing is imaged and moved. The one-line spine to build toward: *a handful of transmitters signal fast or slow, second messengers and neurotrophins read them out, three axes set the tone, imaging shows it, and pharmacology moves it*.

1.6 Cross-references to the Functional Neuroanatomy & Neurophysiology notes: what is already yours

This chapter deliberately does *not* re-teach the anatomy that the Functional Neuroanatomy & Neurophysiology notes established; it builds the chemistry on top of it. Three things are already yours from the Functional Neuroanatomy & Neurophysiology notes and are only cross-referenced here.

Nuclei of origin

The discrete brainstem sources of the ascending modulatory pathways, covered on the Functional Neuroanatomy & Neurophysiology notes: the ventral tegmental area and substantia nigra (dopamine), the raphe nuclei (serotonin), the locus coeruleus (noradrenaline), and the basal forebrain and pedunculopontine nuclei (acetylcholine). Today assumes you can name where each transmitter comes from.

The stress circuit

The limbic-hypothalamic drive of the stress response (amygdala to paraventricular nucleus) was drawn on the Functional Neuroanatomy & Neurophysiology notes; today adds the endocrine arm, the HPA axis and its cortisol feedback, on top of it.

The large-scale networks

The default-mode, salience and executive networks (the Functional Neuroanatomy & Neurophysiology notes) are the substrate that today's neuroimaging topic reads out functionally.

CLINICAL ANCHOR

Neuroinflammation stays on the Functional Neuroanatomy & Neurophysiology notes. The cytokine and microglial story (the inflammatory hypothesis of depression, IL-6 and TNF-alpha, microglial activation) is owned by the Functional Neuroanatomy & Neurophysiology notes and is only cross-referenced today. When a topic here touches an immune signal, point back to the Functional Neuroanatomy & Neurophysiology notes rather than re-teaching it; this chapter's remit is the transmitter, endocrine, imaging and pharmacology layers.

2 · Dopamine pathways and clinical correlates

Dopamine is the neurotransmitter examiners return to more than any other, because a single molecule ties together the phenomenology of psychosis, the whole architecture of antipsychotic drug action, the neurology of Parkinson disease, the pathophysiology of addiction, and the pharmacology of stimulants in ADHD. The trick to owning this topic is to hold three layers in register at once: the **biochemical layer** (how dopamine is made, stored and broken down), the **receptor layer** (two G-protein families with opposite second-messenger signs), and the **anatomical layer** (four projection systems, each with one signature clinical consequence). Almost every single-best-answer item is really asking you to connect a drug action at one layer to a symptom at another.

Exam framing. The four-pathway map is the spine of the topic and the reason Stahl's antipsychotic logic works: an antipsychotic given for a mesolimbic problem inevitably blocks D2 in three other pathways it never meant to touch, and each unwanted blockade is a named side effect. Learn the pathways as a system of trade-offs, not four isolated facts. Cross-reference the the Functional Neuroanatomy & Neurophysiology notes material on the midbrain dopaminergic nuclei: the **ventral tegmental area (VTA)** is the cell body of origin for the two mesocorticolimbic pathways, and the **substantia nigra pars compacta (SNc)** is the origin of the nigrostriatal pathway.

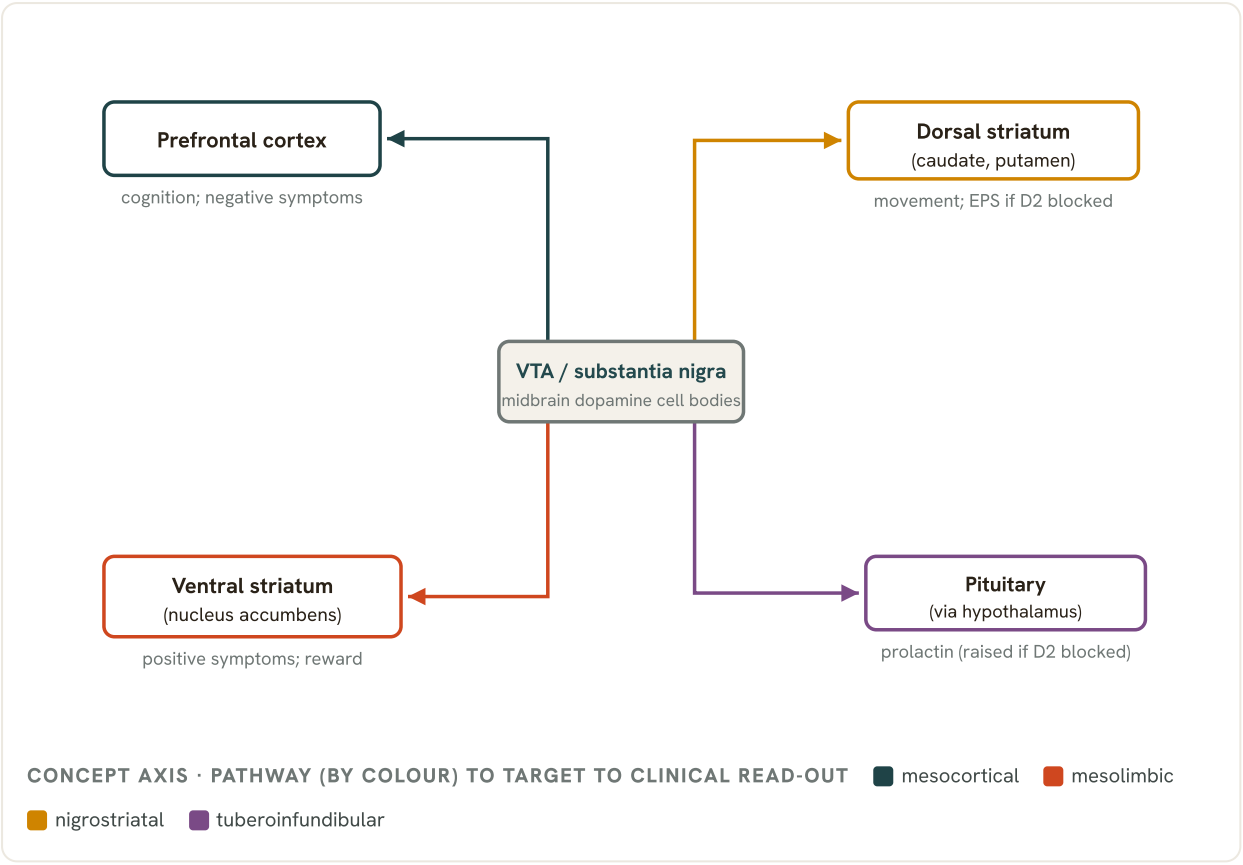


Fig 2.1 The four dopamine pathways from the midbrain nuclei (VTA and substantia nigra), each ending at its target with the clinical read-out a D2 blocker produces there. Mesocortical (petrol) runs to prefrontal cortex, mesolimbic (coral) to ventral striatum, nigrostriatal (marigold) to dorsal striatum, tuberoinfundibular (plum) to the pituitary. Mesolimbic overactivity drives positive symptoms; mesocortical underactivity underlies negative and cognitive symptoms; blocking nigrostriatal D2 gives extrapyramidal side effects; blocking tuberoinfundibular D2 raises prolactin. Benefit and harm are the same drug read on different pathways.

2.1 Synthesis: tyrosine to dopamine, and why tyrosine hydroxylase is the pace-setter

Dopamine sits in the middle of the catecholamine synthetic chain, sharing its first two steps with noradrenaline and adrenaline (Kaplan & Sadock 2024). Bloodborne **tyrosine**, from dietary protein and from phenylalanine, crosses into the brain on the large neutral amino acid transporter and is taken into catecholamine neurons by a high-affinity amino acid transporter.

Step 1: Tyrosine to L-DOPA

In the cytosol, **tyrosine hydroxylase (TH)** hydroxylates tyrosine to L-DOPA (dihydroxyphenylalanine). This is the **rate-limiting step**: it sets the pace of the whole pathway and is the point most open to physiological regulation (end-product inhibition, autoreceptor feedback) and pharmacological attack. TH requires the cofactor *tetrahydrobiopterin (BH4)*, whose own synthesis depends on GTP-cyclohydrolase-1. The competitive TH inhibitor *alpha-methyltyrosine (metyrosine)* depletes catecholamines and is used in phaeochromocytoma.

Step 2: L-DOPA to dopamine

Cytosolic **aromatic amino acid decarboxylase (AADC)**, also called DOPA decarboxylase, decarboxylates L-DOPA to dopamine so avidly that brain L-DOPA levels stay very low. Because exogenous L-DOPA needs only AADC and bypasses the rate-limiting TH step, it is the mainstay of Parkinson disease treatment, restoring depleted striatal dopamine.

Onward (in other neurons only)

In noradrenergic neurons a further vesicular enzyme, *dopamine-beta-hydroxylase (DBH)*, converts dopamine to noradrenaline; adrenaline neurons add *PNMT*. Dopamine neurons lack DBH, which is precisely why they stop at dopamine.

Storage. Newly made dopamine is pumped from cytosol into synaptic vesicles by the **vesicular monoamine transporter (VMAT-2)**, which both concentrates the transmitter for release and shields it from mitochondrial MAO. *Reserpine* irreversibly inhibits VMAT and depletes stores; *tetrabenazine and valbenazine/deutetrabenazine* reversibly inhibit VMAT-2 and are used for chorea and tardive dyskinesia. Amphetamine-class drugs reverse VMAT and the membrane transporter, flooding the synapse.

CLINICAL ANCHOR

The carbidopa/benserazide logic falls straight out of this pathway. Given alone, L-DOPA is decarboxylated to dopamine in the periphery (by AADC in gut and vessels), causing nausea and hypotension and wasting most of the dose. A peripheral AADC inhibitor that cannot cross the blood-brain barrier (carbidopa, benserazide) blocks that peripheral conversion, so more L-DOPA reaches the brain and peripheral side effects fall. Peripheral dopamine also drives emesis via the area postrema, which lies outside the blood-brain barrier, the reason D2 antagonists such as metoclopramide and domperidone are antiemetics.

2.2 Metabolism: MAO, COMT and the HVA read-out

Dopamine is cleared first by reuptake and then by enzymatic degradation through two enzymes acting in either order (Kaplan & Sadock 2024). After release, most dopamine is recaptured by the **dopamine transporter (DAT)** on the presynaptic membrane, the target blocked by *cocaine, methylphenidate and amphetamine*. Degradation then proceeds through:

Monoamine oxidase (MAO)

A mitochondrial (chiefly intraneuronal) enzyme. The **MAO-B** isoform preferentially metabolises dopamine in human brain; its inhibitors (*selegiline, rasagiline, safinamide*) are used in Parkinson disease. MAO oxidatively deaminates dopamine to the intermediate DOPAC.

Catechol-O-methyltransferase (COMT)

A largely extraneuronal, methylating enzyme important in the **prefrontal cortex**, where DAT expression is sparse, so COMT (not reuptake) is the dominant terminator of dopamine action. COMT inhibitors (*tolcapone, entacapone, opicapone*) prolong L-DOPA action. The *COMT Val158Met* polymorphism (Met = lower enzyme activity, higher prefrontal dopamine) is a recurrent exam link to prefrontal cognition and schizophrenia risk.

Homovanillic acid (HVA)

The final, sequential product of MAO and COMT acting together. **HVA** is the principal end-metabolite of dopamine and, in CSF or plasma, is used as an index of central dopaminergic turnover.

PEARL

Fix the end-metabolites by transmitter: dopamine to **HVA**; noradrenaline to **MHPG** (3-methoxy-4-hydroxyphenylglycol); serotonin to **5-HIAA**. The shared dopamine/noradrenaline intermediate DOPAC and the vanilla-family naming (HVA is homovanillic) are common distractors. COMT dominating in the cortex while DAT dominates in the striatum is the single most useful regional contrast on this subtopic.

2.3 Receptors: two families, opposite signs

All five dopamine receptors are G-protein-coupled and sort into two families defined by their effect on adenylate cyclase and cyclic AMP. The D1-like family is stimulatory, the D2-like family inhibitory, and holding that polarity straight explains most of the pharmacology.

FAMILY	MEMBERS	G-PROTEIN / CYCLASE	LOCATION AND CLINICAL NOTE
D1-like	D1, D5	**Gs: stimulate adenylate cyclase, raise cAMP**	D1 densest in striatum and cortex; postsynaptic only; excitatory drive on the direct striatal pathway
D2-like	D2, D3, D4	**Gi/Go: inhibit adenylate cyclase, lower cAMP**	Pre- and postsynaptic; the antipsychotic target; D2 also mediates autoreceptor feedback

The two dopamine receptor families. The discriminator to memorise is the second-messenger sign: D1-like couples to Gs and raises cAMP, D2-like couples to Gi and lowers it.

Within-family detail. D2 is the receptor whose occupancy tracks antipsychotic efficacy and extrapyramidal risk; it exists as short (presynaptic autoreceptor) and long (postsynaptic) isoforms. **D3** concentrates in limbic regions (nucleus accumbens) and is a target of interest for negative symptoms and addiction; *cariprazine* is a D3-preferring D2/D3 partial agonist. **D4** is enriched in cortex and limbic areas, has been linked (weakly and inconsistently) to ADHD and novelty-seeking through the *DRD4 7-repeat* allele, and is notable as a receptor at which *clozapine* has relatively high affinity. Antipsychotic clinical potency correlates tightly with D2 (not D1) affinity, the pharmacological cornerstone of the dopamine hypothesis.

COMMON TRAP

Do not equate "D2 antagonism" with "antipsychotics only". The same D2 blockade that reduces psychosis also produces the antiemetic effect (area postrema), the extrapyramidal effect (nigrostriatal), and hyperprolactinaemia (tuberoinfundibular). Conversely, D2 *agonism* underlies dopamine-agonist treatment of Parkinson disease and prolactinoma. The receptor is neutral; the pathway decides whether an action is therapeutic or an adverse effect.

2.4 The four dopamine pathways as a map

Four projection systems carry the clinical weight of the topic. Two originate in the VTA (mesolimbic, mesocortical), one in the SNc (nigrostriatal), and one in the hypothalamic arcuate

nucleus (tuberoinfundibular). Each maps to one core function and one signature consequence of altered dopamine.

PATHWAY	ORIGIN TO TARGET	NORMAL FUNCTION	CLINICAL CORRELATE
Mesolimbic	VTA to nucleus accumbens / ventral striatum	Reward, motivation, salience	**Hyperactivity to positive symptoms; D2 blockade treats them**
Mesocortical	VTA to prefrontal cortex (DLPFC, VMPFC)	Executive function, affect	**Hypoactivity to negative and cognitive symptoms**
Nigrostriatal	SNc to dorsal striatum (caudate, putamen)	Motor planning, purposeful movement	**Loss to parkinsonism; D2 blockade to EPS and tardive dyskinesia**
Tuberoinfundibular	Arcuate/periventricular hypothalamus to median eminence	Tonic inhibition of prolactin	**D2 blockade to hyperprolactinaemia**

The four dopamine pathways with their signature correlates. The nigrostriatal system holds roughly 80% of brain dopamine, which is why its blockade dominates the motor side-effect profile.

Anatomical anchors. The mesolimbic and mesocortical pathways together form the **mesocorticolimbic system**. The nigrostriatal tract holds about 80% of the brain's dopamine and projects from the SNc to the caudate and putamen. The tuberoinfundibular pathway releases dopamine into the hypophyseal portal circulation to *tonically restrain* prolactin, so anything that lowers dopamine (D2 antagonist, stalk lesion) disinhibits prolactin. Two further minor tracts occasionally appear in vivas: the *hypothalamospinal (diencephalospinal) tract*, implicated in restless legs syndrome, and the *incertohypothalamic pathway* from the zona incerta.

MNEMONIC

"Limbic Lights up, Cortex Cools, Nigra Numbs, Tubero Talks (prolactin)"

Meso**limbic** is hyperactive in psychosis (lights up, positive symptoms). Meso**cortical** is hypoactive (cools, negative/cognitive symptoms). **Nigro**striatal blockade numbs movement (EPS, parkinsonism). **Tubero**infundibular blockade lets prolactin talk (hyperprolactinaemia). Same D2 antagonist, four different pathways, four different outcomes.

HOLD THIS

The receptor is neutral; the pathway decides whether a D2 action is therapeutic or an adverse effect. One D2 blockade reads out as antipsychotic (mesolimbic), EPS (nigrostriatal), antiemesis (area postrema) and hyperprolactinaemia (tuberoinfundibular).

2.5 The dopamine hypothesis of schizophrenia: three versions

The dopamine hypothesis is the most examined single theory in the syllabus, and the modern answer requires you to trace its evolution across three versions rather than reciting only the original (Howes & Kapur 2009).

Version I: the receptor hypothesis (1960s to 1970s)

Built on two pharmacological pillars: antipsychotic clinical potency correlates with **D2 receptor affinity**, and dopamine-releasing drugs (amphetamine, L-DOPA) can induce or worsen psychosis. The claim was a global *hyperdopaminergic* state. Its weakness: it could not explain negative and cognitive symptoms, nor the delay and incompleteness of antipsychotic response.

Version II: the regional / two-pathway hypothesis

Reframed the illness as *hyperactivity of the mesolimbic pathway* (driving positive symptoms) coupled with *hypoactivity of the mesocortical pathway* (driving negative and cognitive symptoms), the frontal hypodopaminergia possibly disinhibiting subcortical dopamine. This is Stahl's working model and reconciles the symptom domains.

Version III: the final common pathway (Howes & Kapur 2009)

The current consensus. Multiple risk factors (genes, obstetric events, drugs, psychosocial stress) converge on a single node: **presynaptic striatal dopamine dysregulation**, that is, increased dopamine synthesis and release capacity, demonstrated on molecular imaging. The lesion is presynaptic, not primarily at the receptor, and it is *associational* (linked to the psychosis, not the diagnostic label). It integrates the glutamatergic (NMDA hypofunction) account, where cortical disinhibition drives the subcortical dopamine excess.

Aberrant salience. The phenomenological bridge, from Kapur 2003, is that a dysregulated hyperdopaminergic state at the "brain" level produces *aberrant assignment of salience* to neutral internal and external stimuli at the "mind" level. Delusions are then a top-down cognitive effort to explain experiences that feel abnormally significant, and hallucinations are the direct experience of aberrant salience of internal representations. Antipsychotics do not erase symptoms but *dampen the salience*, allowing gradual re-learning (extinction-like); stopping them lets the dysregulation and salience return, the model's account of relapse.

> **CLINICAL ANCHOR**
>
> Version III explains three clinical observations at once: why molecular imaging shows elevated striatal dopamine synthesis capacity even in the prodrome, why D2 blockade helps positive symptoms but leaves negative and cognitive symptoms largely untouched (the lesion is upstream and presynaptic), and why roughly a third of patients whose psychosis is *not* dopaminergic (glutamate-driven) respond poorly to D2 antagonists and may need clozapine.

TRAP "Atypical" is a clinical outcome (lower EPS at effective doses), not a single receptor property; do not force one mechanism (5-HT2A block, fast D2 dissociation, D2 partial agonism) onto every atypical.

2.6 Stahl's antipsychotic logic: one blockade, four consequences

The pathway map converts directly into pharmacology. A pure D2 antagonist does not selectively find the mesolimbic pathway; it blocks D2 everywhere, so every pathway contributes a predictable effect (Stahl 2021).

- **Mesolimbic.** D2 blockade here is the intended action: reduced positive symptoms. This is the therapeutic target.

- **Mesocortical.** This pathway is already hypodopaminergic; adding D2 blockade risks worsening negative and cognitive symptoms (secondary negative symptoms, neuroleptic-induced deficit syndrome).
- **Nigrostriatal.** D2 blockade produces acute **extrapyramidal symptoms** (dystonia, parkinsonism, akathisia) and, with chronic blockade and receptor upregulation, **tardive dyskinesia**. High-potency first-generation agents (haloperidol) are the worst offenders.
- **Tuberoinfundibular.** D2 blockade disinhibits prolactin, causing hyperprolactinaemia (galactorrhoea, amenorrhoea, sexual dysfunction, reduced bone density). Risperidone, paliperidone and amisulpride are the classic culprits.

The atypical solution. Second-generation agents soften this by adding **5-HT2A antagonism**: serotonin normally brakes dopamine release in the nigrostriatal and tuberoinfundibular pathways, so blocking 5-HT2A disinhibits dopamine selectively in those tracts, sparing motor function and prolactin while retaining mesolimbic D2 blockade. The *D2 partial agonists* (aripiprazole, brexpiprazole, cariprazine) go further, acting as functional antagonists where dopamine is high (mesolimbic) but as agonists where it is low (mesocortical, tuberoinfundibular), which is why aripiprazole is prolactin-sparing and low in EPS. The 2024 US approval of *xanomeline-trospium*, a muscarinic M1/M4 agonist, is the first antipsychotic to treat psychosis *without* direct D2 blockade, acting upstream on the cholinergic modulation of dopamine and so avoiding EPS and hyperprolactinaemia by design.

COMMON TRAP

"Atypical" is not a receptor property but a clinical outcome (lower EPS at effective doses). The mechanism claimed for it varies: 5-HT2A antagonism (risperidone, olanzapine), fast D2 dissociation (quetiapine, clozapine), or D2 partial agonism (aripiprazole). Amisulpride is atypical yet has no meaningful 5-HT2A action, working through preferential limbic D2/D3 blockade and presynaptic autoreceptor effects at low dose. Do not force one mechanism onto every atypical.

2.7 Reward, addiction and the wanting/liking distinction

The mesolimbic (VTA to nucleus accumbens) pathway is the reward pathway, but its role in addiction is more precise than "the pleasure chemical" (Berridge & Robinson 1998; Koob & Volkow 2010). Phasic dopamine firing encodes a **reward prediction error** (Schultz): dopamine neurons fire to unexpected reward, shift to the predictive cue once learning occurs, and dip below baseline when an expected reward is omitted. This is the neural substrate of reinforcement learning.

Wanting versus liking. The incentive-salience account separates *"wanting"* (incentive motivation, dopamine-dependent) from *"liking"* (hedonic pleasure, more opioid- and endocannabinoid-dependent). Addiction is a pathology of wanting: repeated drug use sensitises the mesolimbic system so that drug cues acquire excessive incentive salience (craving) even as the drug's hedonic impact wanes, explaining why craving outlives pleasure. All major drugs of abuse converge on raising accumbens dopamine (cocaine and amphetamine directly via DAT and VMAT; opioids,

nicotine, alcohol and cannabinoids by disinhibiting VTA neurons). ICD-11 codes these under disorders due to substance use; DSM-5-TR uses the substance use disorder construct.

PEARL

The prediction-error framework also explains a therapeutic paradox: dopamine agonists used for Parkinson disease and restless legs (pramipexole, ropinirole) can trigger *impulse control disorders* (pathological gambling, hypersexuality, compulsive shopping) by over-driving the intact mesolimbic reward circuit while treating the degenerated nigrostriatal one. Same drug, two pathways, opposite valence, the recurring lesson of this topic.

2.8 Neurological correlates: Parkinson, ADHD and restless legs

Beyond psychosis, three disorders anchor dopamine to clinical neurology and neurodevelopment.

Parkinson disease

Progressive degeneration of the **nigrostriatal** dopaminergic neurons of the SNc, with Lewy-body (alpha-synuclein) pathology, producing the classic bradykinesia, rigidity, resting tremor and postural instability once about 60 to 80% of nigral neurons are lost. Treatment restores dopamine (L-DOPA plus carbidopa, dopamine agonists, MAO-B and COMT inhibitors). The mirror-image relationship with antipsychotic-induced parkinsonism (too little nigrostriatal dopamine either way) is a favourite comparison. The toxin *MPTP*, a selective nigrostriatal poison, is the standard chemical model.

ADHD

Framed as hypofunction of dopamine (and noradrenaline) signalling in the **prefrontal cortex and striatum**, impairing attention, working memory and response inhibition (Arnsten & Rubia 2012; Volkow 2009). Stimulants (methylphenidate blocks DAT and NET; amphetamine additionally reverses them and VMAT) raise synaptic dopamine and noradrenaline and are first-line. ICD-11 codes it as attention deficit hyperactivity disorder; DSM-5-TR as ADHD. The *DRD4* and *DAT1 (SLC6A3)* genes are the most replicated candidate associations, though effect sizes are small.

Restless legs syndrome (RLS)

A sensorimotor disorder with an urge to move the legs, worse at rest and in the evening, relieved by movement. The dopaminergic contribution is thought to involve the *hypothalamospinal (A11) diencephalospinal* dopaminergic projection to the cord, compounded by CNS *iron deficiency* (iron is the TH cofactor for dopamine synthesis). Low-dose dopamine agonists and alpha-2-delta ligands (gabapentin enacarbil) are used, though agonists carry a risk of *augmentation* (symptom worsening and spread over time).

INDIA

In Indian practice the dopamine trade-offs surface daily: high-potency first-generation antipsychotics (haloperidol, trifluoperazine) remain widely used for cost reasons, so clinicians must actively watch for EPS, tardive dyskinesia and drug-induced parkinsonism, and for prolactin-related complaints that patients may not volunteer (menstrual change, galactorrhoea, sexual dysfunction). Restless legs is easy to miss and worth screening for in patients on iron-poor vegetarian diets and in pregnancy, where iron deficiency is prevalent; check ferritin before attributing nocturnal restlessness to akathisia or anxiety.

3 · Serotonin system and receptor subtypes

One transmitter, at least fourteen receptors, and almost every drug we prescribe. Serotonin (5-hydroxytryptamine, 5-HT) is the monoamine the paper returns to most, because the serotonergic receptor family is the widest of any neurotransmitter and because the entire first line of antidepressant, anxiolytic and anti-obsessional pharmacology is built on it. The examinable spine of the topic is a chain of cause and effect: a single pool of 5-HT, arising from a handful of brainstem nuclei, is read by a receptor set whose members do opposite things (excite or inhibit, on the cell of origin or on the target), and the clinical phenomena, from the SSRI response lag to serotonin syndrome to the psychedelic experience, fall out of *which* receptor is engaged, *where*, and *for how long*.

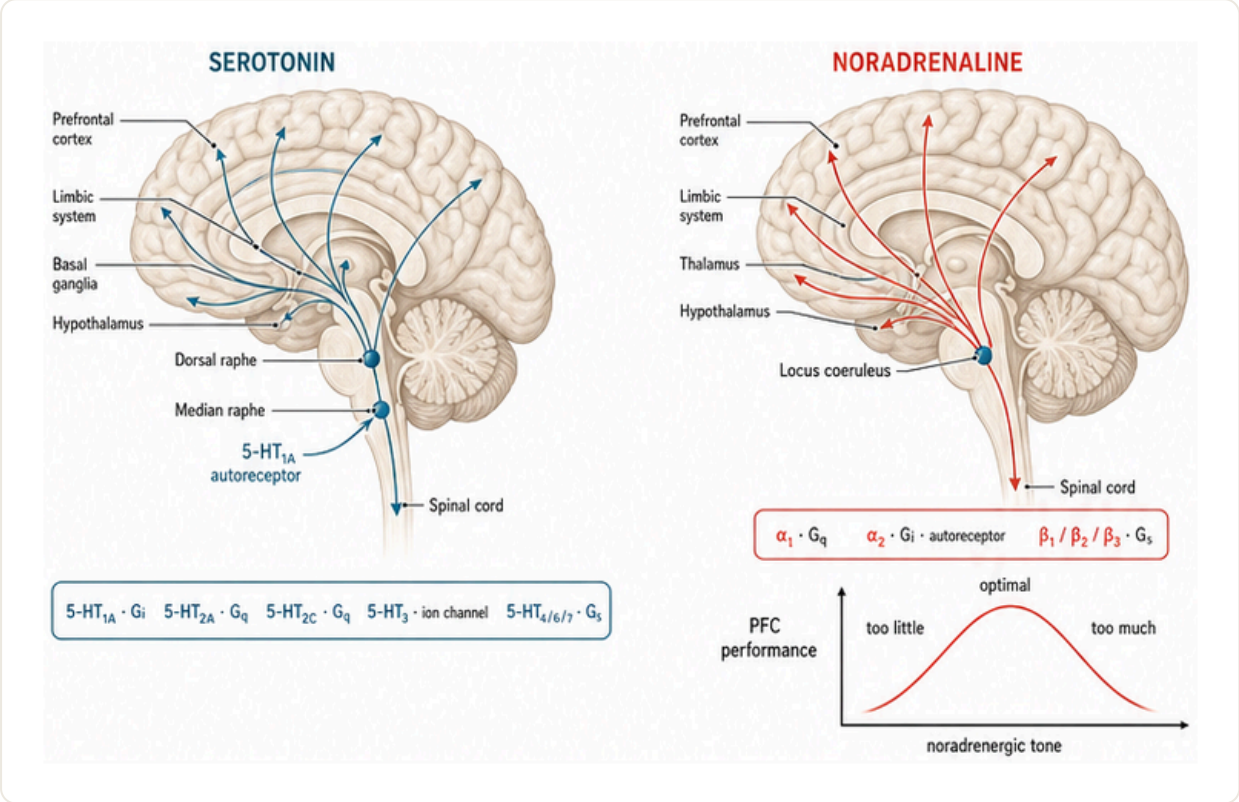


Fig 2.2 Serotonin and noradrenaline systems.

Hold three organising facts before the detail. First, synthesis is **rate-limited by tryptophan hydroxylase** and by substrate availability, which is why dietary and cofactor manipulations move central 5-HT. Second, the raphe nuclei project almost everywhere, so serotonin is a *modulator* of whole networks rather than a point-to-point signal. Third, the receptor families are defined by their signal transduction (Gi, Gq, or a ligand-gated channel), and that coupling predicts function: this is the single most rewarding table in the topic, and it is flagged below (Stahl 2021; Kaplan & Sadock 2024).

3.1 Synthesis: tryptophan to 5-HTP to 5-HT, and the rate-limiting step

The two-step pathway. Synthesis begins with the essential amino acid **tryptophan**, which crosses the blood-brain barrier by an active transporter it shares with the other large neutral amino acids, so its central availability depends on the plasma tryptophan-to-competitor ratio (the

basis of acute tryptophan depletion experiments). Tryptophan is hydroxylated to **5-hydroxytryptophan (5-HTP)** by **tryptophan hydroxylase (TPH)**, the *rate-limiting enzyme*, which requires the cofactor tetrahydrobiopterin (BH4); 5-HTP is then decarboxylated to 5-HT by aromatic L-amino acid decarboxylase (the same DOPA decarboxylase of the catecholamine pathway), which uses pyridoxal-5-phosphate (vitamin B6) as coenzyme (Bamalan 2023).

Two isoforms of the rate-limiting enzyme. The distinction the exam wants is that **TPH2** is the neuronal, brain-specific isoform expressed in the raphe, whereas TPH1 is peripheral (enterochromaffin cells of the gut, pineal). This matters because polymorphisms in the TPH2 gene, not TPH1, are the ones linked to mood and suicidality, and because it explains why the vast peripheral serotonin pool (roughly 90% of body serotonin is gut-derived) is a separate compartment that peripheral drugs can target without central effect.

PEARL

Serotonin is the obligatory precursor of **melatonin**. In the pineal, 5-HT is N-acetylated then O-methylated to melatonin under noradrenergic (dark-driven) control, which is why the serotonergic and circadian systems are biochemically continuous and why agomelatine (an MT1/MT2 agonist that is also a 5-HT2C antagonist) sits at their junction.

3.2 Storage, release and reuptake: the SERT and VMAT2 machinery

Vesicular packaging and the reuptake transporter. Cytoplasmic 5-HT is loaded into synaptic vesicles by the vesicular monoamine transporter (VMAT2), released on depolarisation, and, critically, cleared from the synapse by the **serotonin transporter (SERT, SLC6A4)**, a sodium-coupled plasma-membrane pump. SERT is the molecular target of the SSRIs, the SNRIs, and clomipramine, and its promoter polymorphism (**5-HTTLPR**, short versus long allele) is the classic gene-by-environment candidate for depression vulnerability. Recaptured 5-HT is either repackaged into vesicles or degraded (Bamalan 2023).

COMMON TRAP

Do not conflate the enzyme (TPH, which *makes* serotonin, rate-limiting for synthesis) with the transporter (SERT, which *clears* it, the drug target). SSRIs act on SERT and change nothing about the synthetic rate acutely; the delayed clinical response is a receptor-adaptation story, not a synthesis story (see 3.9).

3.3 Metabolism: MAO-A, 5-HIAA, and what the CSF metabolite tells you

The degradative pathway. Intraneuronal and extraneuronal 5-HT is oxidatively deaminated by **monoamine oxidase**, principally the **MAO-A** isoform (5-HT and noradrenaline are preferential MAO-A substrates; MAO-B prefers phenylethylamine and, jointly with MAO-A, dopamine), to 5-hydroxyindoleacetaldehyde and then by aldehyde dehydrogenase to **5-hydroxyindoleacetic acid (5-HIAA)**, the terminal metabolite excreted in urine and measurable in CSF (Bamalan 2023).

Why 5-HIAA is examinable. Low CSF 5-HIAA is the most durable biological correlate in psychiatry of **impulsive aggression, violent suicide attempts and impulsivity** (the "low-serotonin, low-impulse-control" association of Asberg and others), and 24-hour urinary 5-HIAA is the screening test for **carcinoid syndrome**, where a serotonin-secreting neuroendocrine tumour drives flushing and diarrhoea, a peripheral picture that overlaps symptomatically with serotonin syndrome. MAO-A knockout and the Brunner syndrome point mutation link the enzyme to aggression, closing the loop with the 5-HIAA data.

3.4 Raphe nuclei and the ascending projections (cross-reference the Functional Neuroanatomy & Neurophysiology notes)

The nuclei of origin. Serotonergic cell bodies are almost entirely confined to the midline **raphe nuclei** of the brainstem (Dahlgren and Fuxe's B1 to B9 groups). The rostral group, dominated by the **dorsal raphe and median raphe** of the midbrain and upper pons, supplies the ascending forebrain projection to cortex, striatum, limbic system, hippocampus and hypothalamus; the caudal group projects down the spinal cord to modulate pain (the descending analgesic system) and autonomic outflow. As with the locus coeruleus for noradrenaline, a very small number of neurons innervate the entire forebrain, which is the anatomical reason serotonin acts as a diffuse network modulator (see the Functional Neuroanatomy & Neurophysiology notes for the monoamine nuclei of origin and their projection architecture).

> **CLINICAL ANCHOR**
>
> The dorsal raphe carries the cell-body (somatodendritic) **5-HT1A autoreceptor** that gates the whole ascending system. When an SSRI first floods the synapse, these autoreceptors sense the excess and *shut the raphe down*, blunting the initial response; their desensitisation over two to four weeks is the leading mechanistic account of the therapeutic lag (Stahl 2021). Anatomy here directly predicts a clinical timeline.

3.5 The receptor map: seven families, three transduction logics

The organising principle is signal transduction. All 5-HT receptors are G-protein-coupled except one. The families sort into three functional classes, and knowing the class tells you the direction of the effect. The **5-HT1 family** couples to *Gi/Go*, inhibits adenylyl cyclase, lowers cAMP and opens potassium channels, so it is *inhibitory / hyperpolarising*. The **5-HT2 family** couples to *Gq*, activates phospholipase C and the IP3/DAG cascade, so it is *excitatory / depolarising*. The **5-HT3 receptor** is the odd one out, a *ligand-gated cation channel* (ionotropic, fast, like a nicotinic receptor), and it is excitatory by direct depolarisation. The remaining families, **5-HT4, 5-HT6 and 5-HT7**, couple to *Gs*, raising cAMP (excitatory), and 5-HT5 couples to Gi (Stahl 2021; Kaplan & Sadock 2024). Fix that scaffold and every subtype below hangs off it.

Autoreceptor

A receptor on the serotonergic neuron itself that senses its own transmitter and inhibits further firing or release. Somatodendritic autoreceptors (5-HT1A, on the raphe cell body) reduce firing rate; terminal autoreceptors (5-HT1B/1D, on the axon terminal) reduce release per impulse.

Heteroreceptor

The same receptor subtype sitting postsynaptically on a *non*-serotonergic neuron, where it mediates the network effect rather than feedback. 5-HT1A is thus an autoreceptor on the raphe and a heteroreceptor (postsynaptic, largely inhibitory) on cortical and hippocampal pyramidal cells.

3.6 5-HT1 family: 1A (auto- and heteroreceptor), 1B/1D (terminal autoreceptor and the triptan target)

5-HT1A. The most examined subtype. As a somatodendritic **autoreceptor** in the raphe it brakes firing; as a postsynaptic **heteroreceptor** in hippocampus and cortex it is the target that mediates anxiolysis and antidepressant effect. **Buspirone** and **gepirone** are 5-HT1A partial agonists used in anxiety; several second-generation antipsychotics (aripiprazole, ziprasidone, lurasidone) and the multimodal agent vortioxetine engage 5-HT1A partial agonism, and this partial agonism *increases prefrontal dopamine release*, part of why these agents spare or improve cognition and negative symptoms (Kaplan & Sadock 2024).

5-HT1B and 5-HT1D. These are the **terminal autoreceptors** that dampen serotonin release per impulse, and they are also the pharmacological target of the **triptans** (sumatriptan and congeners), 5-HT1B/1D agonists that abort migraine by cranial vasoconstriction and by suppressing trigeminal CGRP release. The exam pairing is that their cardiac and coronary expression is the reason triptans carry a coronary-vasospasm caution, and that provoking OCD symptoms with the mixed agonist meta-chlorophenylpiperazine (mCPP) implicates this and the 5-HT2C subtype in obsessional pathology.

3.7 5-HT2 family: 2A (the antipsychotic and hallucinogen hub) and 2C

5-HT2A. The pivotal cortical excitatory receptor and arguably the single most clinically loaded subtype. Its antagonism defines the **atypical (second-generation) antipsychotics**: the high 5-HT2A-to-D2 affinity ratio (Meltzer's index) is the classical pharmacological signature of atypicality and underlies the lower liability for extrapyramidal side effects, because 5-HT2A blockade disinhibits nigrostriatal dopamine. 5-HT2A antagonism also mediates the improvement of certain negative and cognitive features and, peripherally, is exploited by the hypnotics (low-dose trazodone, the 5-HT2A antagonist pimavanserin for Parkinson psychosis). Critically, 5-HT2A is the receptor at which the **classical hallucinogens** act (see 3.11).

5-HT2C. A Gq-coupled receptor prominent in the choroid plexus, hypothalamus and mesolimbic circuitry, central to appetite and mood. Its *agonism* suppresses appetite (the mechanism of the former anorectic lorcaserin) and its *antagonism* disinhibits dopamine and noradrenaline (part of the action of mirtazapine and agomelatine, and a contributor to the weight gain of some antipsychotics and to fluoxetine's activating profile via a weak 2C effect). It is also a major site of RNA editing, an examinable molecular-biology detail.

MNEMONIC

"1 is Inhibitory / auto, 2 is Excitatory / cortical, 3 is a Channel"

The three high-yield families in one line. 5-HT**1** = Gi, **i**nhibitory, the autoreceptor family (1A brakes the raphe, 1B/1D brake the terminal, triptan target). 5-HT**2** = Gq, **e**xcitatory, cortical (2A = antipsychotic and hallucinogen hub, 2C = appetite and mood). 5-HT**3** = the only ionotropic **c**hannel (nausea and the vagal gut, ondansetron target). Everything else (4, 6, 7) is Gs and cAMP-raising.

HOLD THIS

The SSRI therapeutic lag is a somatodendritic 5-HT1A autoreceptor-desensitisation story, not a synthesis story. SERT block is immediate; raphe firing recovers only as the autoreceptor desensitises over two to four weeks.

3.8 5-HT3 (ionotropic) and 5-HT4 to 5-HT7: the remaining families

5-HT3

The sole **ligand-gated cation channel** in the family, fast and excitatory, expressed on vagal afferents, the area postrema (chemoreceptor trigger zone) and the enteric nervous system. It mediates nausea and vomiting: **ondansetron** and the "-setron" antiemetics are 5-HT3 antagonists, and 5-HT3 antagonism is why several serotonergic drugs cause nausea early and why mirtazapine (a 5-HT3 blocker) is anti-nauseant and appetite-stimulating.

5-HT4

Gs-coupled, prokinetic in the gut (target of prucalopride for constipation) and implicated in cognition and hippocampal function; a candidate antidepressant mechanism under study.

5-HT5

Gi-coupled, least characterised; possible roles in circadian rhythm and cognition, low examinable yield beyond naming it.

5-HT6

Gs-coupled, almost exclusively central, dense in striatum and cortex; a cognition and antipsychotic-related target (many antipsychotics and antidepressants have appreciable 5-HT6 affinity).

5-HT7

Gs-coupled, involved in circadian entrainment, thermoregulation, sleep and mood; antagonism is part of the profiles of vortioxetine, lurasidone and several atypicals and is a putative antidepressant contributor.

3.9 Functional roles across systems: mood, anxiety, sleep, appetite, sexual function, impulsivity

Because the raphe projects everywhere, serotonin touches nearly every behavioural axis, and the paper likes the receptor-to-function mapping. **Mood and anxiety** run largely through postsynaptic 5-HT1A and modulation of 2A/2C. **Sleep** is dual: serotonin promotes wakefulness and suppresses REM at the raphe, yet is the melatonin precursor, and 5-HT2A antagonism (trazodone, low-dose quetiapine) deepens slow-wave sleep. **Appetite** is 5-HT2C-driven (agonism reduces intake). **Sexual function** is inhibited by serotonin, chiefly via 5-HT2A/2C, which is the receptor basis of SSRI-induced sexual dysfunction and, conversely, why 5-HT2 antagonists

(mirtazapine, the 5-HT1A agonism of buspirone or vortioxetine) can rescue it. **Impulsivity and aggression** track inversely with serotonergic tone, the behavioural correlate of the low-CSF-5-HIAA finding (3.3). Serotonin also has substantial peripheral roles (platelet aggregation, gut motility, vascular tone, respiratory drive) that surface in serotonin syndrome and carcinoid.

CLINICAL ANCHOR

SSRI-emergent sexual dysfunction (delayed ejaculation, anorgasmia, reduced libido) is a 5-HT2-mediated, dose-related, and frequently persistent adverse effect that drives non-adherence. Naming the receptor (5-HT2A/2C) lets you reason about the switch: to an agent that antagonises 2A/2C (mirtazapine) or agonises 1A (vortioxetine, adjunct buspirone), rather than simply lowering the dose.

3.10 Clinical: depression, OCD, and the SSRI / 5-HT2A adaptation story

Depression and the monoamine account. Reduced serotonergic transmission is central to the classical monoamine hypothesis of depression, evidenced by the efficacy of SERT and MAO-A inhibitors, by symptom relapse on acute tryptophan depletion in remitted patients, and by low CSF 5-HIAA in a suicidal subgroup. The account is acknowledged as incomplete (the transmitter change is immediate but the response is delayed), which reframes it as a **receptor-adaptation and neuroplasticity** model: chronic SERT blockade desensitises the somatodendritic 5-HT1A autoreceptor, restoring raphe firing, and downstream downregulates postsynaptic 5-HT2A receptors, with BDNF-mediated plasticity as the final common path (Stahl 2021).

OCD. The serotonergic specificity of obsessive-compulsive disorder (ICD-11 6B20; DSM-5-TR obsessive-compulsive disorder) is a guaranteed exam point: only the serotonergic antidepressants (SSRIs and clomipramine) are effective, noradrenergic-selective agents such as desipramine are not, and the effective dose is typically higher and the latency longer than in depression. Symptom provocation by the mixed serotonergic agonist mCPP implicates 5-HT2C and 5-HT1B/1D subtypes in the pathophysiology.

INDIA

SSRIs (fluoxetine, sertraline, escitalopram) are on the WHO and Indian essential medicines lists and are the pragmatic first line for depression, anxiety and OCD in Indian practice given cost and tolerability. Clomipramine remains widely used and affordable for OCD; the higher target dose and longer trial (10 to 12 weeks) must be counselled explicitly to sustain adherence.

3.11 Clinical: serotonin syndrome and hallucinogens at 5-HT2A

Serotonin syndrome (serotonin toxicity). An excess-serotonin state, usually from a serotonergic drug combination (classically an SSRI or SNRI with an MAOI, tramadol, linezolid, or triptans, or an overdose), evolving over hours. The Hunter triad the exam wants is **neuromuscular excitation** (spontaneous and inducible clonus, ocular clonus, hyperreflexia, tremor, rigidity, with a lower-limb predominance), **autonomic instability** (hyperthermia, diaphoresis, tachycardia, mydriasis, hyperactive bowel sounds and diarrhoea), and **altered mental state** (agitation,

delirium). Management is withdrawal of the offending agents, supportive cooling and benzodiazepines, and the 5-HT2A antagonist **cyproheptadine** in severe cases (Bamalan 2023).

Hallucinogens at 5-HT2A. The classical serotonergic psychedelics (**LSD, psilocybin, DMT, mescaline**) are *agonists at the cortical 5-HT2A receptor*, and 5-HT2A agonism is both necessary and sufficient for the hallucinogenic effect (it is abolished by 5-HT2A antagonists such as ketanserin). The same receptor that atypical antipsychotics *block* is the one hallucinogens *activate*, a symmetry the paper likes. This has re-entered the syllabus with the 2020s trials of psilocybin-assisted therapy for treatment-resistant depression, and it separates the classical psychedelics mechanistically from the NMDA-antagonist dissociatives (ketamine and esketamine) and the entactogens (MDMA, a serotonin releaser).

RULE **5-HT2A is the one receptor atypical antipsychotics block and classical hallucinogens activate.** Same subtype, opposite direction; 5-HT2A agonism is necessary and sufficient for the psychedelic effect.

COMMON TRAP

Serotonin syndrome versus neuroleptic malignant syndrome. Both give hyperthermia and altered mental state, but serotonin syndrome is *hyperkinetic* (clonus, hyperreflexia, rapid onset over hours, offending serotonergic drug) whereas NMS is *hypokinetic* (lead-pipe rigidity without clonus, bradyreflexia, slower onset over days, a dopamine antagonist or dopaminergic withdrawal). Clonus, especially ocular and lower-limb, is the discriminator.

3.12 Serotonin-dopamine interaction: the reciprocal brake

Serotonin holds a tonic brake on dopamine, and releasing that brake at selected receptors is the engine of modern psychopharmacology. Serotonin, acting principally through **5-HT2A** receptors on dopaminergic circuits, inhibits dopamine release along the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular pathways. This single fact explains the atypical antipsychotic advantage: by blocking 5-HT2A, these agents *disinhibit* dopamine specifically in the nigrostriatal pathway (reducing extrapyramidal side effects) and the tuberoinfundibular pathway (limiting hyperprolactinaemia), while their D2 blockade still delivers antipsychotic effect in the mesolimbic system. **5-HT1A** partial agonism adds a complementary pro-dopaminergic push in prefrontal cortex, improving cognition and negative symptoms (Kaplan & Sadock 2024; Stahl 2021). The pharmacological psychosis models (LSD and other 5-HT2A agonists as psychotomimetics) sit on the same axis.

3.13 The receptor-family reference table

The consolidating summary. Read the transduction column first: it predicts the direction of effect, and every drug and function in the last two columns follows from it.

FAMILY	SUBTYPES	TRANSDUCTION / EFFECT	KEY LOCATIONS	FUNCTION & DRUG RELEVANCE
5-HT1	1A, 1B, 1D, 1E, 1F	**Gi/Go, inhibitory (lowers cAMP)**	Raphe (1A soma), axon terminals (1B/1D), cranial vessels	1A auto- and heteroreceptor (buspirone, SSRI-lag); 1B/1D terminal autoreceptor and triptan target
5-HT2	2A, 2B, 2C	**Gq, excitatory (PLC, IP3/DAG)**	Cortex (2A), choroid plexus/hypothalamus (2C), heart valves (2B)	2A = atypical antipsychotic + hallucinogen hub, sexual dysfunction; 2C = appetite, mood; 2B = valvulopathy (fenfluramine)
5-HT3	3A to 3E	**Ligand-gated cation channel, fast excitatory**	Area postrema, vagal afferents, gut	Nausea and emesis; ondansetron ("-setron") antagonists; mirtazapine blockade
5-HT4	single	Gs, excitatory (raises cAMP)	Gut, hippocampus	Prokinetic (prucalopride); cognition; candidate antidepressant target
5-HT5	5A, 5B	Gi, inhibitory	CNS, least characterised	Possible circadian and cognitive roles; low yield
5-HT6	single	Gs, excitatory	Striatum, cortex (CNS-only)	Cognition target; affinity of many antipsychotics and antidepressants
5-HT7	single	Gs, excitatory	Hypothalamus, thalamus, limbic	Circadian, thermoregulation, sleep, mood; antagonism in vortioxetine, lurasidone

Serotonin receptor families by transduction logic: Gi families are inhibitory, Gq (5-HT2) and Gs (4, 6, 7) families are excitatory, and 5-HT3 alone is an ionotropic channel; the coupling predicts the clinical role.

4 · Noradrenergic system

Norepinephrine (NE, noradrenaline) is the catecholamine that tunes the brain's signal-to-noise ratio: it decides how vigilant, aroused and reactive the organism is at any given moment. First isolated by **Ulf von Euler** in the 1940s, it sits one enzymatic step downstream of dopamine and is the workhorse of the ascending arousal and stress-response systems. For Paper I you are

expected to build the full picture: the synthetic cascade and its rate-limiting step, the metabolite you measure clinically (MHPG), the anatomy of the locus coeruleus and its diffuse projections, the adrenoceptor family with its autoreceptor logic, and how all of this maps onto depression, anxiety, PTSD and ADHD together with the drugs that exploit each node.

The examiner's favourite framing is that NE is a **gain-control** transmitter. Unlike a fast point-to-point transmitter, the locus coeruleus fires tonically to set baseline arousal and phasically to flag behaviourally salient stimuli, so noradrenergic tone shapes attention, working memory and threat-detection through an inverted-U dose-response. Too little gives inattention and low arousal; too much gives anxiety, hypervigilance and, at the prefrontal cortex, cognitive collapse. Keep that curve in mind, because every clinical and pharmacological point below hangs off it.

4.1 Synthesis: the catecholamine cascade to noradrenaline

Pathway. NE synthesis is the tail end of the shared catecholamine pathway. Dietary **tyrosine** (or phenylalanine, converted to tyrosine by phenylalanine hydroxylase) crosses the blood-brain barrier and is hydroxylated to **L-DOPA** by **tyrosine hydroxylase**, the *rate-limiting* enzyme of the entire catecholamine pathway and the classic single-mark answer. L-DOPA is decarboxylated to **dopamine** by aromatic L-amino acid decarboxylase (DOPA decarboxylase). In noradrenergic neurons dopamine is transported into synaptic vesicles by the **vesicular monoamine transporter (VMAT2)**, and it is *inside the vesicle* that **dopamine beta-hydroxylase (DBH)** hydroxylates dopamine to norepinephrine (Stahl 2021). DBH is a copper-containing, vitamin-C-dependent enzyme and is the enzyme that defines a cell as noradrenergic.

Exam hook. Two features distinguish this cascade from the dopaminergic one: DBH is the noradrenergic-defining enzyme, and it acts *within the vesicle* rather than in the cytosol, which is why VMAT2 loading precedes the final synthetic step. Tyrosine hydroxylase remains rate-limiting for the whole family.

Tyrosine hydroxylase (TH)

Rate-limiting enzyme; converts tyrosine to L-DOPA; requires tetrahydrobiopterin cofactor.

DOPA decarboxylase (AADC)

Converts L-DOPA to dopamine; pyridoxal-phosphate dependent; not rate-limiting.

Dopamine beta-hydroxylase (DBH)

Vesicular, copper- and ascorbate-dependent; converts dopamine to norepinephrine; noradrenergic-defining.

PNMT

Phenylethanolamine-N-methyltransferase; methylates norepinephrine to epinephrine (adrenaline); needs cortisol induction.

4.2 Epinephrine as a central transmitter: PNMT and the C1-C3 adrenergic neurons

Beyond its familiar role as an adrenal-medullary hormone, **epinephrine (adrenaline)** is also a genuine CNS transmitter in a small dedicated population of neurons. In these cells the enzyme **phenylethanolamine-N-methyltransferase (PNMT)** methylates norepinephrine to epinephrine, using S-adenosylmethionine as the methyl donor. Centrally, PNMT-expressing

adrenergic neurons are clustered in the **C1, C2 and C3 adrenergic cell groups of the rostral ventrolateral and dorsomedial medulla**, and they project to the hypothalamus, the locus coeruleus and other brainstem autonomic nuclei (Kaplan and Sadock 2024). Their central role is minor compared with NE but real: they contribute to central cardiovascular control (baroreflex, blood-pressure and sympathetic set-point) and to neuroendocrine stress reactivity. PNMT is glucocorticoid-inducible, which links adrenaline synthesis mechanistically to the HPA axis and the stress response.

PEARL

Adrenaline in the brain is a medullary phenomenon. If a stem asks where central epinephrine comes from, the answer is the PNMT-positive C1-C3 adrenergic neurons of the medulla, not the locus coeruleus (which is noradrenergic). PNMT needs cortisol to be induced, which is why the adrenal medulla, bathed in cortisol-rich portal blood, is the great epinephrine factory and why chronic stress up-regulates adrenaline synthesis.

TRAP Central adrenaline is not made in the locus coeruleus. It comes from the PNMT-positive C1-C3 medullary neurons; the locus coeruleus is noradrenergic.

4.3 Metabolism: MAO, COMT and the MHPG and VMA end-products

NE is cleared from the synapse chiefly by **reuptake** through the **norepinephrine transporter (NET)**, a sodium- and chloride-dependent presynaptic transporter that is the target of most noradrenergic antidepressants. Recaptured or leaked NE is then degraded by two enzymes: **monoamine oxidase (MAO)**, located on the outer mitochondrial membrane and predominantly intraneuronal, and **catechol-O-methyltransferase (COMT)**, largely extraneuronal and glial. The order in which these two act determines the end-product.

The metabolite that matters. In the *central nervous system* the principal metabolite of NE is **3-methoxy-4-hydroxyphenylglycol (MHPG)**, the answer examiners want for a central NE marker; in the *periphery* complete oxidation in the liver yields **vanillylmandelic acid (VMA)**, the urinary metabolite screened for in phaeochromocytoma. Historically, urinary MHPG was studied as a biomarker to subtype depression and to predict differential response to noradrenergic versus serotonergic antidepressants, though its clinical utility never held up. The MAO isoenzyme distinction is high-yield: **MAO-A** preferentially deaminates NE and serotonin and is the isoform relevant to antidepressant MAOIs, whereas **MAO-B** favours phenylethylamine and is the selegiline target in Parkinson disease.

FEATURE	MHPG	VMA
Compartment	**Chiefly central (CNS) NE**	Peripheral / whole-body NE and adrenaline
Final site of formation	Brain, then some hepatic conversion	**Liver (complete oxidation)**
Enzymes	MAO then COMT, glycol branch (aldehyde reductase)	MAO then COMT, acid branch (aldehyde dehydrogenase)
Clinical use	Research marker of central NE turnover (depression subtyping)	**Urinary screen for phaeochromocytoma and neuroblastoma**

MHPG versus VMA is the classic discriminator: think MHPG for brain norepinephrine turnover and VMA for the phaeochromocytoma urine screen. The branch point is whether the intermediate aldehyde is reduced to a glycol (MHPG) or oxidised to an acid (VMA).

4.4 The locus coeruleus and its projections

Anatomy. The **locus coeruleus (LC)**, the A6 cell group, is a small pigmented (neuromelanin-rich, hence "blue spot") nucleus in the **dorsorostral pons** in the floor of the fourth ventricle, and it is the source of most of the CNS's norepinephrine (cross-referenced with the the Functional Neuroanatomy & Neurophysiology notes brainstem nuclei topic). Despite housing only a few thousand neurons per side, its axons ramify to nearly the entire neuraxis. Two ascending bundles carry the output: the **dorsal noradrenergic bundle** from the LC innervates the neocortex, hippocampus, thalamus and cerebellum, while the **ventral noradrenergic bundle** from LC and lateral tegmental groups supplies the hypothalamus, amygdala and midbrain. The LC also sends descending projections to the spinal cord dorsal horn, part of the endogenous analgesia system and the rationale for noradrenergic action in neuropathic pain.

Firing physiology. LC neurons show two modes. *Tonic* baseline firing sets global arousal and follows the sleep-wake cycle, being fastest in waking, slower in non-REM sleep and virtually silent in REM sleep (making the LC one of the REM-off cells). *Phasic* bursts fire to salient or novel stimuli, transiently boosting cortical gain to favour the current behaviour. The Aston-Jones and Cohen adaptive-gain model ties tonic-phasic balance to the exploitation-versus-exploration trade-off, and the inverted-U relationship between LC output and prefrontal performance underlies why both too little and too much NE impair attention.

4.5 Adrenoceptors: the alpha-1, alpha-2 and beta family

All adrenoceptors are **G-protein-coupled receptors**, and the whole family is examinable by second-messenger coupling, location and function. NE binds them with different affinities: **alpha-2 has the highest affinity, alpha-1 intermediate, beta the lowest**, which matters physiologically because low-level tonic release preferentially engages the inhibitory alpha-2 autoreceptor.

Alpha-1 (a1A, a1B, a1D)

Postsynaptic; Gq to phospholipase C, raising IP3 and DAG and intracellular calcium; excitatory. Mediates arousal and, peripherally, smooth-muscle contraction and vasoconstriction. Prazosin is the antagonist used for PTSD nightmares.

Alpha-2 (a2A, a2B, a2C)

Both pre- and postsynaptic; Gi/o, lowering cAMP; inhibitory. The presynaptic a2 is the **autoreceptor** that shuts off further NE release (negative feedback). Postsynaptic prefrontal a2A mediates working-memory enhancement (the guanfacine target).

Beta-1

Gs, raising cAMP and activating PKA; excitatory. Cortical and cardiac; role in memory consolidation and cardiac chronotropy.

Beta-2

Gs (and some Gi); glial and vascular; bronchodilation and vasodilation peripherally.

Beta-3

Adipose tissue; lipolysis and thermogenesis; minimal direct CNS role.

Autoreceptor logic. The presynaptic **alpha-2 autoreceptor** is the pivot of noradrenergic pharmacology. Agonists such as clonidine and guanfacine stimulate it, suppressing NE release (antiadrenergic, useful in ADHD, withdrawal states and hypertension), whereas antagonists such as **yohimbine** and idazoxan block it, increasing NE release, which is exploited both as a research challenge and, in mirtazapine's case, therapeutically (Kaplan and Sadock 2024). Mirtazapine blocks alpha-2 autoreceptors and heteroreceptors, disinhibiting both NE and serotonin release.

COMMON TRAP

Do not confuse the two directions at the alpha-2 receptor. Clonidine and guanfacine are alpha-2 *agonists* that *lower* NE release (antiadrenergic); yohimbine and idazoxan are alpha-2 *antagonists* that *raise* NE release (proadrenergic). A common error is to assume that agonising a receptor always increases the transmitter's effect; at a presynaptic autoreceptor, agonism suppresses release.

4.6 Functions: arousal, attention, stress and vigilance

The noradrenergic system's core CNS jobs are **arousal and wakefulness**, **selective attention and vigilance**, **stress reactivity** and the enhancement of **emotionally salient memory**. Through cortical gain modulation the LC sharpens signal detection and biases attention toward salient stimuli; through beta-adrenergic action in the basolateral amygdala it strengthens the consolidation of emotionally arousing memories, the substrate of flashbulb and traumatic memory (a mechanism directly relevant to PTSD). Peripherally, NE and adrenaline drive the classic *fight-or-flight* response: pupillary dilatation, tachycardia, bronchodilation, vasoconstriction, increased renin release and inhibited gut peristalsis, alongside metabolic mobilisation through glycogenolysis, gluconeogenesis and lipolysis.

MNEMONIC

"A-VATS": Arousal, Vigilance, Attention, Threat-response, Stress-memory

The five central jobs of norepinephrine map onto the LC's gain-control role: it keeps you Aroused and awake, sustains Vigilance, focuses Attention on salient input, mounts the Threat (fight-or-flight) response, and stamps in emotionally Stressful memories via the amygdala. All five are versions of one idea: turning up the gain on what matters right now.

HOLD THIS

At a presynaptic alpha-2 autoreceptor, agonism suppresses noradrenaline release. Clonidine and guanfacine (agonists) lower NE; yohimbine (antagonist) raises it and reliably provokes panic.

4.7 Clinical correlations and pharmacology

Depression. The **monoamine hypothesis** posits a relative deficiency of NE and serotonin. Noradrenergic drugs exploit this at several nodes: **SNRIs** (venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran) block both NET and the serotonin transporter, with NET inhibition becoming prominent at higher doses; the selective NET inhibitor **reboxetine** and the noradrenergic-and-dopaminergic **bupropion** act more purely on the catecholamine side; **tricyclics** such as desipramine and nortriptyline are strongly noradrenergic; **mirtazapine** works presynaptically by alpha-2 blockade; and non-selective **MAOIs** raise NE by blocking its degradation (Stahl 2021). Paradoxically, some data show *increased* tyrosine hydroxylase and urinary NE in depression, so the monoamine story is best taught as a downstream, receptor-adaptive model rather than a simple deficiency.

Anxiety and PTSD. Noradrenergic overactivity underlies the hyperarousal of anxiety disorders. The **yohimbine challenge** (an alpha-2 antagonist that floods the synapse with NE) reliably provokes panic and flashbacks in patients with panic disorder and PTSD, historic evidence for LC hyperexcitability in these conditions (Kaplan and Sadock 2024). This is the rationale for the alpha-1 antagonist **prazosin** in PTSD-related nightmares and for beta-blockers (propranolol) in the somatic symptoms of performance anxiety. PTSD (ICD-11 6B40; DSM-5-TR post-traumatic stress disorder) and panic disorder (ICD-11 6B01; DSM-5-TR panic disorder) are the disorders to name here.

ADHD. Prefrontal noradrenergic (and dopaminergic) hypofunction is central to ADHD (ICD-11 6A05; DSM-5-TR attention-deficit/hyperactivity disorder). Optimal prefrontal function needs a moderate level of NE acting on postsynaptic **alpha-2A** receptors, and the treatments follow this directly: the selective NET inhibitor **atomoxetine** raises synaptic NE and dopamine in the prefrontal cortex, while the alpha-2A agonists **guanfacine** and **clonidine** (extended-release) directly stimulate the postsynaptic receptor to strengthen prefrontal network connectivity (Stahl 2021). Stimulants also raise catecholamines by blocking and reversing their transporters.

AGENT / CLASS	NORADRENERGIC MECHANISM	MAIN INDICATION
SNRIs (venlafaxine, duloxetine)	NET plus SERT blockade	Depression, anxiety, neuropathic pain
Atomoxetine	**Selective NET inhibitor (non-stimulant)**	ADHD
Reboxetine	Selective NET inhibitor	Depression (limited availability)
Guanfacine, clonidine	**Alpha-2A agonist (postsynaptic; presynaptic autoreceptor)**	ADHD, tics, withdrawal, hypertension
Prazosin	**Alpha-1 antagonist**	PTSD nightmares

AGENT / CLASS	NORADRENERGIC MECHANISM	MAIN INDICATION
Propranolol	Beta-adrenergic antagonist	Performance anxiety, akathisia, tremor
Mirtazapine	Alpha-2 auto/heteroreceptor antagonist	Depression (noradrenergic and serotonergic disinhibition)
MAOIs	Block MAO-mediated NE degradation	Refractory / atypical depression
Yohimbine	**Alpha-2 antagonist (raises NE): panic challenge, not a treatment**	Research challenge; historic ED use

The noradrenergic pharmacopoeia sorted by node: reuptake blockers raise synaptic NE, alpha-2 agonists calm the system, alpha-1 and beta antagonists block downstream effects, and yohimbine is the provocation agent that maps NE overactivity onto panic and PTSD.

INDIA

In Indian practice, atomoxetine is the non-stimulant most readily prescribed for ADHD given that stimulant methylphenidate is a Schedule X / controlled substance with tighter prescription rules; guanfacine and clonidine extended-release formulations are less consistently available, so plain clonidine is sometimes substituted. Prazosin for PTSD nightmares is inexpensive and widely stocked, making it a practical first choice where specialised agents are hard to source.

4.8 Noradrenergic degeneration in neurodegenerative disease

The LC is one of the earliest sites of pathology in **Alzheimer disease**, where neurofibrillary (hyperphosphorylated tau) tangles accumulate and LC neurons are lost, reducing NE's endogenous anti-inflammatory and neuroprotective actions on the cortex and hippocampus. In **Parkinson disease**, alpha-synuclein deposition and LC neuronal loss contribute to the non-motor features (cognitive slowing, mood and autonomic symptoms) that dopaminergic therapy does not address. For the exam, the take-home is that LC noradrenergic loss is an early, under-recognised contributor to the cognitive and affective burden of both diseases, and current anti-amyloid monoclonal antibodies target the amyloid arm only, leaving noradrenergic decline unaddressed.

5 · Glutamate and NMDA receptor subtypes (hypofunction model)

Glutamate is the brain's principal excitatory neurotransmitter, present at the vast majority of fast synapses, and it is the axis on which the modern neurochemistry of both psychosis and depression now turns. For decades psychiatry was dopamine-centric; the field's centre of gravity shifted once it became clear that the **NMDA receptor hypofunction** model explained things the dopamine hypothesis could not, above all the negative and cognitive symptoms of schizophrenia and the psychotomimetic profile of phencyclidine and ketamine (Stahl 2021). The same receptor then reappeared as the target of the first genuinely novel antidepressant mechanism in a generation.

Examiners love this topic because it braids together basic pharmacology (a ligand-gated channel with an unusual co-agonist requirement and a voltage-dependent magnesium block), a disease model (disinhibition of cortical circuits), a therapeutics story (ketamine, esketamine, memantine) and a neuroimmunology vignette (anti-NMDA-receptor encephalitis). **Learn it as one circuit, not four facts.** Every clinical entity below is a perturbation of the same receptor.

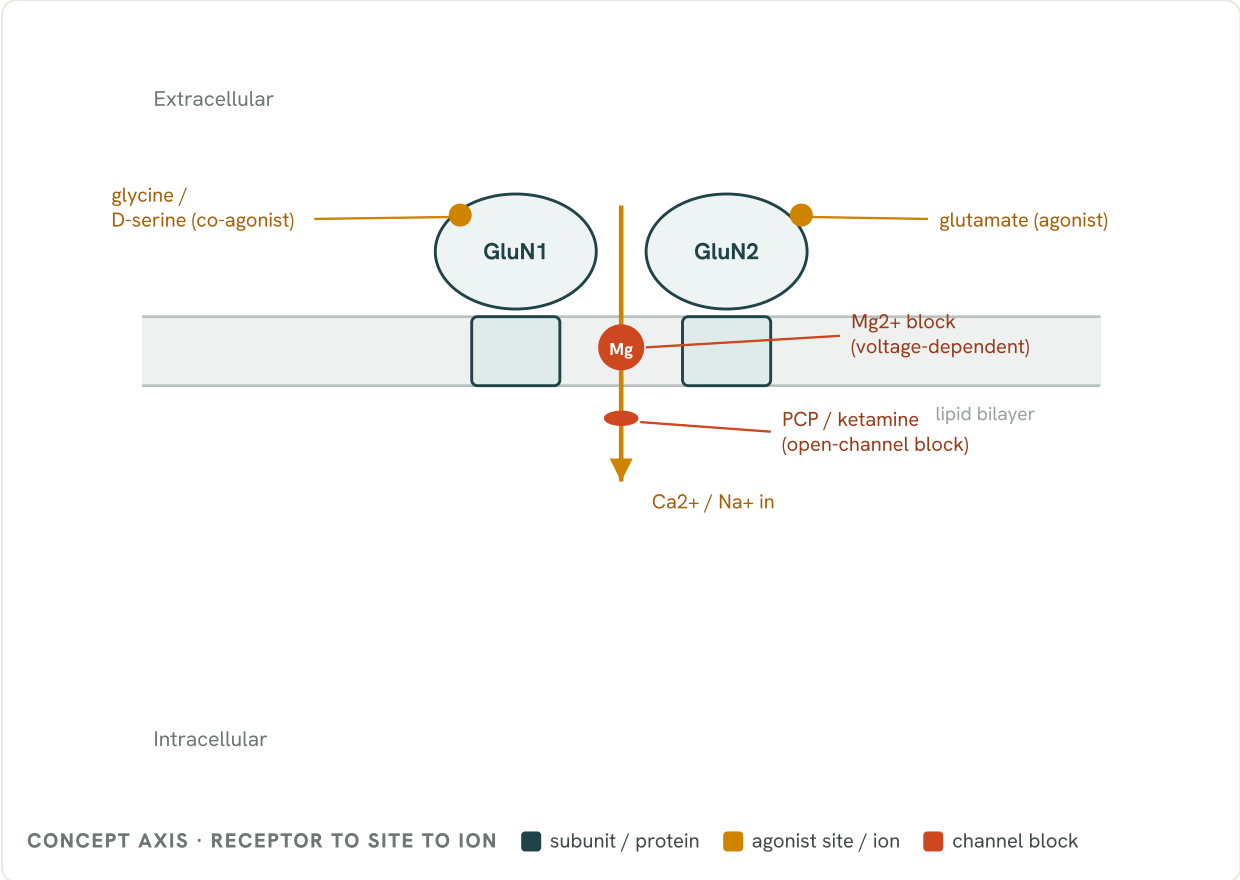


Fig 2.3 The NMDA receptor as a coincidence detector. Opening needs two things at once: the agonist glutamate at GluN2 and the co-agonist glycine or D-serine at GluN1, plus depolarisation to expel the voltage-dependent Mg2+ block from the pore. Only then do Ca2+ and Na+ flow in. Ketamine and PCP are open-channel blockers acting inside the pore; NMDA hypofunction on GABA interneurons is the disinhibition model of psychosis.

5.1 The glutamate-glutamine cycle and the EAAT reuptake system

Synthesis and packaging. Unlike monoamines there is no single dedicated synthetic enzyme with an obvious rate-limiting step; glutamate is made largely from glutamine by the neuronal enzyme *glutaminase*, and also arises from the Krebs-cycle intermediate alpha-ketoglutarate by transamination (Stahl 2021). It is then concentrated into synaptic vesicles by vesicular glutamate transporters (**vGluT**) ready for release.

Clearance is by uptake, not enzymatic breakdown. This is the single most examinable contrast with acetylcholine. After release, glutamate is not degraded in the cleft; it is removed by **excitatory amino acid transporters (EAAT1 to EAAT5)**, members of the SLC1 solute-carrier family, sited predominantly on surrounding *glia* (Stahl 2021). Rapid glial uptake keeps synaptic glutamate low and is what protects the synapse from the excitotoxicity described in 5.4.

The cycle closes in glia. Inside the astrocyte, glutamate is converted to the inert, non-neuroactive amino acid *glutamine* by **glutamine synthetase**. Glutamine is exported back to the

neuron, where glutaminase reconverts it to glutamate, and the loop begins again. This **glutamate-glutamine shuttle** is why glia are not passive scaffolding but active partners in excitatory transmission, and why glutamine is the peak that magnetic resonance spectroscopy often reports alongside glutamate as the combined "Glx" signal.

5.2 Ionotropic receptors: NMDA, AMPA and kainate

Glutamate acts on two receptor superfamilies. The **ionotropic** receptors are ligand-gated ion channels assembled from four subunits (a tetramer, in contrast to the pentameric nicotinic and GABA-A channels), and there are three families named for their selective agonists (Stahl 2021).

AMPA receptor

The workhorse of fast excitatory transmission. Opening lets sodium in to depolarise the postsynaptic membrane over milliseconds. Trafficking of AMPA receptors into the synapse is a molecular substrate of *long-term potentiation* and is central to the ketamine antidepressant story (5.6).

Kainate receptor

A less prominent ionotropic receptor, modulating both postsynaptic depolarisation and, presynaptically, transmitter release. Lower yield for exams than NMDA and AMPA, but name it.

NMDA receptor

The star of the topic. A calcium-permeable channel with three defining peculiarities: an obligatory co-agonist, a voltage-dependent magnesium block, and a role as a molecular coincidence detector. Detailed in 5.3.

NMDA receptors are heteromers built from an obligatory **GluN1** subunit (older nomenclature NR1) paired with **GluN2** subunits (NR2A to NR2D) and sometimes GluN3 (Stahl 2021). The GluN2 composition sets the channel's kinetics and pharmacology: GluN2B-rich receptors, for instance, are the target of the selective antagonist ifenprodil, and subunit switching over development is one substrate of the neurodevelopmental hypofunction idea.

5.3 The NMDA receptor: co-agonist, magnesium block and coincidence detection

The co-agonist requirement. The NMDA receptor is unique among fast receptors in that glutamate alone cannot open it. A second, obligatory **co-agonist** must occupy a separate glycine-binding site on the GluN1 subunit. That co-agonist is either *glycine* or *D-serine*, the latter an unusual D-amino acid manufactured in glia by **serine racemase** from L-serine (Stahl 2021). D-serine has high affinity for the glycine site and is now regarded as the principal endogenous co-agonist at many forebrain synapses. This co-agonist dependence is a druggable node: glycine, D-serine and D-cycloserine (a partial agonist at the glycine site) have all been trialled as augmentation strategies to enhance NMDA function in schizophrenia.

The magnesium block. At resting membrane potential the channel pore is physically plugged by an extracellular **magnesium ion**. Even with glutamate and co-agonist bound, no current flows until the membrane is depolarised enough (by neighbouring AMPA-receptor activity) to expel the Mg^{2+} plug in a voltage-dependent manner (Stahl 2021).

Coincidence detection. Because opening requires both chemical binding (glutamate plus co-agonist) and electrical depolarisation (to relieve the Mg block) at the same moment, the NMDA

receptor functions as a molecular **coincidence detector.** Only when presynaptic release and postsynaptic activity coincide does calcium flood in to trigger the intracellular cascades of synaptic plasticity. This is the cellular logic of Hebbian learning and the reason the NMDA receptor sits at the heart of memory and of the plasticity theories of both schizophrenia and depression.

RULE **The NMDA receptor is a coincidence detector: it needs glutamate, a glycine-site co-agonist and depolarisation to expel the magnesium plug, all at once.** Ketamine and PCP block a fourth thing entirely, sitting inside the open pore.

PEARL

Three keys open the NMDA channel and all three must turn together: glutamate at its site, glycine or D-serine at the co-agonist site, and depolarisation to remove the magnesium plug. Dissociative anaesthetics (ketamine, PCP) block a fourth thing entirely: they sit deep inside the open channel at the PCP or dizocilpine site. This is why they are *uncompetitive, open-channel* blockers rather than competitive antagonists at the glutamate site.

5.4 Metabotropic glutamate receptors (mGluR groups I to III)

The second superfamily is the **metabotropic** glutamate receptors, G-protein-coupled receptors that act slowly through second messengers rather than by gating an ion channel. There are at least eight subtypes sorted into three groups by sequence, signalling and pharmacology (Stahl 2021).

GROUP	MEMBERS	LOCATION AND SIGNALLING	NET EFFECT ON GLUTAMATE TONE
Group I	mGluR1, mGluR5	Mainly postsynaptic; couple to Gq to raise intracellular calcium	**Excitatory: facilitate and strengthen glutamate responses**
Group II	mGluR2, mGluR3	Presynaptic autoreceptors; couple to Gi to lower cyclic AMP	**Inhibitory: reduce glutamate release (autoreceptor brake)**
Group III	mGluR4, mGluR6, mGluR7, mGluR8	Predominantly presynaptic autoreceptors; Gi-coupled	Inhibitory: reduce glutamate release

The three mGluR groups. The exam discriminator: Group I is postsynaptic and excitatory, whereas Groups II and III are presynaptic autoreceptors that dampen release. mGluR6 sits atypically in the retina.

The presynaptic Group II and III autoreceptors are of therapeutic interest precisely because agonists that stimulate them *reduce* excess glutamate release; Group II (mGluR2/3) agonists were investigated as non-dopaminergic antipsychotics on exactly this logic, though pivotal efficacy proved inconsistent (Stahl 2021).

5.5 Excitotoxicity: when a good transmitter turns lethal

The very calcium permeability that makes the NMDA receptor useful for learning makes it dangerous when glutamate signalling runs unchecked. **Excitotoxicity** is neuronal death driven

by excessive glutamate-mediated calcium influx: sustained NMDA-receptor activation raises cytosolic calcium (and zinc) to concentrations that activate proteases, lipases, nitric oxide synthase and free-radical cascades, culminating in cell death.

This is the final common pathway of calcium-mediated injury in **stroke, traumatic brain injury, epilepsy and hypoglycaemia**, and it also contributes to the slower neurodegeneration of Huntington disease and Alzheimer disease. It is the theoretical rationale for the neuroprotective aspiration of NMDA antagonists, and it explains the apparent paradox that both too little NMDA signalling (the hypofunction of 5.7) and too much (excitotoxicity) are pathological. The therapeutic window is narrow, which is why a partial, gentle channel blocker such as memantine (5.8) succeeded clinically where high-affinity blockers failed.

5.6 The NMDA hypofunction hypothesis of schizophrenia

The pharmacological cornerstone is simple and reproducible: **phencyclidine (PCP) and ketamine**, both NMDA open-channel blockers, produce in healthy volunteers a syndrome that mimics schizophrenia more fully than any dopaminergic drug does, reproducing not just positive symptoms but the negative symptoms, cognitive impairment and thought disorder that amphetamine psychosis leaves untouched (Stahl 2021). If blocking NMDA receptors makes a healthy brain schizophrenia-like, then a hypofunctioning NMDA receptor may be intrinsic to the illness.

The disinhibition circuit. The elegance of the model lies in where the lesion sits. NMDA receptors are hypofunctional not on the principal glutamate neurons themselves but on inhibitory **GABAergic interneurons** in the prefrontal cortex, in particular the fast-spiking parvalbumin-expressing interneurons that normally restrain cortical glutamate output. If those interneurons are under-driven, they fail to inhibit; the cortical glutamate projection neurons are thereby *disinhibited* and fire excessively (Stahl 2021).

Downstream dopamine. This cortical disinhibition then propagates to the classical dopamine circuits: excess glutamatergic drive to the ventral tegmental area produces *mesolimbic hyperdopaminergia* (positive symptoms) while a separate deficient drive leaves the *mesocortical* dopamine projection hypoactive (negative and cognitive symptoms). In this way the NMDA hypofunction model does not replace the dopamine hypothesis; it sits upstream of it and generates it, unifying positive and negative symptoms under one initiating abnormality.

CLINICAL ANCHOR

The ketamine and PCP models are why glutamatergic agents are pursued in schizophrenia, and why a clinician seeing a young patient with an acute schizophrenia-like psychosis after recreational ketamine or PCP use is watching the hypofunction model unfold in real time. The 2024 arrival of the muscarinic agent xanomeline-trospium (a genuinely non-dopaminergic antipsychotic acting on cholinergic rather than glutamatergic targets) shows the field is finally moving beyond D2 blockade, though direct NMDA-enhancing strategies (glycine, D-serine, bitopertin, glycine-transporter inhibitors) have so far disappointed in pivotal trials.

5.7 Ketamine and esketamine as antidepressants: paradoxical plasticity

Here the same receptor block that models psychosis produces, at sub-anaesthetic doses, a rapid and robust antidepressant effect, often within hours, in patients with treatment-resistant depression (Molero et al. 2018). Reconciling this with the hypofunction model is the intellectual heart of the topic.

The disinhibition-to-glutamate-surge mechanism. Low-dose ketamine preferentially blocks NMDA receptors on the same GABAergic interneurons, transiently disinhibiting cortical glutamate neurons and producing a brief *glutamate surge*. That surge activates **AMPA receptors**, whose downstream signalling releases **BDNF** and activates the **mTOR** pathway (mammalian target of rapamycin), driving a rapid burst of synaptogenesis and dendritic-spine formation in the prefrontal cortex. The antidepressant effect is thus not the NMDA block per se but the AMPA-BDNF-mTOR synaptic remodelling it triggers, restoring the synaptic connectivity that chronic stress and depression erode (cross-reference the neurotrophins topic for the BDNF-TrkB cascade).

The pharmaceutical translation. **Esketamine**, the S-enantiomer, delivered as an intranasal spray, gained US regulatory approval in 2019 for treatment-resistant depression and subsequently for major depressive disorder with acute suicidal ideation or behaviour, always used alongside an oral antidepressant and administered under supervision because of the dissociation, sedation and blood-pressure rise, with a mandatory post-dose monitoring period. Racemic intravenous ketamine remains widely used off-label (Molero et al. 2018).

> **COMMON TRAP**
>
> Do not say ketamine treats depression "by blocking NMDA receptors" and leave it there: that would make every NMDA antagonist an antidepressant, which is false. The mechanism is the *downstream* AMPA-BDNF-mTOR synaptogenic burst produced by transient disinhibition. Also do not confuse the enantiomers: *es*ketamine is the approved intranasal S-enantiomer; *arketamine* (the R-enantiomer) is investigational. And do not overlook the abuse-liability and bladder-toxicity (ketamine cystitis) that shadow chronic use.

5.8 Memantine and the therapeutic uses of channel blockade

Memantine is the clinical proof that NMDA antagonism can be beneficial rather than psychotomimetic, and the difference lies in the kinetics. It is a *low-affinity, uncompetitive, open-channel blocker* that enters the pore only after the receptor is activated and, crucially, leaves it quickly (fast off-rate, "low-trapping"). This lets it dampen the pathological, tonic, low-level over-activation that drives excitotoxicity while sparing the sharp, phasic, high-amplitude signalling needed for normal synaptic transmission and learning.

Memantine is approved for **moderate-to-severe Alzheimer disease**, where it is neither a cure nor disease-modifying but offers symptomatic benefit and is often combined with a cholinesterase inhibitor. It is used off-label in Huntington disease, where excitotoxicity contributes to striatal degeneration. The contrast with ketamine and PCP (high-affinity, deeply trapping blockers that produce dissociation and psychosis) is the exam-favourite discriminator

and a clean lesson in how binding kinetics, not just the target, determine a drug's clinical face (Stahl 2021).

MNEMONIC

MEMANTINE = "MEMory, MEek block"

MEMory names its indication (moderate-to-severe Alzheimer disease); a **ME**ek, low-affinity, fast-off block is why it is tolerated where the greedy, deeply-trapping block of PCP and ketamine causes dissociation and psychosis. Same target, opposite clinical personality.

HOLD THIS

NMDA hypofunction on GABAergic interneurons disinhibits glutamate; that one lesion is both the schizophrenia model and the ketamine antidepressant. The antidepressant effect is the downstream AMPA-BDNF-mTOR burst, not the NMDA block itself.

5.9 Anti-NMDA-receptor encephalitis: the receptor as an antigen

The final clinical face is neuroimmunological and a high-yield can-not-miss for psychiatry, because it presents to psychiatrists first. **Anti-NMDA-receptor encephalitis** is an autoimmune encephalitis in which IgG autoantibodies target the *GluN1 (NR1) subunit* of the NMDA receptor, causing receptor internalisation and a functional, antibody-mediated NMDA hypofunction (Dalmau et al.).

The classic evolution. A young woman (though any age and sex occurs) develops a prodrome, then a *psychiatric phase* of anxiety, agitation, delusions, hallucinations and disorganised behaviour that is readily mistaken for a primary psychotic or affective illness, followed by seizures, movement disorder (orofacial dyskinesias are characteristic), autonomic instability and a declining level of consciousness. The diagnosis rests on detecting anti-NMDA-receptor (anti-GluN1) antibodies, ideally in *cerebrospinal fluid*. A substantial proportion, especially young women, harbour an underlying **ovarian teratoma** providing the ectopic neural antigen, so tumour search is mandatory.

Treatment is tumour removal where present plus immunotherapy (corticosteroids, intravenous immunoglobulin, plasma exchange, and second-line rituximab or cyclophosphamide), and recovery, though often slow, is possible. In ICD-11 this is coded under autoimmune encephalitis rather than as a primary mental disorder, and any young patient with new psychosis plus seizures, dyskinesias, autonomic lability or a fluctuating conscious level should trigger a request for anti-NMDA-receptor antibodies before the presentation is filed as schizophrenia.

INDIA

In Indian psychiatric practice, where a young woman with acute-onset psychosis, catatonia or unexplained seizures may present first to psychiatry, anti-NMDA-receptor encephalitis is an important organic mimic to keep on the differential, particularly when there are neurological soft signs, autonomic instability or catatonia poorly responsive to usual treatment. CSF antibody testing and pelvic imaging for teratoma are the decisive steps; missing it means treating a reversible autoimmune illness as if it were a lifelong psychiatric disorder. This entity is the strongest single argument for a low threshold to investigate atypical first-episode psychosis organically.

6 · GABA receptor subtypes and pharmacology

The brake on the brain. Gamma-aminobutyric acid (**GABA**) is the principal fast inhibitory neurotransmitter of the mature CNS; nearly half of all central synapses carry a GABA receptor of some kind. Almost every drug that sedates, calms anxiety, aborts a seizure, or covers alcohol withdrawal converges on GABAergic signalling, which is why this receptor family is the single most examined target in basic psychopharmacology. The recurring exam distinction is **ionotropic GABA-A** (a ligand-gated chloride channel giving fast, millisecond inhibition) versus **metabotropic GABA-B** (a G-protein-coupled receptor giving slow, sustained inhibition), and the map of allosteric sites layered onto the GABA-A pentamer.

For the exam, three threads recur: the synthesis-and-metabolism loop (GAD, GABA-transaminase, the pyridoxine link), the allosteric-site architecture of GABA-A (benzodiazepine, barbiturate, neurosteroid, anaesthetic, alcohol, Z-drug, picrotoxin sites and the flumazenil antagonist), and the newest clinical translation, neurosteroid antidepressants brexanolone and zuranolone (Kaplan & Sadock 2024; Stahl 2021).

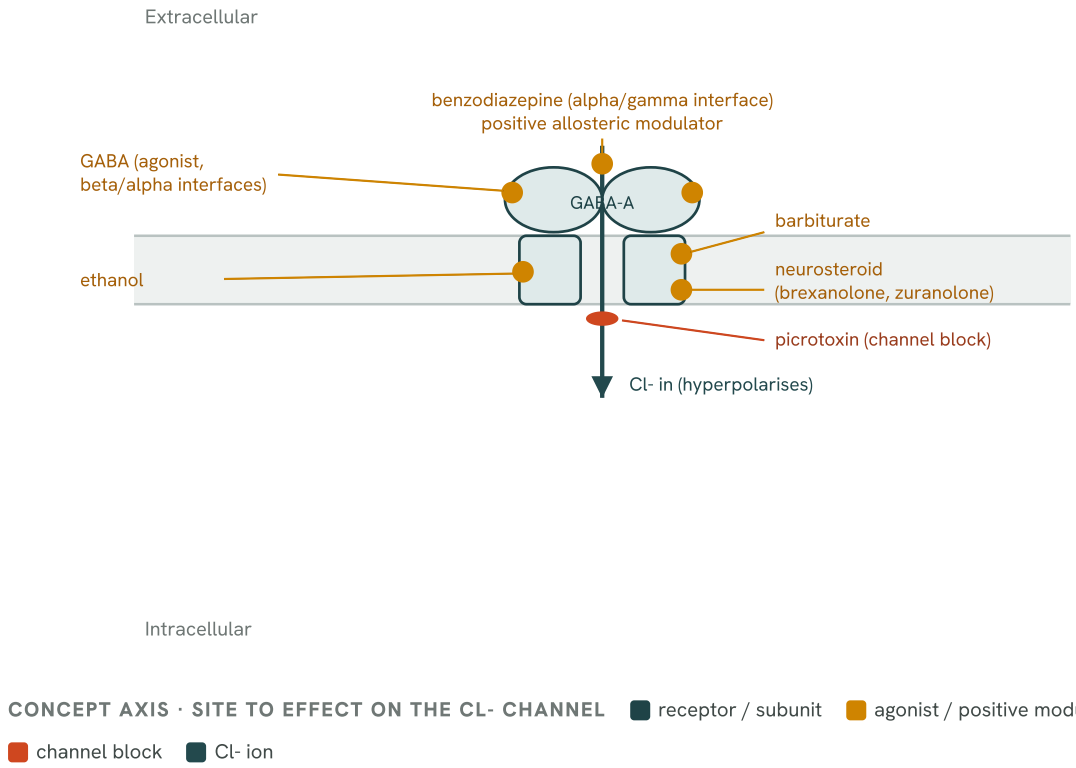


Fig 2.4 The GABA-A receptor is one chloride channel with many doors. GABA itself opens it at the beta/alpha subunit interfaces; benzodiazepines bind the separate alpha/gamma site and increase the frequency of opening (flumazenil blocks this site); barbiturates increase the duration of opening; neurosteroids (allopregnanolone, and the drugs brexanolone and zuranolone) and ethanol are further positive modulators; picrotoxin blocks the pore. All converge on more chloride entry and inhibition.

6.1 Synthesis: glutamate to GABA via GAD

The excitatory-inhibitory pivot. GABA is synthesised in a single decarboxylation step from the excitatory transmitter glutamate by **glutamic acid decarboxylase (GAD)**, the rate-limiting enzyme, which requires **pyridoxal-5-phosphate** (the active cofactor of pyridoxine, vitamin B6). Two isoforms exist, GAD65 (membrane-associated, activity-dependent vesicular pool) and GAD67 (cytosolic, tonic pool). Newly formed GABA is loaded into synaptic vesicles by the vesicular inhibitory amino-acid transporter (VIAAT/VGAT) and released by calcium-dependent exocytosis. Because a single enzyme converts a stimulant into a depressant transmitter, GAD is a mechanistic bottleneck: anything that impairs pyridoxal-phosphate synthesis collapses GABA production and unmasks seizures (StatPearls 2026; Companion to Psychiatric Studies).

6.2 Termination: reuptake and the GABA-transaminase shunt

Recycled into the Krebs cycle. Synaptic GABA is cleared by GABA transporters (GAT-1 to GAT-3) on neurons and astrocytes, then degraded by **GABA-transaminase (GABA-T)**, a mitochondrial enzyme, into **succinic semialdehyde**. Succinic semialdehyde dehydrogenase (SSADH) then oxidises this to succinic acid, which feeds the citric-acid cycle. The transamination is coupled: GABA-T simultaneously converts alpha-ketoglutarate to glutamate, regenerating the precursor and closing the "GABA shunt". This metabolic loop is the substrate for several

anticonvulsants (vigabatrin irreversibly inhibits GABA-T; valproate partially inhibits it) and for a set of rare inborn errors of GABA metabolism (StatPearls 2026).

COMMON TRAP

SSADH deficiency, not GABA-T deficiency, is the commonest inherited disorder of GABA metabolism (and the most prevalent neurotransmitter metabolic disease). Blocked SSA oxidation diverts succinic semialdehyde to **gamma-hydroxybutyrate (GHB)**, so both GABA and GHB rise in serum and urine; the MRI clue is increased globus pallidus signal, with language delay, hypotonia and seizures (StatPearls 2026).

6.3 GABA-A: the pentameric chloride channel

Fast phasic inhibition. The GABA-A receptor is a **pentamer** assembled from a menu of subunits (six alpha, three beta, three gamma, plus delta, epsilon, theta, pi and rho); the most common synaptic isoform is 2 alpha, 2 beta, 1 gamma, typically 2 alpha-1, 2 beta-2, 1 gamma-2. The two orthosteric GABA-binding sites sit at the **beta-alpha interfaces**. Agonist binding opens the intrinsic chloride channel; in the mature neuron the electrochemical gradient drives Cl into the cell, producing **hyperpolarisation** and reduced excitability. GABA-A mediates fast, millisecond-scale synaptic (phasic) inhibition and is concentrated in limbic structures and retina (StatPearls 2026; Kaplan & Sadock 2024).

PEARL

In the fetal and early postnatal brain GABA is **excitatory**, not inhibitory: high intracellular chloride (low KCC2 expression) means channel opening drives Cl out and depolarises the cell. GABA is the first active transmitter in the developing brain and drives progenitor proliferation and migration; the switch to inhibition follows KCC2 maturation (StatPearls 2026).

6.4 Allosteric sites on GABA-A: the modulator map

One channel, many doors. Layered onto the GABA orthosteric site are distinct allosteric sites, each a drug target. A **positive allosteric modulator (PAM)** has no effect without GABA present; it only amplifies GABA's action, which is why these agents have a ceiling and are far safer in overdose than direct agonists. The pharmacologically load-bearing distinction is **benzodiazepines increase the frequency of channel opening** whereas **barbiturates increase the duration of opening** (and, at high dose, open the channel directly, losing the ceiling and becoming lethal) (StatPearls 2026; Stahl 2021).

Benzodiazepine (omega) site

At the alpha-gamma interface; requires a gamma-2 subunit and an alpha-1/2/3/5 subunit. Increases opening frequency. Diazepam, lorazepam, alprazolam, clonazepam.

Z-drug site

Same benzodiazepine pocket but selective for alpha-1-containing receptors (the "omega-1" sedative-hypnotic subtype). Zolpidem, zopiclone, zaleplon; sedative-hypnotic with lower anxiolytic/anticonvulsant profile.

Barbiturate site

Distinct from the benzodiazepine site; prolongs opening duration and directly gates at high dose. Phenobarbital, thiopental.

Neurosteroid site

Transmembrane site distinct from both; potentiates synaptic and extrasynaptic (delta-containing) receptors. Allopregnanolone, brexanolone, zuranolone.

Anaesthetic / alcohol sites

Propofol, etomidate and volatile anaesthetics are GABA-A PAMs; ethanol potentiates GABA-A (notably extrasynaptic delta subtypes) alongside NMDA antagonism.

Picrotoxin / convulsant site

In the channel pore; a non-competitive antagonist (channel blocker), pro-convulsant. Bicuculline is the competitive orthosteric antagonist.

> **CLINICAL ANCHOR**
>
> **Flumazenil** is a competitive antagonist at the benzodiazepine site: it reverses benzodiazepine and Z-drug sedation but does not touch the barbiturate, alcohol or neurosteroid sites, so it is useless in pure barbiturate or ethanol overdose. In benzodiazepine-dependent patients it can precipitate withdrawal seizures, so it is used cautiously and is not a routine reversal agent (StatPearls 2026).

6.5 Subunit selectivity maps to clinical effect

Why one benzodiazepine site gives many effects. The alpha subunit at the benzodiazepine pocket dictates the pharmacological signature: alpha-1 mediates sedation, amnesia and anticonvulsant action (and is the Z-drug target); alpha-2 and alpha-3 mediate anxiolysis and muscle relaxation; alpha-5 (hippocampal) is linked to memory and cognition. This subunit logic is the rationale behind subtype-selective drug design, including the goal of an anxiolytic without sedation, and explains why zolpidem is hypnotic but weakly anxiolytic (Kaplan & Sadock 2024). Note the neurosteroids bind subunits (including alpha-4 and alpha-6) that benzodiazepines do not, a clue to their distinct spectrum.

- **alpha-1** - sedation, amnesia, anticonvulsant action; the Z-drug (zolpidem) target.
- **alpha-2 / alpha-3** - anxiolysis and muscle relaxation.
- **alpha-5** - hippocampal, memory and cognition.

6.6 GABA-B: the metabotropic receptor and baclofen

Slow, sustained inhibition. The **GABA-B receptor** is a G-protein-coupled (Gi/Go) obligate heterodimer of B1 (B1a/B1b) and B2 subunits. It signals through a second-messenger cascade rather than an intrinsic channel. Presynaptically, it reduces adenylyl cyclase activity and inhibits voltage-gated calcium channels, cutting neurotransmitter release (autoreceptor and heteroreceptor). Postsynaptically, it opens inward-rectifying (GIRK) potassium channels, letting K out and producing a slow hyperpolarising IPSP. **Baclofen** is the prototype GABA-B agonist, licensed as a muscle relaxant for spasticity and used off-label (unlicensed) in alcohol dependence with mixed evidence; gamma-hydroxybutyrate is also a GABA-B agonist (StatPearls 2026; Maudsley Prescribing Guidelines).

FEATURE	GABA-A	GABA-B
Receptor class	**Ionotropic, ligand-gated Cl channel**	**Metabotropic, Gi/Go-coupled**
Structure	Pentamer (e.g. 2 alpha, 2 beta, 1 gamma)	Obligate heterodimer (B1 + B2)
Ion / effector	Cl influx, direct	**K efflux (GIRK) + Ca channel inhibition**
Speed	**Fast (milliseconds), phasic**	**Slow (100s of ms), sustained**
Agonist	Muscimol; GABA	**Baclofen; GHB**
Antagonist	Bicuculline (competitive), picrotoxin (channel)	Saclofen, phaclofen
Key drugs	Benzodiazepines, barbiturates, Z-drugs, neurosteroids, propofol	Baclofen (spasticity)

Core discriminators between the two principal GABA receptor families; the third type, GABA-C, is a rho-subunit-only pentameric Cl channel of the retina.

TRAP Gabapentin and pregabalin are not GABAergic despite the name: they block the alpha-2-delta calcium-channel subunit and cut glutamate release.

6.7 Tonic versus phasic inhibition

Two modes of GABA-A signalling. **Phasic inhibition** is the classic fast IPSP: vesicular GABA hits synaptic GABA-A receptors (gamma-2-containing) transiently. **Tonic inhibition** is a persistent background chloride conductance mediated by high-affinity **extrasynaptic GABA-A receptors**, characteristically **delta-subunit**-containing (alpha-4-beta-delta, alpha-6-beta-delta), activated by low ambient GABA that spills out of the synapse. Tonic inhibition sets the neuron's gain and excitability threshold. It is clinically pivotal because **neurosteroids and ethanol preferentially potentiate extrasynaptic delta-containing receptors**, and this tonic pool is the proposed substrate of the neurosteroid antidepressants (Kaplan & Sadock 2024).

6.8 Clinical translation I: anxiety, epilepsy, alcohol withdrawal

The GABAergic workhorses. Benzodiazepines are PAMs used short-term for panic disorder, generalised anxiety disorder and insomnia, as abortive therapy for status epilepticus (lorazepam, diazepam, midazolam), and as first-line cover for **alcohol withdrawal**, where they prevent withdrawal seizures and delirium tremens (chlordiazepoxide, diazepam, or lorazepam in hepatic impairment). The mechanistic rationale in withdrawal is that chronic alcohol downregulates GABA-A and upregulates glutamatergic tone; abrupt cessation leaves an unopposed excitatory state that a GABA-A PAM restores. The 2020 FDA boxed warning covers dependence, life-threatening withdrawal seizures on abrupt cessation, and respiratory-depressant synergy with opioids (StatPearls 2026; Maudsley Prescribing Guidelines).

COMMON TRAP

Not every "GABA analog" acts on GABA transmission. **Gabapentin and pregabalin**, despite the name, do not bind GABA receptors; they inhibit the alpha-2-delta subunit of voltage-gated calcium channels and reduce glutamate release. **Isoniazid** (and hydrazine, and false-morel gyromitrin) deplete pyridoxal phosphate, shut down GAD, and cause benzodiazepine-refractory seizures treated with high-dose **pyridoxine** (StatPearls 2026).

6.9 Clinical translation II: neurosteroid antidepressants

Brexanolone and zuranolone. **Allopregnanolone** (3-alpha,5-alpha-tetrahydroprogesterone), a metabolite of progesterone, is an endogenous neurosteroid PAM of synaptic and extrasynaptic GABA-A receptors. Its levels fall sharply after delivery, the proposed trigger for postpartum mood collapse. **Brexanolone** (Zulresso), an IV allopregnanolone formulation, is FDA-approved for postpartum depression, given as a 60-hour infusion under monitoring for sedation and loss of consciousness. **Zuranolone** (SAGE-217, Zurzuvae) is the orally available analog, a 14-day bedtime course approved for postpartum depression (its trials in major depressive disorder more broadly were mixed) (Kaplan & Sadock 2024; Practical Psychopharmacology). Both are restricted to the postpartum window (up to one year), cause psychomotor impairment (no driving), and preclude breastfeeding during treatment. These are the first mechanistically GABAergic antidepressants, contrasting the delayed monoamine reuptake inhibitors with a rapid, days-scale response.

INDIA

Brexanolone and zuranolone are not routinely available in Indian practice, so postpartum depression management here remains SSRI-led (sertraline preferred in lactation for high protein binding and short half-life) with psychotherapy. For alcohol withdrawal in Indian ICUs, benzodiazepine-based regimens (chlordiazepoxide, diazepam) remain the mainstay, consistent with observed practice patterns (Gopaldas et al. 2023).

6.10 ICD-11 mapping and diagnostic anchors

Where these drugs land nosologically. The disorders driving GABAergic prescribing map to ICD-11 as: alcohol withdrawal within disorders due to use of alcohol (cross-mapped to DSM-5-TR alcohol withdrawal); anxiety and fear-related disorders including generalised anxiety disorder and panic disorder (DSM-5-TR anxiety disorders); depressive disorders including a peripartum-onset specifier (the target for brexanolone and zuranolone; DSM-5-TR MDD with peripartum onset). Epilepsy is neurological rather than an ICD-11 mental-disorder category. Specific ICD-11 alphanumeric codes are omitted here where certainty is incomplete (see gaps).

MNEMONIC

"FRequency vs duRation: Benzos are FRequent, Barbs enduRe."

Benzodiazepines increase the **fr**equency of GABA-A chloride channel opening; barbiturates increase the du**r**ation. Barbiturates additionally open the channel directly at high dose, which is why they lack the benzodiazepine ceiling and are lethal in overdose.

HOLD THIS

Benzodiazepines raise frequency, barbiturates raise duration; barbiturates also gate the channel directly at high dose, so they lose the ceiling and become lethal. This single contrast explains the benzodiazepine's wider therapeutic index.

7 · Cholinergic systems

Acetylcholine is the oldest neurotransmitter in psychiatry's story: it was the first chemical proven to carry a nerve signal (Loewi's 1921 vagusstoff experiment) and it remains the transmitter whose *loss* gave us the first rationally designed dementia drugs. For the exit exam the cholinergic system pays back in four distinct currencies, and a strong answer keeps them separate: the **molecular pharmacology** (synthesis by ChAT, breakdown by AChE, and the split between nicotinic ion channels and five muscarinic G-protein-coupled receptors), the **central anatomy** (two forebrain and two brainstem source nuclei with named projection targets), the **physiology** (memory, cortical arousal, and the generation of REM sleep), and the **clinical translation** (the cholinergic hypothesis of Alzheimer disease and cholinesterase inhibitors, anticholinergic burden and delirium in the elderly, the smoking-schizophrenia link, and the 2024 arrival of muscarinic agonism as an antipsychotic principle with xanomeline-trospium).

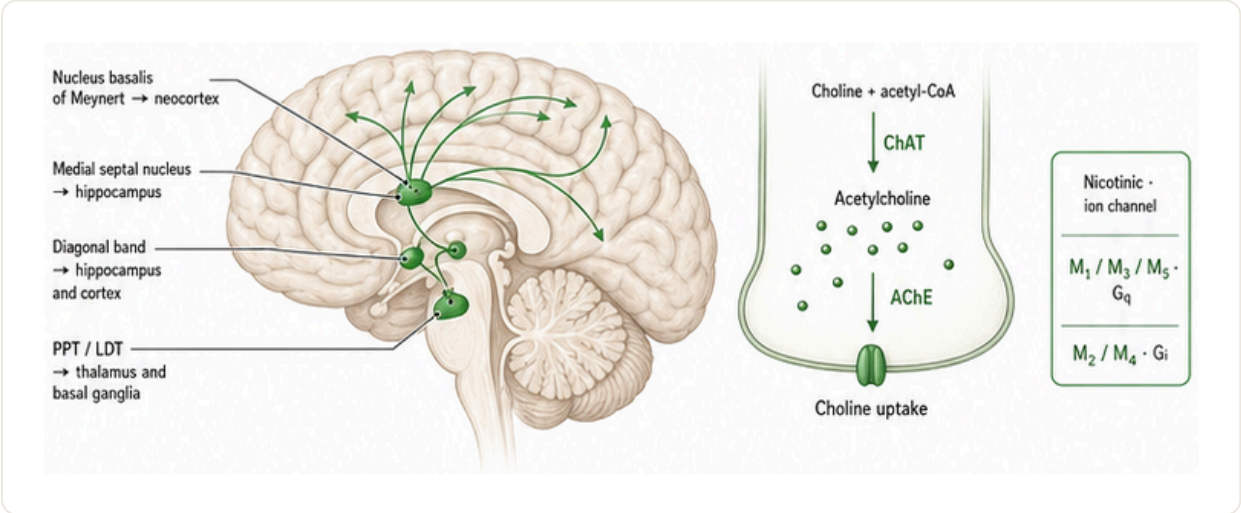


Fig 2.5 Central cholinergic systems.

Why it recurs. Cholinergic pharmacology is the through-line that connects a neurochemistry viva, a geriatric-psychiatry station, and a psychopharmacology question in a single sitting. The same M1 receptor that anticholinergics block to treat drug-induced parkinsonism is the receptor whose blockade causes the memory clouding of anticholinergic delirium; the same muscarinic system that xanomeline stimulates to quiet psychosis is the one whose peripheral M2/M3

activation trospium is added to suppress. Understanding the wiring once lets you reason your way through all of these rather than memorising each in isolation.

7.1 Synthesis, storage, release and inactivation

Synthesis. Acetylcholine (**ACh**) is an ester of acetic acid and choline, assembled in the axon terminal by **choline acetyltransferase** (ChAT, older abbreviation CAT), which transfers an acetyl group from mitochondrial acetyl-coenzyme A onto choline. Choline is the limiting substrate: it comes from the diet (egg yolk, liver, legumes) and from hepatic synthesis, crosses the blood-brain barrier, and is scavenged back into the terminal by a **high-affinity, sodium-dependent choline transporter** whose uptake is the true rate-limiting step in ACh production (Sam and Bordoni 2023). ChAT is manufactured in the soma and shipped down the axon; because it is uniquely present in cholinergic neurons, **ChAT immunostaining is the definitive marker of a cholinergic cell**, and its reduction in Alzheimer cortex is the biochemical cornerstone of the cholinergic hypothesis.

Storage and release. New ACh is pumped into synaptic vesicles by the **vesicular acetylcholine transporter** (VAChT), which exchanges one cytoplasmic ACh for one vesicular proton using the gradient built by a vesicular H-ATPase. Arrival of an action potential opens voltage-gated calcium channels; calcium triggers SNARE-mediated vesicle fusion (synaptobrevin as the v-SNARE, SNAP-25 and syntaxin-1 as t-SNAREs, synaptotagmin as the calcium sensor), releasing ACh into the cleft (Sam and Bordoni 2023). Two classic toxins bracket this step and are examiner favourites: **botulinum toxin cleaves SNARE proteins and blocks ACh release** (flaccid paralysis, exploited therapeutically for dystonia, spasticity and cosmesis), whereas **black widow (alpha-latrotoxin) venom forces massive ACh release** and exhausts the terminal.

Inactivation. Unlike the monoamines, ACh is not reclaimed by reuptake of the intact transmitter; it is **hydrolysed in the cleft** into choline and acetate by **acetylcholinesterase** (AChE), a fixed, GPI-anchored or soluble enzyme, with the liberated choline recaptured for resynthesis. AChE is extraordinarily fast, which makes cholinergic transmission crisp and short-lived; a second enzyme, **butyrylcholinesterase** (BuChE, pseudocholinesterase, made mainly in liver and glia), also degrades ACh and becomes relatively more important as AChE-bearing neurons are lost in advancing dementia. This two-enzyme architecture is the direct rationale for the cholinesterase inhibitors in subtopic 7.6.

> **PEARL**
>
> **ACh is the transmitter defined by its enzyme, not its transporter.** Serotonin, dopamine and noradrenaline are terminated by reuptake (hence SSRIs and reuptake inhibitors); acetylcholine is terminated by *enzymatic hydrolysis* in the cleft. That single difference explains why the drug class that boosts ACh is a group of *esterase inhibitors*, not reuptake inhibitors, and why organophosphate and nerve-agent poisoning (irreversible AChE inhibition) produces a cholinergic crisis.

7.2 Nicotinic receptors: the ionotropic arm

Nicotinic acetylcholine receptors (nAChRs) are **ligand-gated cation channels**, members of the pentameric Cys-loop superfamily alongside GABA-A, glycine and 5-HT3 receptors. Five subunits ring a central pore; binding of two ACh molecules opens the channel to sodium, potassium and calcium, depolarising the cell and driving fast excitatory transmission (Companion to Psychiatric Studies). Two broad classes matter. The **muscle type** (N1, subunit stoichiometry 2-alpha, beta, delta, gamma or epsilon) sits at the neuromuscular junction and is the receptor destroyed by autoantibodies in **myasthenia gravis**. The **neuronal type** (N2) is built from alpha and beta subunits and populates autonomic ganglia, the adrenal medulla and the brain, concentrated in the ventral tegmental area, nucleus accumbens, hippocampus, prefrontal cortex and amygdala (Sam and Bordoni 2023).

Two subtypes carry the psychiatry. The **alpha-4-beta-2** nAChR is the high-affinity target for nicotine and the site of the reinforcing, dependence-producing dopamine surge in the mesolimbic system; it is the target of the smoking-cessation partial agonist *varenicline* (Stahl 2021). The homomeric **alpha-7** nAChR is highly calcium-permeable, enriched in hippocampus and cortex, and implicated in sensory gating and cognition, making it a repeatedly pursued (and repeatedly disappointing) drug target for the cognitive deficits of schizophrenia. A defining feature of nAChRs is **desensitisation**: with prolonged agonist exposure the channel enters a non-conducting but agonist-bound state. Because AChE normally clears ACh within milliseconds the receptor rarely desensitises to its own transmitter, but **nicotine is not a substrate for AChE**, so it lingers, desensitises and then inactivates the receptor over the course of a single cigarette, which explains the characteristic dosing rhythm of smoking (Stahl 2021).

7.3 Muscarinic receptors: the five metabotropic subtypes

Muscarinic acetylcholine receptors (mAChRs) are **seven-transmembrane G-protein-coupled receptors**, subtypes M1 through M5, all five expressed in the CNS. They divide cleanly by their coupling, and this coupling is the single most examinable fact about them. The **odd-numbered receptors (M1, M3, M5)** couple to **Gq**, activating phospholipase C to generate IP3 and diacylglycerol, raising intracellular calcium and activating protein kinase C: broadly *excitatory/stimulatory*. The **even-numbered receptors (M2, M4)** couple to **Gi/Go**, inhibiting adenylyl cyclase and lowering cAMP (M2 also opens potassium channels): broadly *inhibitory* (Sam and Bordoni 2023).

SUBTYPE	G-PROTEIN / SECOND MESSENGER	NET EFFECT	KEY LOCATIONS (EXAM-RELEVANT)
M1	**Gq → PLC, IP3/DAG ↑Ca**	Excitatory	Cortex, hippocampus, striatum, gastric/salivary glands; cognition and memory
M2	**Gi → ↓cAMP, ↑K**	Inhibitory (autoreceptor)	Heart (bradycardia), CNS presynaptic autoreceptor limiting ACh release
M3	**Gq → PLC, IP3/DAG ↑Ca**	Excitatory	Smooth muscle (bronchi, bladder, gut), exocrine glands; pupillary constriction
M4	**Gi → ↓cAMP**	Inhibitory	Striatum (dopamine modulation), hippocampus; antipsychotic-relevant
M5	Gq → PLC	Excitatory	Substantia nigra/VTA (dopamine neurons), cerebral vasculature; least understood

The odd/even coupling rule: M1, M3, M5 are Gq-coupled and excitatory; M2 and M4 are Gi-coupled and inhibitory. Peripherally, M2 is the cardiac (vagal bradycardia) receptor and M3 the smooth-muscle/glandular receptor, which is why non-selective antimuscarinics produce the dry-mouth, blurred-vision, tachycardia, constipation and urinary-retention picture.

COMMON TRAP

Do not label all muscarinic receptors "inhibitory" because the parasympathetic system is often taught as the calming counterpart to sympathetic drive. At the receptor level M1, M3 and M5 are **excitatory** Gq signals; the parasympathetic *slowing* of the heart is a special case mediated by M2 opening potassium channels. Marrying the odd/even numbering to the Gq/Gi split (odd = Gq = excitatory, even = Gi = inhibitory) is the reliable way to avoid the error.

HOLD THIS

Muscarinic odd numbers are Gq and excitatory (M1, M3, M5); even numbers are Gi and inhibitory (M2, M4). Vagal cardiac slowing is the M2-opens-potassium special case, not proof that all muscarinic receptors inhibit.

7.4 Central cholinergic projection systems (cross-reference the Functional Neuroanatomy & Neurophysiology notes)

Central ACh arises from two source regions, one in the basal forebrain and one in the brainstem, giving **four named nuclei** whose projection targets are high-yield (these overlay the ascending arousal/reticular systems mapped on the Functional Neuroanatomy & Neurophysiology notes). Learn them as two pairs.

Nucleus basalis of Meynert (Ch4)

The large-celled (magnocellular) basal forebrain nucleus that supplies the **diffuse cholinergic innervation of the entire neocortex and the amygdala**. Its degeneration is the anatomical lesion of the Alzheimer cholinergic deficit; there is a documented correlation between the depth of amnesia and the extent of nucleus basalis damage (Tasman Psychiatry).

Medial septal nucleus and diagonal band (Ch1-Ch2)

The **septohippocampal** projection, running through the fornix to the hippocampus (and to entorhinal cortex). Medial-septal cholinergic neurons **pace the hippocampal theta rhythm** that is essential for encoding new declarative memory; their loss produces the forgetfulness of hippocampal ACh depletion (Companion to Psychiatric Studies).

Pedunculopontine tegmental nucleus (PPT/PPN)

Part of the mesopontine (brainstem) cholinergic group projecting rostrally to the **thalamus, basal forebrain and basal ganglia**; a component of the ascending reticular activating system that drives cortical arousal and, with the LDT, gates REM sleep.

Laterodorsal tegmental nucleus (LDT)

The second mesopontine nucleus, closely allied with the PPT; together the **PPT/LDT** constitute the "REM-on" cholinergic generator of the brainstem (subtopic 7.5).

A separate, purely local cholinergic population, the **striatal cholinergic interneurons (tonically active neurons)**, does not project but sets the dopamine-acetylcholine balance within the striatum that underlies extrapyramidal side effects and their anticholinergic treatment (subtopic 7.7).

7.5 Functions: memory, cortical arousal and REM sleep

Memory and attention. Cortical and hippocampal ACh is permissive for **encoding new information and for attention**, not for retrieving old memories. The pharmacological proof is scopolamine, a centrally acting antimuscarinic that reproducibly **impairs the learning of new material** while leaving established memory intact (Sam and Bordoni 2023); this "scopolamine model of amnesia" is the mirror image of the therapeutic logic behind cholinesterase inhibitors. Basal-forebrain ACh also sharpens signal-to-noise in sensory cortex, supporting selective attention.

Cortical arousal. The brainstem (PPT/LDT) and basal-forebrain cholinergic systems are core components of the **ascending reticular activating system**. Cholinergic tone **desynchronises the cortical EEG**, shifting it from the slow high-voltage rhythms of drowsiness to the fast low-voltage activity of wakefulness and REM, which is why anticholinergic drugs sedate and cloud consciousness.

REM sleep. ACh is the pro-REM transmitter. The **reciprocal-interaction (McCarley-Hobson) model** frames REM as the output of "REM-on" cholinergic PPT/LDT neurons switched off by "REM-off" aminergic (noradrenergic locus coeruleus, serotonergic raphe) neurons; REM occurs when cholinergic activity is high and aminergic activity is low. This maps directly onto two exam points: cholinergic REM facilitation explains the **REM rebound and vivid dreaming seen with cholinesterase inhibitors**, and the reduced REM latency of depression is read as a relative cholinergic-aminergic imbalance.

MNEMONIC

"ACh WAKES you to LEARN and to DREAM"

Acetylcholine drives cortical arousal (WAKES: EEG desynchronisation), consolidation of new memory (LEARN: hippocampal theta and encoding), and REM sleep (DREAM: PPT/LDT REM-on neurons). Block it (scopolamine, atropine, deliriant plants) and you get the opposite triad: sedation, amnesia for new events, and a confusional, dream-like delirium.

TRAP Acetylcholine is not cleared by reuptake. It is hydrolysed in the cleft, which is why the drugs that raise it are esterase inhibitors, not reuptake inhibitors.

7.6 The cholinergic hypothesis of Alzheimer disease and cholinesterase inhibitors

The hypothesis. The **cholinergic hypothesis** holds that the cognitive decline of Alzheimer disease reflects **progressive loss of basal-forebrain cholinergic neurons** (the nucleus basalis of Meynert), with fallen cortical ChAT and ACh (Maudsley Prescribing Guidelines). It was the first mechanistic account to yield a drug class, but it is now understood as one strand rather than the whole story: the deficits are not confined to ACh, and cholinergic replacement is symptomatic, not disease-modifying. Contemporary texts (Stahl 2021) accordingly de-emphasise it relative to the amyloid and tau pathways while retaining it as the basis of current symptomatic therapy.

Cholinesterase inhibitors (ChEIs). These raise synaptic ACh by blocking its hydrolysis; three are licensed for mild-to-moderate (and, in guidance, severe) Alzheimer dementia and give **modest symptomatic benefit** without altering the underlying course.

DRUG	ENZYME SELECTIVITY	EXTRA MECHANISM	NOTES
Donepezil	**Selective reversible AChE-I**	None	Once daily; best tolerated of the three; 23 mg formulation for moderate-severe AD
Rivastigmine	**AChE + BuChE (pseudo-irreversible)**	Dual esterase inhibition	Oral or transdermal patch (better GI tolerability); also licensed in Parkinson disease dementia
Galantamine	Selective reversible AChE-I	**Allosteric nicotinic receptor potentiation**	Additional nicotinic modulation; more peripheral adverse-effect profile

The three ChEIs differ mechanistically (donepezil pure selective AChE inhibition, rivastigmine dual AChE plus BuChE, galantamine AChE inhibition plus allosteric nicotinic potentiation) but head-to-head trials show broadly similar efficacy; choice is driven by tolerability and formulation (Maudsley Prescribing Guidelines).

Adverse effects and combination. The predictable price of raised ACh is **cholinergic excess**: nausea, vomiting, diarrhoea, anorexia and weight loss, bradycardia and syncope (caution in sick sinus syndrome and conduction block), muscle cramps, and vivid dreams; slow titration reduces these. For **moderate-to-severe AD**, NICE and other guidelines recommend an AChE-I *plus* the

NMDA-receptor antagonist **memantine** rather than an AChE-I alone, a combination supported by network meta-analysis and Cochrane review (Maudsley Prescribing Guidelines). Newer disease-modifying anti-amyloid monoclonal antibodies (for example lecanemab, donanemab) act on a different pathway and do not displace symptomatic ChEI therapy.

CLINICAL ANCHOR

ChEIs are also first-line for the cognitive symptoms of **dementia with Lewy bodies** and Parkinson disease dementia, where the cholinergic deficit is often even more marked than in Alzheimer disease and the response can be striking; rivastigmine is specifically licensed for Parkinson disease dementia. Conversely, in **myasthenia gravis** the same principle is applied peripherally: the reversible AChE inhibitor *pyridostigmine* raises ACh at the neuromuscular junction to overcome antibody-mediated loss of N1 receptors.

7.7 Anticholinergic burden, delirium and the dopamine-acetylcholine balance

The striatal balance. Within the nigrostriatal system dopamine and ACh sit in **reciprocal opposition**: dopamine at D2 receptors normally suppresses striatal cholinergic interneurons, so *blocking* D2 receptors with an antipsychotic releases ACh and produces the rigidity and bradykinesia of drug-induced parkinsonism (Stahl 2021). Adding an **antimuscarinic (M1-blocking) anticholinergic**, trihexyphenidyl, benztropine or procyclidine, restores the balance and relieves parkinsonism and acute dystonia (intramuscular anticholinergic is near-uniformly effective within about 20 minutes for acute dystonia). Akathisia, by contrast, responds poorly to anticholinergics and is better treated with a beta-blocker or benzodiazepine.

The cost of blockade. The same central M1 blockade that treats extrapyramidal symptoms carries a cognitive price: **constipation, dry mouth, blurred vision, urinary retention, drowsiness and, critically, memory and attention impairment**, the pharmacological counterpart of the scopolamine amnesia model (Stahl 2021). The concept of **anticholinergic burden** captures the additive antimuscarinic load of a patient's whole regimen, since many non-psychiatric drugs (oxybutynin, some antihistamines, tricyclics, low-potency antipsychotics) carry hidden anticholinergic activity.

CLINICAL ANCHOR

Anticholinergic delirium should always be considered in an agitated or confused older adult (Tasman Psychiatry). Central antimuscarinic toxicity produces the classic picture: agitation and visual hallucinations, disorientation and fluctuating consciousness, with peripheral signs of "mad as a hatter, hot as a hare, dry as a bone, red as a beet, blind as a bat" (delirium, hyperthermia, anhidrosis, flushing, mydriasis). High cumulative anticholinergic burden is an independent, and modifiable, risk factor for both delirium and longer-term cognitive decline in the elderly, which is why deprescribing antimuscarinics is a standard geriatric-psychiatry intervention.

INDIA

Antimuscarinic anti-parkinsonian drugs, especially **trihexyphenidyl**, are widely and often reflexively co-prescribed with first-generation antipsychotics such as haloperidol in Indian practice, and trihexyphenidyl carries a recognised potential for **misuse** (euphoriant and hallucinogenic at high dose). Good practice is to reserve it for established extrapyramidal symptoms rather than prophylaxis, review the need periodically, and stay alert to diversion, particularly given the high anticholinergic-burden risk in older and physically comorbid patients.

7.8 Smoking and schizophrenia; the alpha-7 and nicotinic story

Rates of cigarette smoking in schizophrenia are strikingly high (well above the general population), and the relationship is more than a lifestyle association. The leading explanation is a **self-medication / sensory-gating hypothesis**: nicotine, acting on **alpha-7 and alpha-4-beta-2 nicotinic receptors**, transiently improves the impaired auditory sensory gating (the P50 evoked-potential deficit) and some attentional and working-memory deficits characteristic of schizophrenia, deficits linked to reduced alpha-7 nicotinic function and to the CHRNA7 gene. Nicotine also induces hepatic CYP1A2, so **smoking lowers plasma levels of clozapine and olanzapine** (both CYP1A2 substrates); abrupt smoking cessation can raise levels sharply and precipitate toxicity, a frequently examined interaction. This nicotinic-cognitive link is the same rationale that drove alpha-7 agonist drug programmes for cognitive impairment in schizophrenia, which have so far largely failed to deliver a licensed agent.

COMMON TRAP

When a stabilised inpatient smoker on clozapine is admitted to a smoke-free ward, or stops smoking, expect clozapine levels to **rise** (loss of CYP1A2 induction), not fall. The mechanism is nicotine-independent (it is the polycyclic aromatic hydrocarbons in tobacco smoke, not the nicotine, that induce CYP1A2), so nicotine-replacement therapy does *not* maintain the induction. Anticipate a dose reduction and monitor levels.

7.9 Muscarinic agonism as an antipsychotic: xanomeline-trospium (2024)

The most important recent development in cholinergic psychopharmacology is the arrival of a **muscarinic mechanism of antipsychotic action**, the first genuinely new antipsychotic principle in decades and one that does not rely on direct dopamine D2 blockade. **Xanomeline** is a central agonist selective for the **M1 and M4** muscarinic receptors. Via M4 it *indirectly* reduces dopamine cell firing in the ventral tegmental area (theoretically damping positive psychotic symptoms), and via M1 it raises prefrontal dopamine and acetylcholine (theoretically aiding negative, cognitive and affective symptoms), achieving antipsychotic effect without touching the D2 receptor and therefore **without the extrapyramidal, prolactin and metabolic liabilities of dopamine blockers** (Stahl 2021).

Xanomeline alone was historically limited by peripheral cholinergic side effects from M2 and M3 stimulation (nausea, vomiting, sweating, salivation, GI upset). The solution is the **co-formulation with trospium**, a peripherally restricted antimuscarinic that **does not cross the blood-brain barrier** and so blocks the offending peripheral M2/M3 receptors while sparing the central

M1/M4 agonism that carries the therapeutic effect (Stahl 2021). This combination, developed as **KarXT** (xanomeline-trospium, brand name Cobenfy), gained **US FDA approval for schizophrenia in adults in September 2024**, establishing the muscarinic system as a validated antipsychotic target and vindicating a line of research that began with xanomeline trials in Alzheimer disease decades earlier.

PEARL

KarXT is the clean worked example of exploiting the blood-brain barrier for selectivity. **Xanomeline works centrally (M1/M4 agonism → antipsychotic); trospium works only peripherally (M2/M3 antagonism → blocks cholinergic side effects) because it cannot enter the brain.** Contrast this with the older strategy in Parkinson disease, where a peripheral decarboxylase inhibitor (carbidopa) is added to levodopa for the analogous reason: keep the therapeutic action central and the unwanted action peripheral.

8 · Neuropeptides (substance P, CRF, oxytocin and others)

Neuropeptides are the second, slower transmitter language of the brain. Where the classical small-molecule transmitters (glutamate, GABA, the monoamines, acetylcholine) are packaged in small clear vesicles and act in milliseconds at the synaptic cleft, neuropeptides are chains of amino acids, stored in large dense-core vesicles, released more diffusely (from the axon, from dendrites, sometimes far from any synapse) and act over seconds to minutes through **G-protein-coupled receptors**. They almost never work alone: most are *co-transmitters* released alongside a monoamine or amino acid, and they tune the gain of that faster circuit rather than carrying the primary message. For the examiner this topic is a checklist of "who does what, which receptor, and which drug story went with it," and the single most reliable trap is the one built into the whole field: peptide biology is beautiful in rodents and has repeatedly disappointed in humans.

This fragment covers the co-transmission principle, then substance P, CRF, the oxytocin-vasopressin pair, the endogenous opioid peptides (a Paper-1 must-have), and the shorter roster of NPY, CCK, galanin and orexin, closing on why translation has been so hard. It cross-references the the Functional Neuroanatomy & Neurophysiology notes stress circuit and the HPA axis topic of this same day, since CRF is the molecular hinge of both.

8.1 The co-transmission principle

One neuron, more than one transmitter. Dale's original one-neuron-one-transmitter rule was overturned once immunohistochemistry showed peptides sitting inside the same neurons as classical transmitters. The organising fact is **co-localisation**: neuropeptide Y coexists with noradrenaline in the locus coeruleus and with GABA and somatostatin elsewhere; galanin coexists with noradrenaline in the locus coeruleus and with serotonin in the dorsal raphe; substance P co-exists with serotonin in raphe neurons (Tasman 2013). The peptide is generally released only at higher firing frequencies than the fast transmitter, so it acts as a *state-dependent modulator*, engaged when the circuit is driven hard, as in stress.

Storage and release

Peptides are made as large precursors in the cell body, cleaved and packaged into **large dense-core vesicles**, then released by calcium-triggered exocytosis. Release is *not* confined to the synapse or axon terminal: it occurs along the axon and from dendrites, giving diffuse, paracrine-like signalling.

Precursor economy

A single gene product often yields several active peptides. Pro-opiomelanocortin (POMC) is the exemplar: differential cleavage gives beta-endorphin, ACTH and the melanocyte-stimulating hormones from one precursor, tissue-specifically.

Receptors

Almost all neuropeptide receptors are *metabotropic*, seven-transmembrane GPCRs (the same superfamily as monoamine receptors), which is why peptide actions are slow and modulatory rather than fast and ionotropic.

Inactivation

There is no reuptake transporter for peptides; they are terminated by extracellular *peptidases*. This is a practical drug-design problem, since peptides are also degraded in the gut and cross the blood-brain barrier poorly.

> **PEARL**
>
> The "no reuptake, degraded by peptidases, poor blood-brain-barrier penetration" triad explains two recurring facts: why most peptide-based drugs are given intranasally (oxytocin, NPY) to reach the brain, and why the successful drugs in this space are small-molecule *receptor* ligands (antagonists at NK1, CRF1, orexin receptors) rather than the peptides themselves.

8.2 Substance P and the NK1 receptor: the aprepitant story

The tachykinin of pain, stress and emesis. Substance P is an 11-amino-acid **undecapeptide** of the tachykinin family, discovered in the 1930s and among the most studied of all neuropeptides. It signals mainly through the **neurokinin-1 (NK1) receptor**, a GPCR densely expressed in limbic regions (amygdala, hypothalamus, periaqueductal grey) that govern the stress and fear response; the family also includes NK2 (largely peripheral smooth muscle) and NK3 (central) receptors. Substance P is a classic pain neurotransmitter in the dorsal horn, and its central injection is anxiogenic in the elevated-plus-maze.

The psychiatric signal. Depressed and PTSD patients show elevated CSF substance P (Tasman 2013), which made NK1 antagonism an attractive antidepressant strategy. The landmark result was **MK-869 (later aprepitant)**: an early trial reported it superior to placebo and comparable to paroxetine in moderate-to-severe major depression (Kramer 1998). This was the great hope of the peptide era.

The disappointment, and the pivot. Subsequent adequately powered phase-III trials of aprepitant in major depression *failed* to separate from placebo, and the antidepressant programme was abandoned. The molecule was not wasted: NK1 antagonism is a powerful antiemetic, and **aprepitant was approved (as Emend) for chemotherapy-induced and post-operative nausea and vomiting**, the durable clinical legacy of the substance P story. This is the

template for the whole topic: rodent-validated, human-disappointing on the primary psychiatric endpoint, salvaged by an adjacent indication.

TRAP When a neuropeptide antagonist is linked to emesis rather than mood, think substance P / NK1 and aprepitant: it failed as an antidepressant but succeeded as an antiemetic.

CLINICAL ANCHOR

When a question links a neuropeptide antagonist to *emesis* rather than mood, think substance P / NK1 and aprepitant. Its antiemetic use, especially with highly emetogenic chemotherapy, is the fact most likely to be tested, and it is the counterexample to the claim that peptide drugs "never made it."

8.3 CRF/CRH: the master driver of the stress axis

The peptide that starts the cascade. Corticotropin-releasing factor (CRF, also CRH) is the apical hypothalamic peptide of the stress response. Parvocellular neurons of the **paraventricular nucleus (PVN)** synthesise CRF and release it into the hypophyseal portal system to drive pituitary ACTH, and thence adrenal cortisol; this is the **HPA axis** covered in detail in the HPA topic of these notes, and CRF is the same molecule that opens the the Functional Neuroanatomy & Neurophysiology notes stress circuit. Vasopressin, co-secreted from the PVN, is a permissive co-secretagogue that potentiates CRF-driven ACTH release (Kaplan & Sadock 2024).

Central versus endocrine CRF. Beyond the neuroendocrine axis, CRF acts as a genuine *extrahypothalamic neurotransmitter*, notably in the amygdala and the bed nucleus of the stria terminalis, where it mediates the behavioural and emotional (rather than hormonal) components of stress, anxiety and fear. Two receptors matter: **CRF1**, the anxiogenic, pro-stress receptor, and **CRF2**, with a more complex, sometimes counter-regulatory role. CRF1-knockout mice show decreased anxiety and a blunted stress response (Smith 1998).

The translational failure. Hyperactivity of the CRF system is a robust correlate of chronic stress and depression, and CRF1 antagonists looked like a rational antidepressant/anxiolytic class. An open-label CRF1-antagonist trial hinted at antidepressant activity, but controlled trials of CRF1 antagonists in depression and anxiety did not deliver convincing efficacy (Paez-Pereda 2011), and the class stalled, another rodent-to-human disappointment. Vasopressin V1b antagonism was pursued in parallel for the same axis; the V1b antagonist SSR149415 was discontinued in 2008 for lack of clinical efficacy.

CLINICAL ANCHOR

CRF hyperdrive is the biochemical bridge between early-life adversity, chronic stress and depression. Elevated CSF CRF and non-suppression on the dexamethasone suppression test both index this overactivity and both tend to normalise with clinical recovery, one of the more reliable state markers linking the HPA topic to affective illness.

8.4 Oxytocin and vasopressin: bonding, trust and the social brain

A nine-amino-acid pair from the same nuclei. Oxytocin and arginine vasopressin (AVP) are structurally near-identical **nonapeptides** (9 amino acids, differing at two positions) synthesised in the **paraventricular and supraoptic nuclei** of the hypothalamus and released both peripherally via the posterior pituitary and centrally within the brain (Kaplan & Sadock 2024). Peripherally, oxytocin drives uterine contraction and milk let-down; centrally, it is the prosocial, stress-buffering peptide.

Oxytocin: prosocial and anxiolytic

Anxiogenic and stressful stimuli trigger central oxytocin release, which *dampens* the HPA axis and reduces anxiety. Intranasal oxytocin in healthy men reduces amygdala reactivity to fearful faces, lowers anxiety and improves emotion recognition and social memory. Oxytocin exerts inhibitory effects on the HPA axis and facilitates extinction of social fear (Kaplan & Sadock 2024).

Vasopressin: arousal and aggression

AVP acts through **V1a** (anxiety, social recognition, aggression) and **V1b** (HPA-axis modulation, co-driving ACTH). V1a-knockout mice are less anxious; V1a-overexpressing mice are more anxious (Kaplan & Sadock 2024). Oxytocin and vasopressin are functional opposites in the central amygdala, exciting distinct neuronal populations.

Autism and trust. Oxytocin is the peptide most tied to social cognition. Reduced CSF oxytocin is reported after early-life stress, and oxytocin-receptor gene polymorphisms and reduced OXTR methylation associate with social anxiety and with heightened cortisol and amygdala reactivity. Intranasal oxytocin has been trialled in autism spectrum disorder to improve social reciprocity, and in social anxiety disorder as an augment to exposure therapy, with modest and inconsistent benefit. Note a recurring *sex difference*: several oxytocin effects seen in men are not reproduced in women.

> **COMMON TRAP**
>
> Do not overstate the "trust hormone" and "autism cure" claims. Intranasal oxytocin's effects in human trials are small, context- and sex-dependent, and large controlled trials in autism have been largely negative for core social deficits. In an exam, the safe statement is that oxytocin modulates social cognition, amygdala reactivity and HPA-axis tone, not that it is an established treatment.

8.5 Endogenous opioid peptides: three families, three receptors

The brain's own morphine system. This subtopic is a Paper-1 must-have. The **endogenous opioid** system is a neuropeptide system with three families of peptides, each derived from its own precursor, acting on three classical opioid receptors (Oxford Handbook of DBT 2018). The mnemonic pairing of family to receptor is high-yield.

Endorphins (from POMC)

Beta-**endorphin** is cleaved from pro-opiomelanocortin, the same precursor that yields ACTH and MSH, so endorphin release is intrinsically coupled to HPA-axis activation. Beta-endorphin is the highest-affinity endogenous agonist at the **mu (μ)** receptor, the receptor of reward, euphoria and analgesia.

Enkephalins (from proenkephalin)

Enkephalins (met- and leu-enkephalin) are short pentapeptides preferring the **delta (δ)** receptor (with mu activity too). They are widely distributed in pain-modulating and limbic circuits; alcohol releases enkephalins in the nucleus accumbens, part of alcohol's rewarding action (Stahl, Substance Use).

Dynorphins (from prodynorphin)

Dynorphins are the endogenous agonists of the **kappa (κ)** receptor. Kappa signalling is the dark mirror of mu: rather than euphoria it produces *dysphoria*, aversion and stress-like states, and dynorphin in the central amygdala disinhibits somatostatin neurons to generate anxiety (Kaplan & Sadock 2024).

PEPTIDE FAMILY	PRECURSOR	PREFERRED RECEPTOR	SIGNATURE EFFECT
Beta-endorphin	POMC (proopiomelanocortin)	Mu (μ)	**Reward, euphoria, analgesia; HPA-linked**
Enkephalins (met-, leu-)	Proenkephalin	Delta (δ)	Analgesia, mood, limbic reward
Dynorphins	Prodynorphin	**Kappa (κ)**	**Dysphoria, aversion, stress**

The three endogenous opioid families mapped to precursor, receptor and effect. The discriminator is the kappa/dynorphin axis, which drives dysphoria rather than reward.

Reward, analgesia and stress in one system. The mu system underlies opioid analgesia and the euphoric "high" of exogenous opioids and is a core node of the brain reward circuit; descending endogenous-opioid projections to the periaqueductal grey and dorsal horn gate nociceptive input, which is the endogenous analgesia mimicked by exogenous opioids (Stahl 2021). The kappa/dynorphin system, by contrast, mediates the aversive, dysphoric side of stress and has become a target for anti-anhedonic and anti-addiction agents (kappa antagonists). Clinically, this circuitry underpins naltrexone (a mu antagonist) in alcohol and opioid use disorder, and the endogenous-opioid dysregulation hypothesis of non-suicidal self-injury, where tissue damage releases beta-endorphin against a low baseline tone (Oxford Handbook of DBT 2018).

MNEMONIC

END-en-DYN → μ-δ-κ; Kappa = Krummy

ENDorphin to **mu** (μ), **EN**kephalin to **delta** (δ), **DYN**orphin to **kappa** (κ), read in that order. And "**Kappa is Krummy**": kappa/dynorphin produces dysphoria and aversion, the opposite of the mu/endorphin high.

HOLD THIS

Endorphin-mu, enkephalin-delta, dynorphin-kappa; the kappa/dynorphin arm produces dysphoria, the mirror of the mu high. That aversive kappa axis is the anti-anhedonia and anti-addiction target.

CLINICAL ANCHOR

Two agents make this concrete. **Naltrexone** and **naloxone** are non-selective opioid antagonists (mainly mu) used in opioid overdose (naloxone) and in alcohol and opioid use disorder (naltrexone), where they blunt endogenous-opioid-mediated reward. Kappa-directed compounds are an active 2020s research front for treatment-resistant depression and anhedonia.

8.6 The shorter roster: NPY, CCK, galanin and orexin

Four more peptides with clean exam handles. Each has one or two facts examiners favour; the table fixes the discriminators and the prose gives the mechanism.

Neuropeptide Y (NPY)

A 36-amino-acid peptide, one of the most abundant and conserved in the brain, concentrated in locus coeruleus, hypothalamus and amygdala. It is the endogenous **anxiolytic and stress-resilience** peptide: Y1-receptor activation is anxiolytic and antidepressant, Y2 activation is anxiogenic (Kaplan & Sadock 2024). Intranasal NPY has shown early promise in PTSD and depression.

Cholecystokinin (CCK)

A gut-brain peptide whose brain form (CCK-8) sits in cortex, hippocampus and amygdala. Its exam identity is **panicogenesis**: the CCK-2 (CCK-B) agonists *CCK-4* (tetrapeptide) and pentagastrin reliably provoke panic attacks in humans and are used as a laboratory panic-challenge model. CCK-2 antagonists were trialled as anti-panic drugs and failed to beat placebo (Kaplan & Sadock 2024).

Galanin

A 29-to-30-amino-acid peptide co-expressed with noradrenaline in the locus coeruleus and with serotonin in the dorsal raphe, acting as an inhibitory neuromodulator through GalR1-3. GalR1 activation is anxiolytic; galanin buffers mood and anxiety, particularly under high noradrenergic (high-stress) drive.

Orexin / hypocretin

Two peptides, orexin-A (33 aa) and orexin-B (28 aa), from a single prepro-orexin precursor, made by a small set of **lateral hypothalamic** neurons that project across the neuroaxis. They act at OX1R and OX2R to promote **wakefulness and arousal**, feeding, and reward (via the ventral tegmental area). Loss of orexin neurons causes **narcolepsy with cataplexy (type 1)**, marked by very low CSF orexin-A.

PEPTIDE	HEADLINE RECEPTOR/SUBTYPE	EXAM-FAVOURITE ASSOCIATION
NPY	Y1 (anxiolytic), Y2 (anxiogenic)	**Endogenous anxiolytic and resilience peptide**
CCK	CCK-2 / CCK-B	**CCK-4 and pentagastrin provoke panic**
Galanin	GalR1-3 (GalR1 anxiolytic)	Co-transmitter in locus coeruleus, buffers stress
Orexin / hypocretin	OX1R, OX2R	**Deficiency causes narcolepsy; target of DORAs**

The four supporting peptides with their receptors and the single association examiners test. Orexin is the one that yielded an approved drug class.

Orexin is the peptide success story. Where substance P and CRF antagonism failed, the orexin system delivered a marketed class by working *with* the biology rather than against a disease correlate. Because orexin drives wakefulness, **orexin-receptor antagonists** promote sleep. The **dual orexin receptor antagonists (DORAs)**, suvorexant, lemborexant and daridorexant, block both OX1R and OX2R and are licensed for insomnia, a mechanism-based hypnotic class that avoids the GABA-A dependence profile of the benzodiazepines and Z-drugs. Orexin biology also explains why the same lateral-hypothalamic neurons couple arousal, appetite and reward, and why the system is being probed in addiction and mood.

INDIA

The DORAs (suvorexant, lemborexant, daridorexant) remain expensive and not yet widely stocked in most Indian pharmacies, so benzodiazepines, Z-drugs and low-dose sedating antidepressants still dominate insomnia prescribing here. Knowing the orexin mechanism matters more for exams and for counselling than for day-to-day availability, but the class is worth flagging to patients asking about non-benzodiazepine options. CSF orexin-A assay for suspected narcolepsy type 1 is available only at a few tertiary centres.

8.7 Translation and its disappointments

Why the peptide era over-promised. The through-line of this topic is a translational gap. Neuropeptide manipulation produces clean, replicable effects on anxiety- and depression-like behaviour in rodents, yet the human drug programmes have mostly failed on their primary psychiatric endpoints: NK1 (substance P) antagonists in depression, CRF1 antagonists in depression and anxiety, vasopressin V1b antagonists in anxiety, and CCK-2 antagonists in panic all separated poorly or not at all from placebo in controlled trials (Kaplan & Sadock 2024).

Several reasons recur and are worth stating in a viva. First, **redundancy**: peptide systems overlap and compensate, so blocking one rarely collapses the behaviour. Second, **pharmacokinetics**: peptides degrade fast, cross the blood-brain barrier poorly and lack reuptake handles, forcing reliance on small-molecule ligands or intranasal delivery. Third, a **biomarker-versus-target confusion**: an elevated peptide (CSF substance P, CSF CRF) can be a downstream correlate of illness rather than a causal, druggable node. The instructive contrast is orexin: the DORAs succeeded because they targeted a *physiological function* (arousal) with a clear behavioural readout (sleep), not a disease-correlated peptide level. That is the lesson the field carries into the 2020s as kappa-opioid and oxytocin programmes continue.

COMMON TRAP

A tempting but wrong answer is that neuropeptide drugs "failed and the field is dead." The accurate framing: the *antidepressant/anxiolytic* peptide-antagonist programmes largely failed, but the same molecules succeeded in adjacent indications (aprepitant for emesis, DORAs for insomnia), and mechanism-first targets (orexin, kappa opioid) remain live. Say "disappointing for mood and anxiety, productive elsewhere," not "abandoned."

9 · Novel and gasotransmitters: endocannabinoids, nitric oxide, trace amines

Beyond the classical amine and amino-acid transmitters sits a class of unconventional messengers that break almost every rule the standard synapse taught you. They are not pre-packaged into vesicles, several are not proteins or even discrete molecules but dissolved gases, several travel *backward* across the cleft, and several act inside the target cell rather than on a surface receptor. For the exit exam this cluster is high-yield precisely because it is a favourite viva probe: the examiner uses it to test whether a candidate genuinely understands what defines a neurotransmitter, or has merely memorised a list. A strong answer keeps three families straight: the lipid **endocannabinoids** (anandamide and 2-AG), the **gasotransmitters** (nitric oxide, carbon monoxide, hydrogen sulfide), and the **trace amines** acting through TAAR1, with a footnote on purinergic signalling.

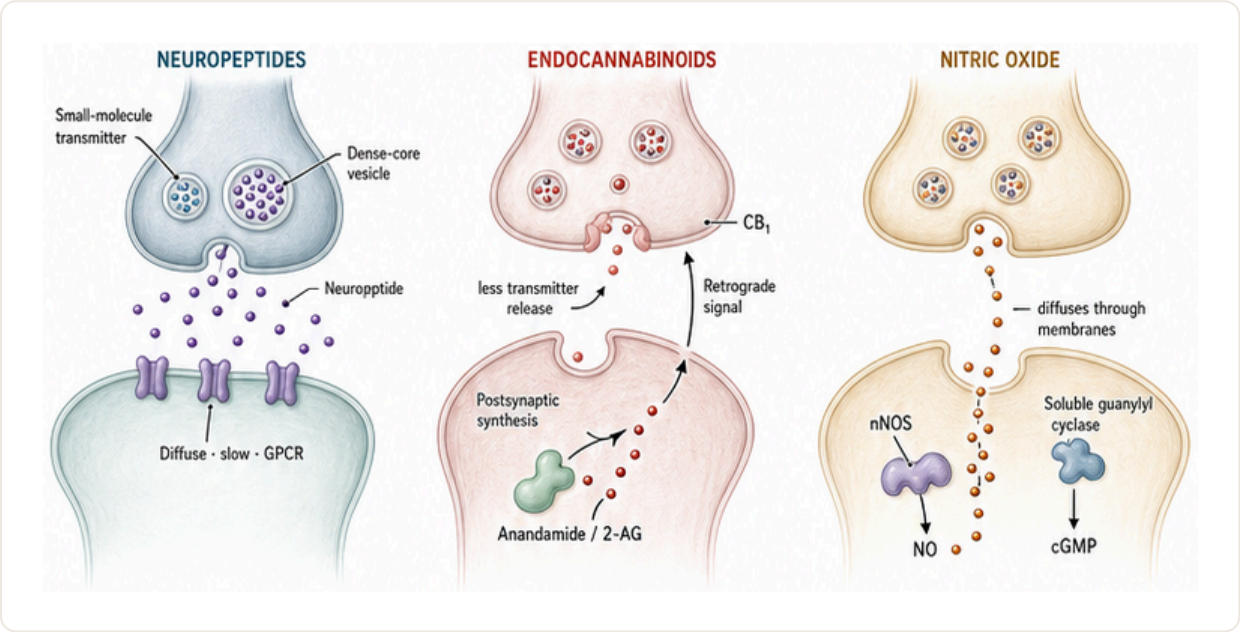


Fig 2.6 Unconventional neurotransmission.

Why it recurs. Each family carries a piece of live clinical currency. Endocannabinoids explain both the appeal of cannabis and the cautionary collapse of the anti-obesity drug rimonabant; nitric oxide is the worked example of a gas that carries signal and the mechanism behind the phosphodiesterase-5 inhibitors; and TAAR1 agonism is the most talked-about non-dopaminergic antipsychotic principle of the decade, embodied by ulotaront. Learn the shared theme, on-demand synthesis and unconventional signalling, and each drug story becomes deducible rather than memorised (Kaplan and Sadock 2024, Stahl 2021).

9.1 Endocannabinoids: the on-demand lipid messengers

The ligands. The two principal **endocannabinoids** are **anandamide** (N-arachidonoylethanolamine, named from the Sanskrit *ananda*, bliss) and **2-AG** (2-arachidonoylglycerol). Both are lipids built from the omega-6 fatty acid arachidonic acid, which is also the precursor of prostaglandins and leukotrienes (Kaplan and Sadock 2024). Anandamide was the first isolated, by Mechoulam and colleagues in 1992, after the CB1 receptor had already been cloned in the late 1980s and the field reasoned that an endogenous ligand must exist. Minor

endocannabinoids (noladin ether, virodhamine, N-arachidonoyldopamine) exist but are not exam-critical.

Synthesised on demand, not stored. The single most examinable structural fact is that endocannabinoids are **not pre-packaged in synaptic vesicles**; they are manufactured from membrane phospholipid precursors at the moment of need, exactly as the gasotransmitters are. Neuronal depolarisation raises intracellular calcium, which activates the synthetic enzymes (NAPE-PLD for anandamide, diacylglycerol lipase for 2-AG), and the freshly made lipid diffuses out of the cell (Kaplan and Sadock 2024). Because they are highly lipophilic they cross membranes freely rather than being released by classical exocytosis.

Inactivation. Anandamide is degraded postsynaptically by **fatty acid amide hydrolase** (FAAH) into arachidonic acid and ethanolamine; 2-AG is broken down mainly presynaptically by monoacylglycerol lipase (MAGL). FAAH inhibition raises endocannabinoid tone and has been pursued as an anxiolytic strategy, the endocannabinoid analogue of the MAO inhibitor logic for monoamines (Kaplan and Sadock 2024).

9.2 Cannabinoid receptors: CB1 versus CB2

Two G-protein-coupled receptors carry endocannabinoid signalling, and their contrast is a reliable one-line question.

CB1

The dominant **central nervous system** cannabinoid receptor, possibly the most abundant GPCR in the brain, densest in basal ganglia, cerebellum, hippocampus, hypothalamus, anterior cingulate and frontal cortex. It sits **presynaptically** on axons and nerve termini, couples through Gi/Go to inhibit adenylyl cyclase, opens potassium channels and blocks N-type calcium channels, thereby *suppressing neurotransmitter release*. CB1 mediates the psychoactive "high" of THC and the appetite, mood, memory and reward effects of the system (Kaplan and Sadock 2024).

CB2

Predominantly expressed on **immune cells** (white blood cells, microglia), with only small amounts in brain. It carries the immunomodulatory and neuroinflammatory arm of endocannabinoid signalling and is not responsible for the central psychoactive effects.

Of the ligands, anandamide is relatively CB1-selective, whereas 2-AG does not strongly discriminate between CB1 and CB2 (Kaplan and Sadock 2024).

9.3 Retrograde signalling and DSI/DSE

Backward across the cleft. Endocannabinoids are the textbook example of a **retrograde messenger**. Classical transmission runs presynaptic to postsynaptic; endocannabinoids run the other way. A presynaptic dopamine or glutamate neuron fires and depolarises the postsynaptic cell; the resulting postsynaptic calcium rise triggers on-demand endocannabinoid synthesis; the lipid then diffuses **back** across the synapse to activate presynaptic CB1 receptors, which dampen further transmitter release (Kaplan and Sadock 2024). This gives the postsynaptic neuron a way to turn down its own inputs, a form of short-term synaptic plasticity.

DSI and DSE. When the suppressed presynaptic terminal is *inhibitory* (GABAergic), the phenomenon is called **depolarisation-induced suppression of inhibition** (DSI); when it is *excitatory* (glutamatergic), it is depolarisation-induced suppression of excitation (DSE). CB1 antagonists and CB1 knockout abolish hippocampal DSI, which is the experimental proof that endocannabinoids are the retrograde mediator. Endocannabinoids are also implicated in long-term depression (LTD) and other plasticity (Kaplan and Sadock 2024).

PEARL

Two of these novel messengers are **retrograde**, and it is worth pairing them: endocannabinoids diffuse from postsynaptic to presynaptic to *suppress transmitter release*, while nitric oxide diffuses from postsynaptic to presynaptic to *strengthen* transmission in LTP. Same direction of travel, opposite functional sign, and both are made on demand rather than stored, which is the unifying theme of the whole topic.

9.4 Physiological roles: appetite, anxiety, memory and reward

Appetite. CB1 activation in the hypothalamus and limbic circuitry **stimulates appetite**, the neural basis of the cannabis "munchies" and the reason CB1 blockade was pursued for weight loss (subtopic 9.5). **Anxiety and mood.** Endocannabinoid tone is broadly **anxiolytic**: CB1-deficient animals are more anxious in novel or stressful settings, and anandamide and 2-AG rise in the amygdala during aversive learning (Kaplan and Sadock 2024). The system is implicated in the **extinction of aversive memory**, the ability to stop fearing a cue once it no longer predicts harm; CB1 knockouts fail to extinguish conditioned fear, which frames the endocannabinoid system as a candidate target in PTSD and phobias.

Memory. The dense hippocampal CB1 expression underlies the short-term memory impairment that accompanies acute cannabis intoxication. **Reward.** Cannabinoids increase dopamine release in the nucleus accumbens, and this reward-relevant surge requires mu-opioid receptors, linking the endocannabinoid and opioid systems in addiction (Kaplan and Sadock 2024).

9.5 Clinical translation: cannabis and the rimonabant cautionary tale

Cannabis. Exogenous THC is a CB1 agonist; it drives the euphoria, appetite stimulation, memory disruption and, at high or vulnerable exposure, the association with psychosis that make the endocannabinoid system clinically central. **Rimonabant.** The mirror-image experiment was **rimonabant** (Acomplia), a CB1 inverse agonist developed as an anti-obesity and smoking-cessation drug. It did produce weight loss, but blocking a tonically anxiolytic, mood-supporting system exacted a psychiatric price. In a 2007 meta-analysis (Christensen et al.), patients on rimonabant had roughly a **2.5-fold higher risk of discontinuing for depression and a threefold higher risk of discontinuing for anxiety**, and these effects appeared even though people with a history of mood or anxiety disorders had been excluded from the trials (Kaplan and Sadock 2024). Reports of increased suicidal ideation followed, the drug was withdrawn, and rimonabant became the standing cautionary tale that pharmacologically silencing endocannabinoid signalling can precipitate depression, anxiety and suicidality.

CLINICAL ANCHOR

The rimonabant story is the clean exam illustration of the endocannabinoid system's tonic role in emotional regulation: a drug that worked exactly as designed for metabolism unmasked depression and suicidality by removing a background anxiolytic tone. A converging human finding is that postmortem prefrontal cortex from people who died by suicide shows **increased CB1 receptor density**, consistent with a dysregulated endocannabinoid system in mood pathology (Kaplan and Sadock 2024).

CLASSIC TRAP Rimonabant "worked exactly as designed" for weight loss, yet blocking a tonically anxiolytic system unmasked depression, anxiety and suicidality, and it was withdrawn.

9.6 Nitric oxide: the gaseous retrograde messenger of LTP

An atypical transmitter on every count. **Nitric oxide** (NO, written with a dot to mark it as a free radical) was, in the early 1990s, the first gas ascribed a neurotransmitter role, and it violates the classical definition comprehensively: it is **not stored in vesicles**, it is synthesised on demand, it **diffuses freely across membranes** rather than being exocytosed, it has **no cell-surface receptor**, and it has no reuptake, being limited instead by a half-life of a few seconds (Kaplan and Sadock 2024).

Synthesis downstream of the NMDA receptor. NO is made by **nitric oxide synthase** from the amino acid arginine (yielding citrulline as byproduct), using NADPH and oxygen. The brain-predominant isoform is **neuronal NOS (nNOS)**, first described by Bredt and Snyder; the other isoforms are endothelial (eNOS, vasodilatation) and inducible (iNOS, inflammation). Crucially, nNOS is activated by calcium via calmodulin, so NO is generated when **NMDA-receptor activation admits calcium** into the postsynaptic cell (Kaplan and Sadock 2024).

Retrograde messenger in LTP. This is the headline function. **Long-term potentiation**, the synaptic model of learning, is induced by postsynaptic NMDA-receptor calcium influx but maintained partly by presynaptic changes. NO made postsynaptically diffuses **backward** to the presynaptic terminal, where it activates soluble guanylyl cyclase, raising cyclic GMP, and enhances further transmitter release, closing the loop that strengthens the synapse (Stahl 2021, Kaplan and Sadock 2024). NO acts intracellularly, either through the cGMP pathway or by S-nitrosylation of cysteine residues on target proteins, not through a membrane receptor. Peripherally the same nNOS-cGMP axis mediates penile erection, which is why phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil), by preserving cGMP, treat erectile dysfunction, a favourite peripheral tie-in.

9.7 Carbon monoxide and hydrogen sulfide: the other gasotransmitters

Nitric oxide is the prototype but not the only gas. Two further **gasotransmitter**s are recognised, sharing NO's defining features of on-demand synthesis, membrane-permeant diffusion and receptor-independent intracellular action.

Carbon monoxide (CO)

Generated by heme oxygenase during heme breakdown; like NO it can stimulate guanylyl cyclase and cyclic GMP signalling, and the heme oxygenase pathway carries a neuroprotective role that appears impaired in Alzheimer disease (Kaplan and Sadock 2024).

Hydrogen sulfide (H2S)

The newest and once dismissed as merely a toxic, foul-smelling gas. It is generated by cystathionine beta-synthase (CBS), the brain-abundant enzyme, which like the other gas-generating enzymes is calcium/calmodulin-activated. H2S potentiates NMDA-receptor currents, modulates hippocampal LTP and has low-level neuroprotective effects (Kaplan and Sadock 2024).

MNEMONIC

"NO-CO-H2S: Not stored, no receptor, just diffuse"

The three gasotransmitters (nitric oxide, carbon monoxide, hydrogen sulfide) share the trio of exam-defining negatives: **N**ot vesicle-stored, **N**o classical surface receptor, and no reuptake; they are made on demand and act by diffusing into the target cell, typically converging on the guanylyl cyclase / cyclic GMP pathway. State those three negatives and you have answered the "why is X an atypical neurotransmitter" question for any of them.

HOLD THIS

A gasotransmitter is defined by three negatives: not vesicle-stored, no surface receptor, no reuptake. Made on demand, it diffuses into the cell and works on intracellular guanylyl cyclase.

9.8 Trace amines and TAAR1: the ulotaront story

What trace amines are. **Trace amines** are endogenous monoamines present at very low (trace) brain concentrations: the five principal ones are beta-phenylethylamine (PEA), p-tyramine, tryptamine, p-octopamine and p-synephrine (Stahl 2021). They form when the hydroxylase step is skipped during dopamine or serotonin synthesis, and they modulate the uptake and release of the classical monoamines. Their chief receptor is **TAAR1** (trace amine-associated receptor type 1), a GPCR expressed widely in monoaminergic centres, the ventral tegmental area, dorsal raphe and their projection fields, where it acts as a brake tuning dopaminergic and serotonergic tone (Stahl 2021).

Why it matters therapeutically. TAAR1 agonism is the most prominent recent attempt at a **non-D2 antipsychotic mechanism**. The lead compound is **ulotaront** (SEP-363856), a TAAR1 agonist that also has 5-HT1A agonist activity (with additional 5-HT1D and 5-HT7 binding), tested in schizophrenia (Stahl 2021, Maudsley 15th edition). Because it does not block dopamine D2 receptors, it promised antipsychotic effect without extrapyramidal side effects, hyperprolactinaemia or the metabolic burden of D2 antagonists, an attractive profile that placed it alongside the muscarinic agonist xanomeline as a genuinely novel mechanism.

COMMON TRAP

Do not overstate ulotaront's arrival. TAAR1 agonism is a mechanistically exciting, **investigational** principle, and the pivotal phase 3 schizophrenia programme for ulotaront reported negative results, tempering early enthusiasm. Contrast this with the muscarinic agonist principle, which *did* reach the clinic as xanomeline-trospium in 2024. The safe exam line is that TAAR1 agonism is a promising non-dopaminergic strategy exemplified by ulotaront (a TAAR1 and 5-HT1A agonist) whose clinical validation remains unproven, rather than a licensed treatment.

9.9 Purinergic signalling: adenosine, ATP and caffeine

A brief but examinable coda. **Purinergic signalling** uses purine messengers, ATP and its breakdown product adenosine, acting at purinergic receptors: the P1 **adenosine receptors** (A1, A2A, A2B, A3, all GPCRs) and the P2 receptors for ATP, split into ionotropic P2X channels and metabotropic P2Y GPCRs (Goodman and Gilman). A1 receptors couple to Gi (inhibitory), A2A to Gs (stimulatory), giving adenosine its broadly inhibitory, sleep-promoting and neuroprotective tone. The clinically indispensable one-liner is that **caffeine is a non-selective adenosine receptor antagonist, blocking A1 and A2A**; relieving adenosine's inhibitory brake is how caffeine produces arousal and wakefulness. The A2A receptor, densely expressed in striatum where it interacts with dopamine D2 signalling, is an active target of interest in Parkinson disease.

10 · Second messengers and signal transduction

Chemical neurotransmission does not stop at the receptor. When a first-messenger transmitter binds its target, the message is handed inward through a relay of intracellular molecules that Stahl memorably calls a molecular "pony express": a **first messenger** (the transmitter) generates a **second messenger** (a small intracellular signal such as cAMP or calcium), which activates a **third messenger** (a kinase or phosphatase), which modifies a **fourth messenger** (a phosphoprotein), ultimately reaching gene expression and structural change (Stahl 2021). The events at the membrane happen in under a second, but the downstream limb takes hours to days and can last the lifetime of the synapse. This time-lag is the single most examinable idea in the topic: it explains why antidepressants and antipsychotics have a therapeutic latency of two to three weeks despite occupying their receptors within hours, because the clinically relevant change is in gene transcription and plasticity, not receptor occupancy.

Why it recurs. Signal transduction is the connective tissue of the whole paper. It supplies the receptor pharmacology behind every transmitter section (the Gq/Gi split that defines muscarinic and adrenergic subtypes), the molecular target of lithium (inositol monophosphatase and GSK-3), the mechanism of antidepressant latency (CREB and BDNF), and the 2020s frontier of rational drug design (biased agonism, the muscarinic antipsychotics, PDE inhibitors). A candidate who can draw the cAMP and phosphoinositide cascades and place lithium, caffeine, and sildenafil on them can answer a dozen apparently separate questions from one diagram.

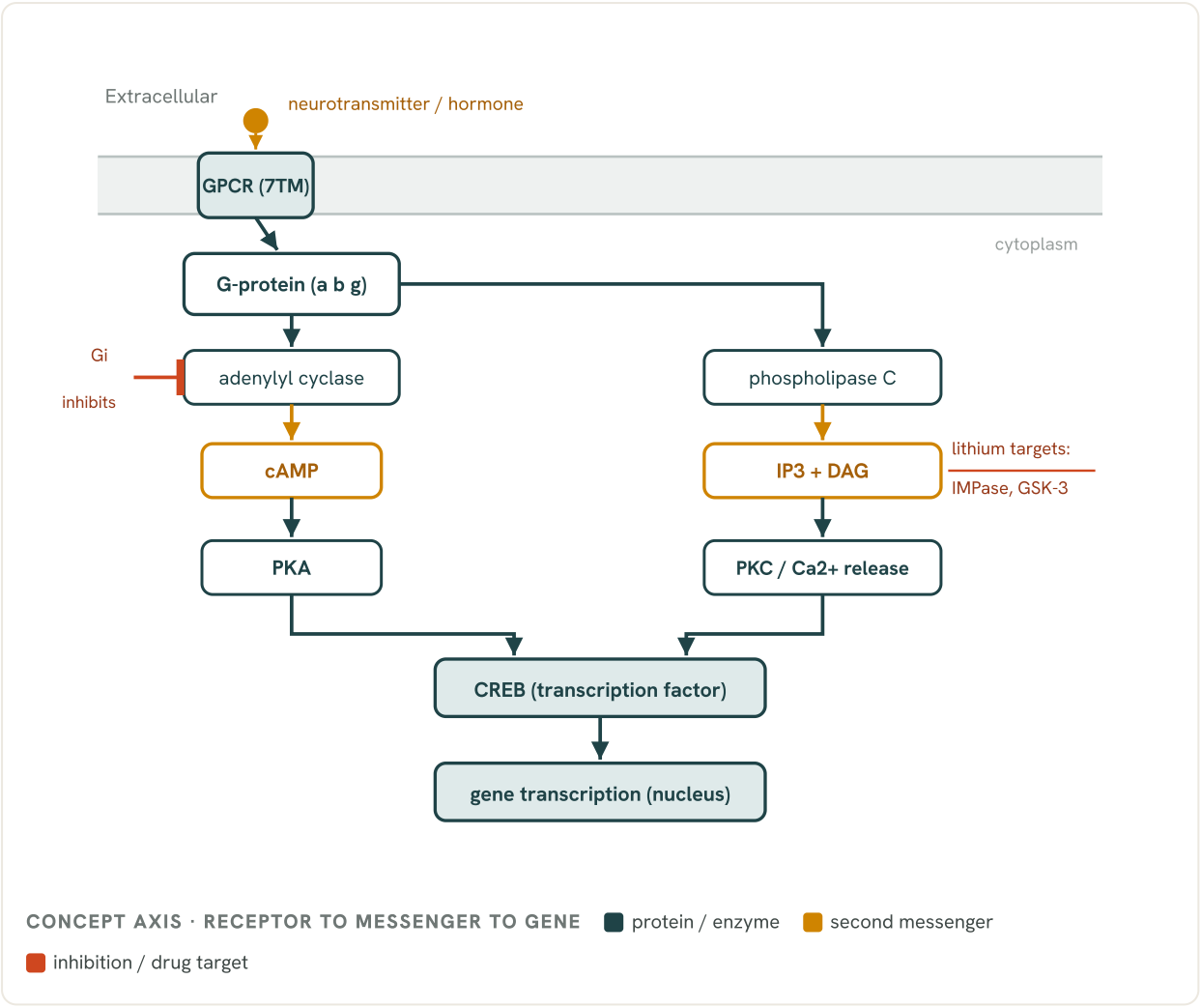


Fig 2.7 The two main G-protein-coupled cascades. Gs drives adenylyl cyclase to cAMP to PKA; Gq drives phospholipase C to IP3 and DAG, raising intracellular Ca2+ and activating PKC; Gi inhibits adenylyl cyclase. Both converge on CREB and gene transcription, the slow, plasticity-relevant layer that explains the delay in antidepressant action. Lithium acts here, inhibiting inositol monophosphatase and GSK-3.

10.1 The G-protein cycle: how a bound receptor becomes an intracellular signal

The switch. G-protein-coupled receptors (GPCRs) are the **seven-transmembrane superfamily** that carries most slow, modulatory neurotransmission. The transducer is a **heterotrimeric G protein** (alpha, beta, gamma subunits) sitting on the inner membrane leaflet. At rest the alpha subunit holds GDP. Agonist binding changes the receptor conformation so it can engage the G protein, catalysing exchange of **GDP for GTP** on the alpha subunit; the trimer then dissociates into a free GTP-bound alpha subunit and a beta-gamma dimer, both of which regulate downstream effectors (Kaplan and Sadock 2024). Signalling is self-terminating: the alpha subunit has **intrinsic GTPase activity** that hydrolyses GTP back to GDP and reassembles the inactive trimer.

Four alpha families, two main effectors. The particular alpha class a receptor couples to dictates which second messenger is made. The four neurotransmitter-relevant classes are **Gs**, **Gi**, **Gq**, and **G12/13**. Gs and Gi both act on the cAMP system (stimulating and inhibiting adenylate cyclase respectively); Gq drives the phosphoinositide system; G12/13 modulates Rho/Rac cytoskeletal signalling and is rarely examined (Kaplan and Sadock 2024). Crucially, a single receptor can

recruit more than one G protein and each active G protein can turn over many effector molecules, giving the **signal amplification** that lets a few occupied receptors produce a large intracellular response.

Turning it off. Two brakes are worth naming. **Regulators of G-protein signalling (RGS proteins)** are GTPase-activating proteins that accelerate alpha-subunit GTP hydrolysis and so shorten the signal; over 20 subtypes exist, and reduced striatal RGS9 (which restrains Gi-linked dopamine signalling) has been reported in schizophrenia postmortem brain, consistent with excess dopamine signalling (Kaplan and Sadock 2024). Separately, agonist-occupied receptors are phosphorylated by **G-protein-coupled receptor kinases (GRKs)**, which recruit arrestin to uncouple and internalise the receptor: the molecular basis of desensitisation, tolerance, and part of the delayed therapeutic response to psychotropics (subtopic 10.7).

PEARL

The G protein is a molecular timer, not a switch you flip. Its "on" duration equals the interval before the alpha subunit hydrolyses its own GTP. RGS proteins are the tuning knob that speeds this up; cholera toxin (locks Gs on) and pertussis toxin (locks Gi off) are the classic experimental probes that freeze the timer in one position and thereby prove which limb a receptor uses.

10.2 The cAMP / PKA pathway (Gs and Gi)

The cAMP system, discovered by Sutherland and Rall in the 1950s, is the **prototypical second-messenger cascade** (Kaplan and Sadock 2024). A Gs-coupled receptor activates the membrane enzyme **adenylate cyclase**, which converts ATP to **cyclic AMP (cAMP)**; a Gi-coupled receptor inhibits the same enzyme and lowers cAMP. The net cAMP level at a given synapse is therefore the arithmetic of its Gs- and Gi-coupled receptors, illustrated classically by noradrenaline *raising* cAMP through beta-adrenergic receptors and *lowering* it through alpha-2 receptors on the same cell.

cAMP's principal target is **protein kinase A (PKA)**, a tetramer of two regulatory and two catalytic subunits. At baseline the regulatory subunits inhibit the catalytic ones; when cAMP binds the regulatory subunits they release the catalytic subunits, which then **phosphorylate serine and threonine residues** on a broad range of substrates: ion channels (fast effects), transmitter-synthetic enzymes (slower effects), and, critically, transcription factors that alter gene expression (slowest effects). The signal is terminated by **phosphodiesterases (PDEs)**, which cleave cAMP to AMP (Kaplan and Sadock 2024).

CLINICAL ANCHOR

Three drugs sit directly on this pathway and recur in vivas. **Caffeine** nonselectively inhibits PDEs (and antagonises adenosine receptors), raising cAMP. **Rolipram**, a PDE4 inhibitor, showed antidepressant promise but was limited by nausea; **PDE10A inhibitors** have been pursued as antipsychotics. And **sildenafil** works on the parallel cGMP system by inhibiting the PDE5 isoform enriched in vascular smooth muscle. The unifying principle: block the phosphodiesterase, and you prolong the cyclic-nucleotide signal.

10.3 The phosphoinositide pathway (Gq): PLC, IP3, DAG, PKC and calcium

Many receptors do not touch cAMP at all; they couple through **Gq** to the phosphoinositide (PI) system, which parallels the cAMP system but branches into three signals (Kaplan and Sadock 2024). Gq activates **phospholipase C (PLC)**, which cleaves the membrane lipid **phosphatidylinositol bisphosphate (PIP2)** into two second messengers at once: **diacylglycerol (DAG)** and **inositol trisphosphate (IP3)**.

DAG

Hydrophobic, so it stays in the membrane and recruits **protein kinase C (PKC)** from the cytoplasm to the membrane, where PKC is activated and phosphorylates numerous substrates. Some PKC isoforms additionally require calcium.

IP3

Water-soluble, so it diffuses to the endoplasmic reticulum and binds the **IP3 receptor** (a ligand-gated calcium channel), releasing large stores of intracellular Ca2+.

Ca2+ (third arm)

Released calcium is itself a second messenger. It directly triggers vesicle release and opens calcium-activated channels, and it acts more slowly through **calmodulin**: four calcium ions bind calmodulin, and the complex activates **calcium/calmodulin-dependent kinase (CaMK)** and other targets, converging on gene transcription.

The odd-numbered muscarinic (M1, M3, M5) and alpha-1 adrenergic receptors are the exam-favourite Gq couplings; the pathway is terminated by lipases degrading DAG, calcium pumps clearing Ca2+, and inositol phosphatases recycling IP3 back to inositol, the step lithium blocks (subtopic 10.6).

MNEMONIC

"Q cuts PIP2 into a DIP"

Gq activates PLC to *cut* PIP2 into **D**AG (activates PKC) and **IP**3 (releases calcium). The odd muscarinic receptors (1, 3, 5) and alpha-1 use this line; the even muscarinics (2, 4), alpha-2, D2, and 5-HT1A use Gi to *lower* cAMP. Odd equals Gq equals excitatory; even equals Gi equals inhibitory.

10.4 Minor cascades: cGMP / nitric oxide and arachidonic acid

Two smaller lipophilic-signal systems round out the GPCR-linked repertoire and appear as single-mark discriminators. **cGMP and nitric oxide.** Unlike cAMP, **cyclic GMP** is made by guanylate cyclases that are **not directly activated by G proteins**; the cytoplasmic form is switched on by the gas **nitric oxide (NO)**, itself synthesised by NO synthase after activation by calcium-calmodulin (Kaplan and Sadock 2024). NO is small enough to diffuse across membranes and can act as a **retrograde messenger** back onto the presynaptic terminal, blurring the line between intracellular and intercellular signalling; cGMP then acts through protein kinase G (PKG). **Arachidonic acid.** Certain receptors activate **phospholipase A2**, which liberates arachidonic acid from membrane phospholipid; cyclooxygenase converts it to prostaglandins and thromboxanes, lipoxygenase to leukotrienes. These lipophilic metabolites can leave the neuron

and act on GPCRs elsewhere, and COX inhibition has been explored as adjunctive treatment in schizophrenia and depression via anti-inflammatory effects (Kaplan and Sadock 2024).

10.5 Receptor tyrosine kinases: the neurotrophin cascade

The GPCR pathways signal through diffusible small molecules; the fourth great cascade does not. **Receptor tyrosine kinases (RTKs)** are transmembrane receptors with a **tyrosine kinase enzyme built into their own intracellular tail**, and they carry the neurotrophic factors NGF and BDNF rather than classical transmitters (Kaplan and Sadock 2024). Neurotrophins bind the **Trk family** of RTKs (BDNF binds TrkB), which causes two receptors to **dimerise** and cross-phosphorylate each other on tyrosine residues, a process called **autophosphorylation**. The new phosphotyrosines become docking sites: the adaptor Grb2 (via its SH2 domain) binds and recruits the exchange factor SOS, which switches on the **small G protein Ras** (GTP for GDP). Active Ras drives the **MAPK cascade**, a conserved relay of kinases (Raf, then MEK, then ERK), and ERK activates ribosomal S6 kinase and transcription factors to change gene expression, synaptic plasticity, and neuronal survival.

Two contrasts with the GPCR pathways are high-yield. First, RTK signalling produces **no small-molecule second messenger**: the message passes as a chain of protein phosphorylations, not as cAMP or calcium. Second, the small G proteins (Ras, Rho, Ral) resemble the alpha subunit but are activated by separate GEFs rather than directly by the receptor, and are switched off by GAPs, the exact analogue of RGS proteins on heterotrimeric G proteins (Kaplan and Sadock 2024).

FEATURE	GPCR PATHWAYS	RECEPTOR TYROSINE KINASE PATHWAY
First messenger	Classical transmitters, hormones	**Neurotrophins (NGF, BDNF)**
Transducer	Heterotrimeric G protein (Gs/Gi/Gq)	**Small G protein (Ras), via Grb2-SOS**
Second messenger	cAMP, IP3/DAG, Ca2+	**None; a kinase cascade instead**
Core kinase relay	PKA, PKC, CaMK	Raf to MEK to ERK (MAPK)
Timescale, main role	Fast to slow modulation, transmission	Slow: growth, plasticity, survival

GPCR and RTK cascades converge on transcription (both can phosphorylate or induce CREB), but differ in transducer and in whether a small-molecule second messenger is generated; the RTK route is the molecular substrate of the neurotrophic hypothesis of mood disorders (subtopic 10.8).

10.6 Lithium's molecular targets: inositol monophosphatase and GSK-3

Lithium is the exam's favourite worked example of a psychotropic acting on second messengers rather than receptors, and it has **two mechanistically distinct targets. Inositol depletion.** Lithium inhibits **inositol monophosphatase (IMPase)**, the enzyme that dephosphorylates inositol monophosphate to free inositol needed to regenerate membrane PIP2. Blocking it depletes free inositol and runs down the phosphoinositide cycle, the **inositol depletion hypothesis** proposed by Berridge and colleagues (Berridge et al 1982); over time this downregulates specific PKC isoforms with downstream changes in transmitter release

(Companion to Psychiatric Studies). The hypothesis is almost certainly too simple as a whole-brain account but may hold in specific regions and cell types.

GSK-3 inhibition. Lithium is a potent inhibitor of **glycogen synthase kinase 3 (GSK-3, especially the beta isoform)** (Stambolic et al 1996). GSK-3 phosphorylates and modulates a wide set of substrates that link lithium to plasticity and neuroprotection: Wnt-pathway proteins and beta-catenin, microtubule-associated tau (whose hyperphosphorylation forms Alzheimer tangles), and the transcription factors AP-1 (jun) and CREB (Companion to Psychiatric Studies). Inhibiting GSK-3 is thought to underlie lithium's neuroprotective and possibly pro-cognitive effects; the Lithium Handbook links lithium's advantages (reduced suicide and dementia risk) to falling IP3, GSK-3-beta inhibition, and reduced telomere shortening (Nelson and Meyer 2023).

PEARL

The two lithium targets map onto the two great cascades. **IMPase inhibition acts on the Gq/phosphoinositide arm** (inositol depletion, PKC downregulation); **GSK-3 inhibition acts on the plasticity arm** shared with the neurotrophin/Wnt pathways. There is even a third thread: dopamine D2 receptors signal through a non-canonical **beta-arrestin-2 pathway** that *raises* GSK-3-beta activity to drive amphetamine-like hyperlocomotion, and lithium blunts this too, a molecular link between lithium and its antimanic action (Nelson and Meyer 2023).

RULE **Lithium acts inside the cell, not at a receptor.** IMPase inhibition (inositol depletion) hits the Gq/phosphoinositide arm; GSK-3 inhibition hits the plasticity arm shared with the neurotrophin pathways.

10.7 Desensitisation, arrestin, and biased agonism (functional selectivity)

The classical model, then its revision. The old teaching was that a given ligand is a full agonist, partial agonist, or antagonist and behaves the same across every pathway a receptor can access. This is now known to be incomplete. **Biased agonism** (also called **functional selectivity**) is the finding that a ligand can preferentially activate one downstream pathway while leaving another relatively untouched (Kaplan and Sadock 2024). The best-characterised split is between **canonical G-protein signalling and beta-arrestin signalling**: after GRK phosphorylation, arrestin not only desensitises and internalises the receptor but also acts as a scaffold for its own signalling, notably MAPK/ERK. A biased agonist can therefore favour the therapeutic limb and spare the limb that mediates side effects or tolerance.

Why it matters for drug design. The canonical example is the **mu-opioid receptor**: arrestin-knockout mice show less morphine tolerance, prompting development of G-protein-biased opioids (such as oliceridine) intended to keep analgesia while reducing respiratory depression, though whether the real-world benefit holds remains contested and dependence persists (Kaplan and Sadock 2024). Bias arises because different ligands stabilise different receptor conformations, and it can also be produced by receptor dimerisation or by signalling from intracellular membrane compartments (location bias). The concept now shapes rational psychiatric drug design and is a recurring viva prompt on the future of pharmacology.

COMMON TRAP

Do not equate biased agonism with partial agonism. A **partial agonist** produces a submaximal response through *all* pathways equally (lower efficacy everywhere). A **biased agonist** can be a full agonist at one pathway and near-silent at another (different pathways, not different ceilings). Aripiprazole is usually taught as a D2 partial agonist; a G-protein-biased opioid is a distinct idea about *which* pathway is engaged, not *how much*.

10.8 The molecular bridge to mood and plasticity: CREB and BDNF

All roads in this topic converge on the nucleus, and the shared endpoint is **CREB (cAMP response element-binding protein)**. PKA (from the cAMP arm), CaMK (from the calcium arm), and RSK (from the neurotrophin/MAPK arm) all phosphorylate CREB; once phosphorylated, CREB binds **cAMP response elements (CREs)** in target-gene promoters and drives transcription of genes for neuronal survival, plasticity, and long-term memory (Kaplan and Sadock 2024). This is where a receptor event on the millisecond scale becomes a lasting structural change.

The neurotrophic hypothesis of depression. The most examinable clinical translation is the CREB-BDNF link. Chronic stress lowers hippocampal **BDNF** and causes atrophy of CA3 neurons, mirroring the modest hippocampal volume loss seen on MRI in depression and PTSD (Kaplan and Sadock 2024). Serotonin and noradrenaline reuptake inhibitors **upregulate BDNF, CREB, and TrkB** in the hippocampus on a timescale of roughly ten to twenty days that matches their therapeutic latency, and CREB drives BDNF gene expression. This is the mechanistic answer to "why do antidepressants take weeks to work": receptor blockade is immediate, but the plasticity change (CREB activation to BDNF induction to synaptic and structural remodelling) unfolds over weeks. The picture is not uniform, exogenous BDNF in the mesolimbic dopamine circuit is *pro*-depressive rather than antidepressant, underscoring that BDNF's effect is region-specific (Kaplan and Sadock 2024).

CLINICAL ANCHOR

The rapid antidepressants exploit this cascade from a different entry point. Ketamine and esketamine block NMDA receptors to trigger a fast burst of glutamate, AMPA-receptor activation, and a surge of **BDNF-TrkB and downstream mTOR signalling** that drives rapid synaptogenesis, which is the leading account of antidepressant effect within hours rather than weeks. Whichever pathway is used, the therapeutic common denominator is convergence on neurotrophin-driven plasticity, the molecular bridge between transmitter, gene, and mood.

HOLD THIS

Antidepressant latency is a gene-transcription story: receptor occupancy is immediate, but the CREB-to-BDNF-to-plasticity change takes weeks. Lithium acts here too (IMPase, GSK-3), inside the cell, not at a receptor.

10.9 Exam integration: placing drugs and diseases on the cascade

The examiner reward for this topic is the ability to locate any agent or lesion on a single map. Positive-symptom antipsychotics act on Gi-coupled D2 receptors (lowering cAMP), and the newest antipsychotic principle, **xanomeline-trospium**, works through M1/M4 muscarinic GPCRs rather than direct D2 blockade. Mood stabilisers sit downstream: lithium on IMPase and GSK-3, and valproate also modulates GSK-3 and ERK-pathway signalling. Stimulant and caffeine effects run through cAMP/PDE. Antidepressant latency, ketamine's speed, and lithium's neuroprotection all resolve at the level of CREB, BDNF, and synaptic plasticity.

INDIA

Lithium remains a first-line and cost-effective mood stabiliser in Indian practice, and its second-messenger mechanism carries a practical message worth voicing in a viva: because lithium acts on intracellular enzymes with a narrow therapeutic index, **serum-level monitoring, thyroid and renal surveillance, and attention to dehydration and drug interactions (NSAIDs, thiazides, ACE inhibitors)** are integral to safe use in settings where laboratory access can be intermittent. The molecular story is not academic: it is why lithium is monitored the way it is.

11 · Neurodevelopment: migration, pruning, critical periods

The brain is built once, refined twice, and each stage is a separate window through which a disorder can enter. This topic is the developmental backbone of biological psychiatry, and the paper mines it in two directions at once: as a stepwise list of processes (neurulation to myelination) that must be named in order, and as a set of mechanisms whose failure produces named disorders. The examinable logic is temporal. A hit that lands in the first trimester (a migration failure) produces a different phenotype from one that lands in adolescence (a pruning failure), and the two-hit and neurodevelopmental hypotheses of schizophrenia are simply the formal statement that both windows matter. Fix the sequence and the timing, and the clinical associations, heterotopias, schizophrenia, autism, the effect of early sensory deprivation, all hang off it (Stahl 2021; Kaplan & Sadock 2024).

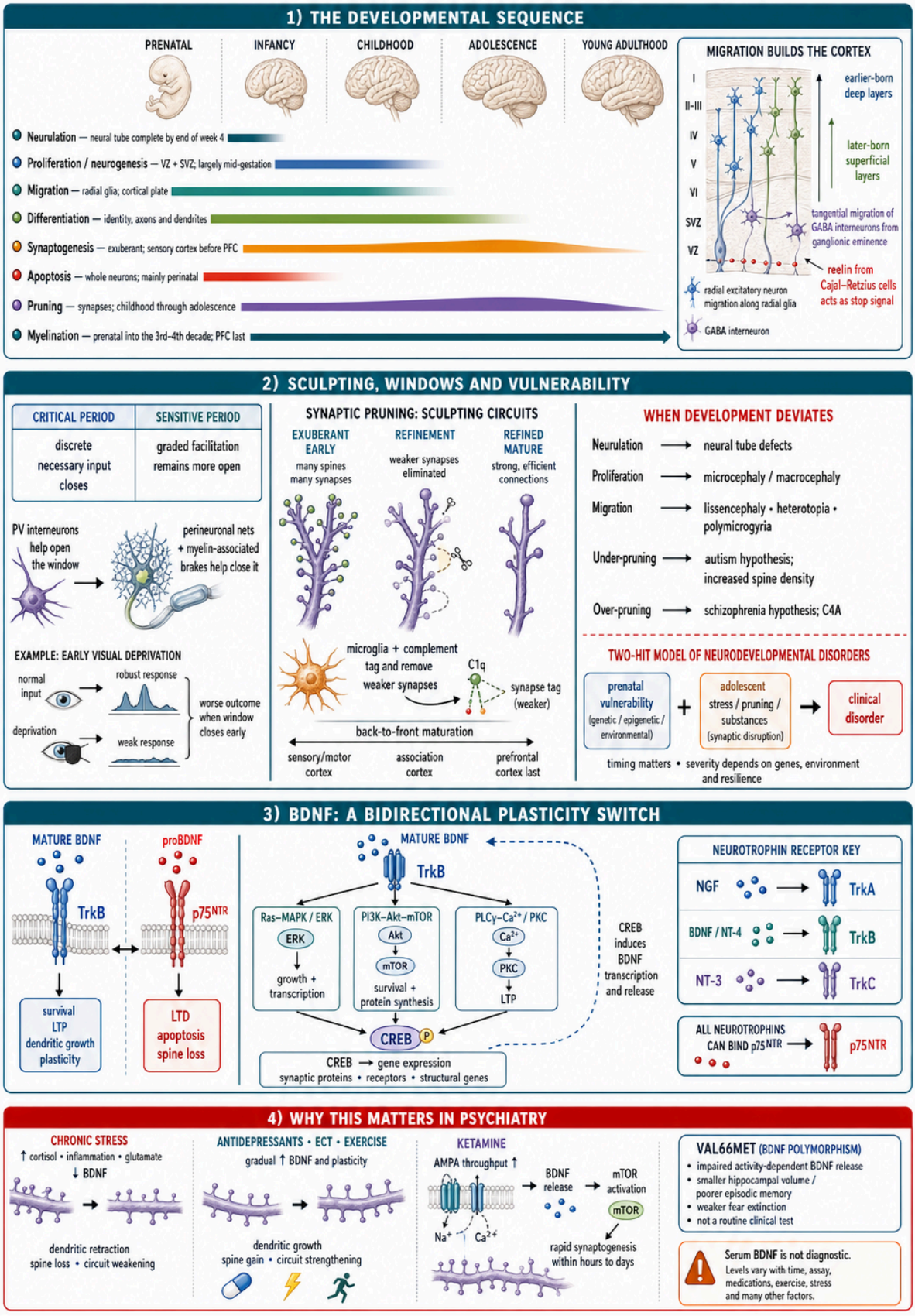


Fig 2.8 Neurodevelopment and BDNF: build, sculpt, rebuild.

Hold three organising ideas before the detail. First, development is *overproduce then eliminate*: the brain makes a surplus of neurons, then of synapses, and sculpts the adult circuit by killing back

the excess (apoptosis for cells, pruning for synapses). Second, the sculpting is **experience-dependent** and time-locked, so there are critical periods when input is not merely helpful but required. Third, the same molecule that guides construction (reelin) or performs the sculpting (complement, microglia) is where the pathology sits, which is why one topic connects fetal neuroanatomy to a 2016 genetics landmark (Sekar 2016).

11.1 The seven stages in order: the examinable sequence

Learn the sequence as an ordered list before anything else; the paper asks it as a bare recall item. Neurodevelopment proceeds through overlapping but ordered stages: **neurulation** (the neural plate folds into the neural tube by the end of the fourth gestational week, the source of the entire CNS); **proliferation / neurogenesis** (mitosis of neural progenitors in the periventricular **ventricular and subventricular zones**, generating the roughly twenty billion neurons of the cortex, largely by mid-gestation); **migration** (young neurons travel from the germinal zones to their final positions, chiefly along radial glial guides); **differentiation** (the settled neuron acquires its transmitter identity, dendritic tree and axon); **synaptogenesis** (formation of synaptic contacts, exuberant and continuing after birth); **apoptosis** (programmed death of the surplus, roughly half of the neurons generated); and **myelination** (oligodendrocyte ensheathing of axons, beginning prenatally in sensorimotor tracts and continuing into the third and fourth decades in prefrontal cortex). Most neurogenesis, selection and migration are complete before birth; differentiation, synaptogenesis and myelination continue for years to decades (Stahl 2021).

MNEMONIC

"Nervous Programmers Make Dozens, Synapse Away, Myelinate" (N-P-M-D-S-A-M)

Neurulation, **P**roliferation, **M**igration, **D**ifferentiation, **S**ynaptogenesis, **A**poptosis, **M**yelination. The order is the answer to most single-line questions, and each transition is a candidate lesion: neural tube defects at N, microcephaly at P, heterotopias at M, schizophrenia-type pruning at the S/A boundary in adolescence.

11.2 Neurulation and proliferation: the neural tube and the germinal zones

Neurulation. The neural plate, an ectodermal thickening, invaginates and fuses dorsally to form the **neural tube**, which closes between roughly the ADHD & specific learning/communication disorders notes and the Perinatal/women's mental health & emergency psychiatry notes of gestation. The rostral tube swells into the three primary vesicles (prosencephalon, mesencephalon, rhombencephalon) that become forebrain, midbrain and hindbrain. Failure of anterior closure yields anencephaly; failure of posterior closure yields spina bifida, the disorders that folate supplementation and periconceptional folic acid target. The lumen of the tube persists as the ventricular system.

Proliferation. Neurons are not born where they live. Progenitors divide in the **ventricular zone (VZ)** lining the tube and the overlying **subventricular zone (SVZ)**; in the primate and human neocortex an additional **outer subventricular zone** populated by *outer radial glia* is the substrate

of the expanded human cortex, a point the current literature stresses because human-evolved regulatory elements are enriched in these cells (Kaplan & Sadock 2024). Peak human cortical neurogenesis is largely a first-and-second-trimester event; a failure of proliferation gives microcephaly, an excess or failure to stop gives megalencephaly.

11.3 Migration: radial glia, the inside-out cortex, and tangential interneurons

Radial migration and the inside-out rule. Most excitatory (glutamatergic pyramidal) neurons migrate *radially* from the VZ to the cortical plate, climbing the fibre scaffold of **radial glial cells** that span from ventricle to pia. The cortex is laid down **inside-out**: the deepest layers (VI and V) are generated and settle first, and each later-born wave migrates *past* the existing neurons to occupy a progressively more superficial layer (IV, then III and II). This counter-intuitive ordering is examinable and is the reason a defined stop signal is needed at the top of the stack, which is reelin (11.10) (New Oxford Textbook 2020).

Tangential migration of interneurons. The cortex has two cellular sources. The glutamatergic pyramidal cells arise from the dorsal VZ/SVZ and migrate radially; the inhibitory **GABAergic interneurons** (parvalbumin, somatostatin and calretinin classes) arise separately in the **ganglionic eminences** (medial, lateral and caudal) of the ventral forebrain and migrate *tangentially* across the cortex before turning into it. The medial ganglionic eminence supplies the parvalbumin basket and chandelier cells and the somatostatin Martinotti cells; the caudal eminence supplies calretinin and reelin-expressing types (New Oxford Textbook 2020). The interneuron origin matters because parvalbumin interneuron dysfunction is a leading account of the cortical circuit abnormality in schizophrenia and of the machinery that opens and closes critical periods (11.8).

> **CLINICAL ANCHOR**
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> **Neuronal migration disorders** are the clinical face of this stage. Complete failure gives *lissencephaly* (smooth, agyric cortex, classically the LIS1 and doublecortin/DCX genes); arrest of a subset of neurons short of the cortex gives *subcortical band heterotopia* ("double cortex") or *periventricular nodular heterotopia*; over-migration and disorganisation gives *polymicrogyria*. These present with epilepsy and intellectual disability and are the concrete answer to "name a consequence of disordered neuronal migration." The same genes (LIS1, DCX, reelin/RELN) recur, tying the syndrome to the molecular stop-signal biology.

11.4 Differentiation and synaptogenesis: overproduction of connections

Differentiation. Once settled, the neuron elaborates its dendritic tree, extends an axon toward its target (guided by chemotropic cues such as netrins, semaphorins and ephrins), and adopts a neurotransmitter phenotype. This is where transmitter-identity genes and the growth-factor environment (BDNF, NT-3, NGF) act, and it continues throughout life at a reduced rate.

Synaptogenesis is deliberately excessive. The developing brain forms a large *surplus* of synapses. Synaptic density in the human cortex rises steeply after birth, overshoots the adult value by a wide margin, and peaks in early childhood (classic primate data from Bourgeois and Rakic in the visual cortex, and Huttenlocher's human counts, show a peak well above adult

density before net decline). The developmental strategy is to build more connections than are needed and then let experience decide which survive, which sets up the pruning phase (11.5). Synaptogenesis is not uniform across the cortex: sensory areas peak and stabilise early, whereas **prefrontal cortex** peaks later and prunes latest, protracting its refinement into the third decade (Kaplan & Sadock 2024).

11.5 Apoptosis and synaptic pruning: two different sculpting knives

The exam repeatedly tests the distinction between killing cells and cutting connections; they are separate processes at separate scales. Apoptosis (programmed cell death) removes whole neurons, chiefly those that fail to secure enough target-derived trophic support (the neurotrophic hypothesis: neurons compete for a limited supply of factors such as NGF, and the losers die). On the order of half of the neurons generated are eliminated this way, mostly perinatally. It is an active, gene-directed process (the caspase cascade, Bcl-2 family regulation), distinct from passive necrosis. **Synaptic pruning** removes connections, not cells: weakly active or redundant synapses are selectively eliminated while active ones are retained and strengthened, the structural correlate of "cells that fire together wire together." Pruning is *activity-dependent* and executed largely by **microglia** and the complement system (11.6), and it is the process that continues, region by region, from early childhood through adolescence (Faust 2021).

Apoptosis

Programmed death of a whole neuron via an intrinsic gene-directed cascade (caspases, Bcl-2/Bax balance), driven by loss of the competition for target-derived neurotrophic factor. Scale: the cell. Timing: predominantly prenatal and early postnatal.

Synaptic pruning

Selective activity-dependent elimination of individual synapses, sparing whole neurons, executed by microglial engulfment of complement-tagged synapses. Scale: the connection. Timing: childhood through adolescence, region-specific.

11.6 The mechanism of pruning: microglia, complement, and the "eat-me" tag

The immune system builds the brain. The molecular executioners of developmental pruning are borrowed from innate immunity. Astrocyte-derived and neuronal signals induce the classical complement proteins **C1q and C3** to be deposited on weak or supernumerary synapses; the C3 breakdown product iC3b acts as an "eat-me" opsonin recognised by **complement receptor 3 (CR3/CD11b)** on **microglia**, which then engulf and digest the tagged synapse (Stevens 2007; Schafer 2012). Complement is not the only route: the microglial fractalkine receptor CX3CR1, TREM2, class-I MHC and pentraxins also drive pruning, and complement-independent pruning occurs in some regions, so the exam-safe statement is that complement-microglial signalling is the *best-characterised* mechanism rather than the sole one (Faust 2021).

PEARL

This mechanism is why neuroinflammation and neurodevelopment are the same topic seen twice. The complement cascade that lyses bacteria in the periphery is repurposed in the CNS to tag synapses for microglial removal. It explains why maternal infection (11.13), which activates this system, is a neurodevelopmental risk factor, and why *C4*, a complement gene, is the strongest common-variant risk locus for schizophrenia (11.11).

11.7 The adolescent pruning peak and the maturational gradient

Adolescence is a second construction window, and its signature is net synaptic loss in the last cortex to mature. After the childhood synaptic peak, the cortex undergoes protracted net elimination that proceeds in a **back-to-front (posterior-to-anterior)** gradient: primary sensory and motor cortex prunes and stabilises first, association cortex later, and the **dorsolateral prefrontal cortex last**, with active synaptic reorganisation continuing well into the twenties (Petanjek's human counts; Gogtay's longitudinal grey-matter mapping). On MRI this reads as a rise in cortical grey-matter volume in late childhood followed by a decline through puberty, mirrored by rising white-matter volume from ongoing myelination. The behavioural correlate is the maturational mismatch of adolescence: a limbic/reward system that matures early against a prefrontal control system that matures late, the standard account of adolescent risk-taking and of the window in which drugs of abuse and social stress bite hardest (Kaplan & Sadock 2024).

COMMON TRAP

Do not equate "adolescent grey-matter loss on MRI" with atrophy or degeneration. It is normal, programmed synaptic pruning and continued myelination (which shifts tissue from the grey to the white compartment), a maturational *gain* in efficiency, not a loss of function. The disease models (schizophrenia) invoke *excessive* or mistimed pruning against this normal backdrop, not pruning per se.

11.8 Critical versus sensitive periods: definitions and the machinery of closure

This distinction is a favourite discriminator. A **critical period** is a discrete, time-limited window during which specific experience is *necessary* to instigate a fundamental and largely irreversible change in a neural circuit; miss the window and the capacity is lost or permanently degraded. A **sensitive period** is a broader, softer window of heightened but not all-or-none plasticity, during which circuits are more malleable by experience but change remains possible outside it (Rice and Barone 2000; Knudsen 2004). The two are a spectrum rather than a dichotomy, but the exam wants the contrast: critical = discrete and necessary and closing; sensitive = graded and facilitatory.

RULE **Critical period = discrete, necessary, closing; sensitive period = graded, facilitatory, stays open.** Interneurons open the window and perineuronal nets shut it.

What opens and closes the window. The maturation of **parvalbumin-positive GABAergic interneurons** and the resulting inhibitory (GABA) tone triggers the *opening* of the visual critical

period; the window is *closed* by structural brakes, chiefly the deposition of **perineuronal nets** (condensed chondroitin-sulphate extracellular matrix that encases parvalbumin cells) and myelin-associated inhibitors (Hensch 2005). Perineuronal net maturation temporally parallels the end of the critical period, degrading them (for example with chondroitinase) reopens plasticity, and their density is reduced in schizophrenia prefrontal cortex. This gives a clean molecular story: interneurons open the window, matrix nets shut it.

11.9 Critical periods in practice: the visual paradigm and its clinical parallels

The Hubel and Wiesel paradigm. The archetypal critical period is **ocular dominance** in visual cortex. Monocular deprivation in a kitten or monkey during the postnatal critical window causes the deprived eye to lose its cortical territory permanently; the identical deprivation in an adult does not (Wiesel and Hubel 1963; Hensch 2005). This is the physiological basis of the clinical parallels: **amblyopia** ("lazy eye") from childhood strabismus or unequal refraction must be treated within the visual critical period, and congenital cataract must be removed early or vision is permanently impaired. Other modalities have their own windows: first-language phonology and the perceptual narrowing of infancy (Maurer and Werker), and the language-acquisition sensitivity that closes around puberty.

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> The critical-period concept is the rationale for early intervention across child psychiatry: early cochlear implantation for congenital deafness, early enriched care for institutionally deprived children (the Romanian orphan / Bucharest Early Intervention findings, where duration of deprivation before foster placement predicted outcome), and early behavioural intervention in autism. The clinical maxim, treat the sensory or social deprivation before the window closes, is a direct application of this biology.

11.10 Reelin: the stop-signal glycoprotein and its psychiatric footprint

What reelin does. **Reelin (RELN)** is a large secreted extracellular-matrix glycoprotein, expressed during development by the **Cajal-Retzius cells** of the cortical marginal zone (the most superficial layer). It is the *stop signal* for radial migration: as each wave of migrating neurons approaches the top of the cortical plate, reelin halts it at the correct position, allowing the next wave to pass beneath and layer above the previous one, which is the mechanism of the inside-out cortex (11.3). Reelin signals through the ApoE receptor family (VLDLR and ApoER2) and the adaptor Dab1 (New Oxford Textbook 2020).

Why psychiatry cares. The *reeler* mouse (reelin-deficient) has an *inverted*, disorganised cortex, the direct demonstration that reelin controls lamination; homozygous human RELN mutation causes lissencephaly with cerebellar hypoplasia. Beyond the frank malformation, **reduced reelin expression** (with reduced GAD67, the GABA-synthesising enzyme) is one of the more replicated post-mortem molecular findings in *schizophrenia and bipolar disorder*, attributed partly to hypermethylation of the RELN promoter, an epigenetic link that connects a fetal patterning molecule to adult psychosis (Kaplan & Sadock 2024).

COMMON TRAP

Reelin is a migration stop signal made by Cajal-Retzius cells in the marginal zone, not a migration motor and not made by the migrating neuron itself. Contrast it with LIS1 and doublecortin (DCX), which are intrinsic to the migrating neuron's cytoskeletal machinery; loss of those *arrests* migration (lissencephaly, heterotopia), whereas loss of reelin *disorganises the layering* because the stop signal is gone.

11.11 The neurodevelopmental hypothesis of schizophrenia and the two-hit model

The core hypothesis. The neurodevelopmental model (Weinberger, Murray and Lewis) holds that schizophrenia originates in abnormal brain development beginning *in utero*, long before the illness declares itself, with the fixed lesion lying dormant until later maturational events unmask it. The classical evidence: an excess of obstetric complications and prenatal insults (famine, maternal influenza) in those who later develop schizophrenia; minor physical anomalies and premorbid neuromotor, cognitive and social deviations in childhood; and post-mortem findings of disturbed cortical cytoarchitecture and neuronal disarray without gliosis, implying a developmental rather than degenerative origin (Tasman 2024). The absence of gliosis is the classic examinable point, it argues the lesion is fetal, not a later scarring injury.

Feinberg's pruning hypothesis and the adolescent second epoch. Feinberg (1982) proposed that schizophrenia reflects a *fault in programmed synaptic elimination during adolescence*, either too much pruning or pruning of the wrong synapses, explaining why an early lesion produces symptoms only at the adolescent pruning peak. This dovetails with the modern genetics: the **C4 (C4A) complement locus**, mapped by Sekar and colleagues (2016) from the MHC schizophrenia signal, is the strongest common-variant risk locus, higher C4A copy number predicts higher C4 expression, and C4 drives complement-mediated synaptic pruning, so the risk allele plausibly causes *excess* pruning during adolescence. Grey-matter loss, reduced dendritic spine density and perineuronal-net reduction in schizophrenia prefrontal cortex all fit an over-pruning account (Sekar 2016; Feinberg 1982).

MNEMONIC

"Two hits: the seed (in utero) and the trigger (adolescence)"

The **two-hit model** formalises the two epochs. **Hit one** is an early (genetic or prenatal) event that creates a latent vulnerability, a mis-wired circuit that is clinically silent. **Hit two** is a later stressor (adolescent synaptic pruning, cannabis, psychosocial stress, HPA-axis activation) acting on the primed substrate to precipitate psychosis. Neither hit alone suffices; the model explains both the fetal origin and the late-adolescent/early-adult onset in one frame.

11.12 Autism as a neurodevelopmental disorder: the opposite pruning imbalance

The mirror-image framing. Autism spectrum disorder (ICD-11 6A02; DSM-5-TR autism spectrum disorder) is neurodevelopmental with earlier onset and a partly opposite structural signature to schizophrenia. Whereas schizophrenia is associated with reduced spine density and grey-matter loss (over-pruning), autism is associated with *increased* dendritic spine density and

early brain **overgrowth** (larger early brain volume, macrocephaly in a subset), consistent with *under-pruning* or deficient early synapse elimination (Kaplan & Sadock 2024). Post-mortem and imaging work reports defects of neurogenesis and neuronal migration, patchy cortical disorganisation, and altered developmental trajectories of the amygdala, hippocampus and cortex. Mechanistically, autism-associated genes converge on *synaptic* function and the excitatory-inhibitory balance (neurexins, neuroligins, SHANK, mTOR-pathway genes as in tuberous sclerosis and fragile X), reframing it as a "synaptopathy" of connectivity.

COMMON TRAP

The clean "schizophrenia = over-pruning, autism = under-pruning" contrast is a useful exam scaffold but a simplification: both are polygenic and heterogeneous, the complement/C4 story is present in only a subset of schizophrenia, and no complement locus reaches genome-wide significance in autism. State the contrast as a *heuristic about the direction of synaptic imbalance*, not as an established single mechanism for either disorder.

11.13 Maternal immune activation: the prenatal environmental hit

The epidemiology and the mechanism. **Maternal immune activation (MIA)** is the leading environmental limb of the neurodevelopmental hypothesis. Epidemiologically, maternal infection during pregnancy (influenza, and prenatal exposures indexed by the 1957 influenza pandemic and famine cohorts) and raised maternal inflammatory markers are associated with increased offspring risk of schizophrenia and autism. The mechanism, worked out in animal models, is that it is the *maternal inflammatory response*, not the pathogen itself, that harms the fetal brain: injecting the viral mimic **poly(I:C)** or the bacterial mimic LPS into pregnant rodents, in the absence of any live infection, produces offspring with behavioural and neuropathological abnormalities. The key mediator is the cytokine **interleukin-6 (IL-6)**: blocking maternal IL-6 prevents the offspring phenotype, and injecting IL-6 alone reproduces it (Kaplan & Sadock 2024).

Why it belongs here. MIA converges on the very machinery of 11.6. Maternal cytokines cross to the fetal compartment, activate fetal microglia and complement, and perturb neurogenesis, migration, interneuron development and synaptic patterning, providing a biologically continuous route from a first-trimester infection to an adult psychiatric phenotype and a mechanistic candidate for "hit one" of the two-hit model.

INDIA

The MIA and prenatal-insult data give a public-health frame that matters in the Indian setting: antenatal care, maternal nutrition (the famine-cohort and folate data), infection control and immunisation in pregnancy, and reduction of obstetric complications are primary-prevention levers for neurodevelopmental risk at the population level, upstream of any psychiatric treatment. The mechanism is a maternal-and-child-health argument, not only a neuroscience one.

11.14 Myelination: the last and longest process

Myelination outlasts every other stage and is the structural engine of protracted cognitive maturation. Oligodendrocytes wrap axons in myelin, raising conduction velocity and enabling fast, synchronised long-range communication. Myelination follows a strict caudal-to-rostral, posterior-to-anterior order: brainstem and sensorimotor tracts myelinate first (prenatally and in infancy), and **association and prefrontal white matter** last, continuing into the third and fourth decades. This is the white-matter counterpart of the back-to-front pruning gradient (11.7): the prefrontal cortex is the last to prune its grey matter and the last to myelinate its connections, which is the neural substrate usually invoked for the late maturation of executive control, judgement and impulse regulation. Diffusion-tensor imaging tracks this maturation as rising fractional anisotropy through adolescence, and disordered white-matter development is a candidate lesion in schizophrenia and in the demyelinating contribution to some neuropsychiatric presentations (Stahl 2021).

11.15 The consolidating table: stage, timing, mechanism, and the disorder of failure

The summary map. Read the timing column first: it predicts *which* disorder a hit at that stage produces, and the last column is the examinable clinical pairing.

STAGE	PEAK TIMING	KEY MECHANISM / MOLECULE	DISORDER OF FAILURE (DISCRIMINATOR)
Neurulation	Week 3 to 4	Neural tube closure; folate	**Anencephaly, spina bifida (neural tube defects)**
Proliferation	1st to 2nd trimester	VZ/SVZ mitosis; outer radial glia	**Microcephaly (too few) / megalencephaly (too many)**
Migration	2nd trimester	Radial glia; reelin stop signal; LIS1, DCX	**Lissencephaly, heterotopia, polymicrogyria**
Differentiation	Prenatal onward	Axon guidance (netrin, ephrin); BDNF	**Connectivity / dendritic anomalies**
Synaptogenesis	Birth to early childhood (overshoot)	Excess synapse formation; neurexin/neuroligin	**Autism: increased spine density (under-pruning)**
Apoptosis	Perinatal	Caspases; neurotrophic competition (NGF)	**Failure gives dysregulated cell number**
Pruning	Childhood to adolescence (back-to-front)	Microglia, complement C1q/C3/C4, CR3	**Schizophrenia: over-pruning (Feinberg; C4A)**
Myelination	Infancy to 3rd to 4th decade	Oligodendrocytes; posterior-to-anterior	**Late prefrontal maturation; white-matter disorders**

The neurodevelopmental timeline as a lesion map: the timing of an insult predicts its phenotype, from first-trimester migration disorders through the adolescent pruning peak that unmasks schizophrenia to the decades-long myelination that paces prefrontal maturation.

HOLD THIS

The timing of the insult predicts the phenotype. A migration failure (first trimester) gives heterotopia; an adolescent pruning failure gives schizophrenia. The two-hit model is just the statement that both windows matter: an in-utero seed and an adolescent trigger.

12 · Neurotrophins and BDNF

The neurotrophins are the growth-factor arm of neurochemistry, and they are the molecular hinge on which the modern **neurotrophic (neuroplasticity) hypothesis of depression** turns. Where the monoamine hypothesis explained why antidepressants raise synaptic serotonin in minutes, it could never explain why the clinical benefit takes weeks; the neurotrophic account fills exactly that gap, proposing that mood disorder is a disorder of stress-driven synaptic loss, and that antidepressants work slowly because they act by rebuilding synapses through **BDNF** rather than by flooding the cleft (Stahl 2021; Kaplan & Sadock 2024). This is why neurotrophins now appear in the same breath as glutamate, ketamine and mTOR.

Examiners return to this topic because it stitches together basic cell biology (a family of secreted growth factors and their two receptor systems), a disease model (stress lowers BDNF, treatments raise it), a pharmacogenetic vignette (the Val66Met polymorphism) and the mechanism of the newest antidepressants (ketamine to AMPA to BDNF to mTOR). **Learn it as one causal chain, not a bag of facts.** Everything below is either an input to BDNF, a receptor for it, or a consequence of having too little of it.

12.1 The neurotrophin family: NGF, BDNF, NT-3 and NT-4/5

Four classic members, one shared logic. The neurotrophins are a family of small secreted polypeptide growth factors comprising **nerve growth factor (NGF)**, **brain-derived neurotrophic factor (BDNF)**, **neurotrophin-3 (NT-3)** and **neurotrophin-4/5 (NT-4)** (Kaplan & Sadock 2024). NGF was the first neurotrophic factor discovered, in the 1950s (Cohen, Levi-Montalcini); BDNF was isolated in the 1980s (Barde 1982), and NT-3 and NT-4 followed. They govern neuronal proliferation, differentiation, survival and, in the adult brain, synaptic plasticity.

Distribution matters clinically. NGF has a restricted distribution: in the periphery it supports sympathetic and nociceptive sensory neurons, and in the CNS it maintains the *basal forebrain cholinergic neurons* that project to the hippocampus and degenerate in Alzheimer disease. BDNF and NT-3 by contrast are the dominant CNS neurotrophins, highly expressed in cortex and hippocampus (Kaplan & Sadock 2024). BDNF specifically rises after stress, injury, neural stimulation and exercise, which is the fact that makes it the mood-relevant member of the family.

12.2 Synthesis, cleavage and the proBDNF story

All neurotrophins begin as precursors. Each is first made as a larger **proneurotrophin** that is then cleaved to release the mature, active protein (a stable non-covalent dimer of roughly 12 to 14 kDa). Cleavage of proBDNF can happen intracellularly (in the Golgi by *furin*, or in dense-core vesicles by proconvertases) or extracellularly (by *plasmin* or matrix metalloproteinases) (Kaplan & Sadock 2024).

The precursor is not inert: it is the biological opposite of mature BDNF. This is the high-yield twist. Mature BDNF signals survival and potentiation through TrkB; **proBDNF** preferentially binds the p75 receptor and drives the opposite program, facilitating *long-term depression (LTD)* and apoptosis (Kaplan & Sadock 2024). At the developing neuromuscular synapse the two act as a "reward" and "punishment" pair: activity-dependent proteases convert proBDNF to mature BDNF at *active* terminals (which are stabilised), while p75-expressing *inactive* terminals bind proBDNF and receive the retraction signal. Chronic stress raises hippocampal proBDNF in rodents, and this normalises with fluoxetine. Human peripheral proBDNF-to-BDNF studies are, however, mixed and do not yet serve as a reliable clinical biomarker.

PEARL

Think of the BDNF gene as producing a Jekyll-and-Hyde protein. The *mature* ligand acting through TrkB means survival, LTP and synapse-building. The uncleaved *proBDNF* acting through p75 means LTD, spine loss and pruning. Whether the balance tips toward growth or retraction is set by proteolytic cleavage and by which receptor is engaged, not merely by how much BDNF is present.

12.3 The two receptor systems: Trk tyrosine kinases and p75

Neurotrophins are unusual in signalling through two structurally unrelated receptors at once (Kaplan & Sadock 2024). The **Trk (tropomyosin-related kinase)** receptors are receptor tyrosine kinases mediating the trophic, pro-survival, pro-plasticity effects. The **p75 neurotrophin receptor (p75NTR)** is a member of the tumour-necrosis-factor receptor superfamily, carrying an intracellular *death domain*, and it can drive apoptosis.

Ligand-receptor specificity is a guaranteed exam item. Each mature neurotrophin has its own preferred Trk, while *all* neurotrophins can bind p75.

RECEPTOR	TYPE	PREFERRED LIGAND(S)	PRINCIPAL EFFECT
TrkA	Receptor tyrosine kinase	**NGF**	Survival of cholinergic and sympathetic/sensory neurons
TrkB	Receptor tyrosine kinase	**BDNF and NT-4**	Synaptic plasticity, LTP, the mood-relevant receptor
TrkC	Receptor tyrosine kinase	**NT-3**	Neuronal differentiation and survival
p75NTR	TNF-receptor superfamily (death domain)	All neurotrophins; proneurotrophins with high affinity	**Apoptosis, LTD; tunes Trk ligand selectivity**

Neurotrophin-receptor pairing. The discriminator to memorise: NGF to TrkA, BDNF (and NT-4) to TrkB, NT-3 to TrkC, and every neurotrophin to p75. Mature ligand plus Trk means survival; proneurotrophin plus p75 means death.

RULE **NGF-TrkA, BDNF-TrkB, NT-3-TrkC; every neurotrophin binds p75.** Mature ligand at Trk means survival, proneurotrophin at p75 means death.

Two refinements worth knowing. First, p75 sharpens specificity: NT-3 can weakly bind TrkA and TrkB, but co-expressed p75 restricts each Trk to its cognate ligand, so with p75 present only BDNF gives a functional TrkB response. Second, the "high vs low affinity" shorthand is technically loose, because proNGF actually binds p75 with high affinity; what really determines the cellular outcome is the ratio of Trk to p75 and whether the ligand is the mature or the pro form (Kaplan & Sadock 2024).

12.4 BDNF to TrkB signalling: three downstream cascades

When BDNF dimers bind TrkB, the receptor dimerises and *autophosphorylates* intracellular tyrosine residues, which become docking sites for adaptor proteins (notably Shc and PLC-gamma). Three signalling arms then diverge (Kaplan & Sadock 2024; Yang et al. 2020):

Ras to MAPK/ERK

Via Shc. The extracellular-signal-regulated kinase pathway drives neurite outgrowth, differentiation and the transcriptional changes of long-lasting plasticity.

PI3K to Akt

Via Shc. The principal *survival* pathway; Akt (protein kinase B) suppresses apoptotic programs and, importantly, feeds into **mTORC1**, the node that couples BDNF signalling to activity-dependent local protein synthesis and spine remodelling.

PLC-gamma to Ca2+/PKC

Generates inositol phosphates and diacylglycerol, raising intracellular calcium and activating protein kinase C; central to TrkB-mediated hippocampal LTP.

The convergence point is transcription. All three arms converge on the transcription factor **CREB** (cyclic-AMP response element-binding protein), and CREB in turn induces the *BDNF gene itself* (Kaplan & Sadock 2024). This creates a self-amplifying loop and is precisely where the monoamine and neurotrophic hypotheses join hands: serotonin and noradrenaline reuptake inhibitors act through G-protein-coupled receptors and cyclic AMP to raise CREB, which raises BDNF, on a 10-to-20-day time course that matches the clinical latency of antidepressant response.

12.5 Activity-dependent plasticity: BDNF and LTP

BDNF is the archetypal **activity-dependent** neurotrophin: its transcription, dendritic transport, secretion and cleavage are all gated by neuronal activity, which is what lets it translate experience into lasting synaptic change (cross-reference the the Functional Neuroanatomy & Neurophysiology notes LTP topic for the induction machinery). BDNF messenger RNA is upregulated by the very high-frequency stimulation that induces LTP in the hippocampus (Yang et al. 2020).

The nuance is "promotes but is not strictly required". BDNF-TrkB signalling *facilitates* hippocampal LTP and is needed for its late, protein-synthesis-dependent phase, yet high-frequency-induced LTP can still occur without it in some paradigms (Kaplan & Sadock 2024). Mechanistically, BDNF acts both presynaptically (enhancing glutamate release) and postsynaptically (increasing synaptic trafficking and insertion of *AMPA receptors*, and driving

actin-dependent dendritic-spine enlargement via ERK and Rho-GTPase pathways). Brief application of exogenous BDNF can itself produce lasting synaptic potentiation, a phenomenon termed "BDNF-LTP". BDNF also stimulates adult hippocampal neurogenesis in the dentate gyrus, tying the growth factor to the structural-plasticity face of depression.

12.6 The neurotrophic hypothesis of depression

The core claim. Stress lowers BDNF and antidepressant treatments raise it, and this bidirectional movement, rather than monoamine level per se, tracks the illness and its treatment (Duman et al. 1997; Kaplan & Sadock 2024; Stahl 2021). Several convergent lines support it:

1. Stress lowers BDNF and damages the hippocampus. In animal models, restraint and chronic stress reduce hippocampal BDNF expression and cause atrophy and death of hippocampal neurons, most markedly in the *CA3* region. Concordantly, MRI shows a small but reproducible reduction in **hippocampal volume** in depression and PTSD (Kaplan & Sadock 2024).

2. BDNF itself is antidepressant. Infusing BDNF into the rodent hippocampus produces antidepressant-like effects in the forced-swim and learned-helplessness paradigms comparable to chronic drug treatment (Shirayama et al. 2002).

3. Antidepressants, ECT and exercise all raise BDNF. Monoamine antidepressants upregulate BDNF, CREB and TrkB in the hippocampus over a time course matching clinical response. **Electroconvulsive therapy** is among the most potent inducers of BDNF transcription and hippocampal sprouting in rodents (though human serum data are mixed and BDNF is a poor predictor of ECT outcome). Physical *exercise* robustly elevates BDNF, the molecular substrate for its antidepressant and pro-cognitive effects (Kaplan & Sadock 2024; Phillips 2017).

Stahl frames the same idea as *neuroprogression*: stress, inflammation, early-life adversity, altered microbiome and disrupted sleep produce epigenetic silencing of the BDNF gene, and the resulting loss of growth factor leads first to failure of synaptic maintenance and then to frank synapse and neuron loss (Stahl 2021). In ICD-11 the relevant disorder is a depressive episode (single episode depressive disorder or recurrent depressive disorder), cross-mapped to DSM-5-TR major depressive disorder; the neurotrophic account is a mechanistic model, not a diagnostic category.

> **COMMON TRAP**
>
> Do not overstate serum BDNF as a diagnostic test. Peripheral (serum or plasma) BDNF tends to be lower in unmedicated depression and rises with treatment at a group level, but it is confounded by platelets, exercise, diet, smoking, storage and diurnal variation, and it does not reliably diagnose an individual or predict response (Kaplan & Sadock 2024). State it as a group-level correlate and candidate biomarker, never as a bedside test. Equally, do not claim the neurotrophic hypothesis has replaced the monoamine hypothesis: it sits downstream of it and explains the therapeutic delay.

12.7 The BDNF Val66Met polymorphism

What it is. **Val66Met** (rs6265) is a common single-nucleotide polymorphism in the *prodomain* of the human BDNF gene, substituting methionine for valine at codon 66. Because it sits in the

pro-region, it does not change the mature protein's sequence; instead it impairs the *intracellular trafficking and activity-dependent secretion* of BDNF, so Met-allele carriers release less BDNF in response to neuronal activity, particularly at dendrites (Kaplan & Sadock 2024).

The phenotype. Met carriers show, on functional imaging, smaller hippocampal volumes and poorer episodic memory, and behaviourally they exhibit *less efficient fear extinction* and heightened anxiety under stress; parallel findings hold in a knock-in mouse carrying the human Met allele (Chen et al. 2006; Kaplan & Sadock 2024). A meta-analysis of gene-by-environment studies found the Met allele significantly moderates the relationship between stressful life events or childhood adversity and depression (Zhao et al. 2018).

Why it matters clinically. The impaired-extinction phenotype has a direct therapeutic implication: Met carriers may need a longer or more intensive course of *exposure therapy* to extinguish conditioned aversive cues, and the polymorphism has been reported to predict exposure-therapy response in PTSD (Felmingham et al. 2013; Kaplan & Sadock 2024). The same allele is also a genome-wide-significant signal for obesity and a risk factor for antipsychotic-associated weight gain and insulin resistance, reflecting BDNF-TrkB's role in hypothalamic (paraventricular) control of satiety and energy balance.

CLINICAL ANCHOR

Val66Met is the cleanest single example of pharmacogenomics touching psychotherapy rather than pharmacotherapy: a growth-factor variant that predicts how a patient will learn to un-fear a stimulus, and therefore how a course of exposure-based CBT should be dosed. It is not yet a routine clinical test, but it is the paradigm case examiners use to show that "biological" and "psychological" treatments share a final common substrate in activity-dependent BDNF release.

12.8 Ketamine to BDNF to mTOR: the rapid-acting pathway

The neurotrophic hypothesis found its sharpest confirmation in the mechanism of **ketamine**, whose antidepressant effect appears within hours and is, at its core, a BDNF phenomenon (cross-reference the glutamate topic for the receptor pharmacology). Two complementary accounts operate (Kaplan & Sadock 2024):

Route one, de-repressing BDNF translation. Blocking NMDA receptors deactivates *eEF2 kinase* (eukaryotic elongation factor-2 kinase); this lifts the brake on BDNF translation, producing a rapid rise in BDNF protein within about 30 minutes that drives spine remodelling and synaptogenesis.

Route two, the AMPA-to-mTOR surge. Transient NMDA blockade on GABAergic interneurons disinhibits cortical glutamate neurons, producing a brief glutamate burst that stimulates **AMPA receptors**. AMPA activation triggers local release of BDNF (and VEGF), which engage TrkB (and Flk-1) to activate *Akt and mTORC1*, driving translation of synaptic proteins and a rapid burst of synaptogenesis in the prefrontal cortex (Kaplan & Sadock 2024). Either way the antidepressant effect is not the NMDA block itself but the downstream **BDNF-mTOR synaptic rebuild** it unleashes.

This mechanism underwrites the newest therapeutics: intranasal **esketamine** (the S-enantiomer, approved 2019 for treatment-resistant depression and later for major depressive disorder with acute suicidality, given under supervision with an oral antidepressant), racemic IV ketamine off-label, and the investigational rapid agents that target the same pathway. It also explains why a TrkB-signalling requirement has been proposed as the common denominator of both slow (SSRI) and fast (ketamine) antidepressants, with the antidepressant binding site now mapped onto TrkB itself in recent work (Kaplan & Sadock 2024).

MNEMONIC

"Stress Bends, Treatment Mends: BDNF"

Stress Bends the synapse down (low BDNF, hippocampal atrophy, smaller volume). **Treatment Mends** it back up (SSRIs, ECT and exercise raise BDNF slowly via CREB; ketamine raises it fast via AMPA to mTOR). The molecule in the middle of both arrows is always BDNF, acting through TrkB.

HOLD THIS

Stress lowers BDNF and treatments raise it, and that movement (not the monoamine level) tracks the illness. Mature BDNF at TrkB builds synapses; uncleaved proBDNF at p75 does the opposite.

12.9 Neurotrophins beyond depression: development, neurodegeneration and pain

Development and critical periods. In the CNS, BDNF governs the maturation of inhibitory parvalbumin GABA interneurons and thereby the timing of experience-dependent *critical periods*, the classic example being ocular-dominance-column formation in visual cortex; BDNF overexpression accelerates visual-acuity development and closes the critical period early (Kaplan & Sadock 2024).

Neurodegeneration. The neurotrophic-deficit logic extends beyond mood. In **Huntington disease**, mutant huntingtin reduces cortico-striatal *anterograde transport of BDNF*, starving the striatal medium spiny neurons that degenerate. In **Alzheimer disease**, loss of NGF support to basal-forebrain cholinergic neurons contributes to the cholinergic deficit, and adding NGF or BDNF to entorhinal cortex or hippocampus improves spatial memory in models (Kaplan & Sadock 2024).

Pain, and the therapeutic difficulty of using neurotrophins. NGF sensitises nociceptors, and anti-NGF monoclonal antibodies (for example tanezumab) reduce osteoarthritis pain, showing the family cuts both ways. Direct delivery of neurotrophins as antidepressants has largely failed: they do not cross the blood-brain barrier, indiscriminate flooding risks seizures, and TrkB downregulates after unregulated BDNF exposure. The tractable strategy is therefore to raise BDNF *indirectly* through antidepressants, ECT, exercise, or small molecules and GPCR ligands (for example A2A and PACAP receptors) that transactivate TrkB, rather than to administer the protein itself (Kaplan & Sadock 2024).

INDIA

Two low-cost, high-yield levers on BDNF are directly relevant to Indian practice, where medication access and affordability are uneven: structured *physical exercise* and adequate *sleep* both raise BDNF and can be prescribed as adjuncts at no drug cost, and ECT (widely available and effective in Indian tertiary centres for severe and treatment-resistant depression) is among the most potent BDNF inducers. Framing exercise and sleep hygiene to patients as biologically active, "growth-factor-raising" interventions rather than soft lifestyle advice improves adherence and fits a resource-conscious, guideline-concordant stepped-care model.

Neuroendocrinology

13 · HPA axis, stress and cortisol

The endocrine home of stress. Of the three neuroendocrine axes on these notes, the hypothalamic-pituitary-adrenal (HPA) axis is the one examiners return to most, because it is where a psychological event becomes a measurable hormone and then a testable psychiatric marker. the Functional Neuroanatomy & Neurophysiology notes drew the *neural* stress circuit (amygdala driving the paraventricular nucleus, with prefrontal and hippocampal brakes); this topic adds the *endocrine arm* on top of it and owns the full cascade, the receptor-level feedback, and the one classical laboratory test of the axis, the dexamethasone suppression test. Cross-reference the amygdala-to-PVN wiring back to the Functional Neuroanatomy & Neurophysiology notes and do not re-derive it here.

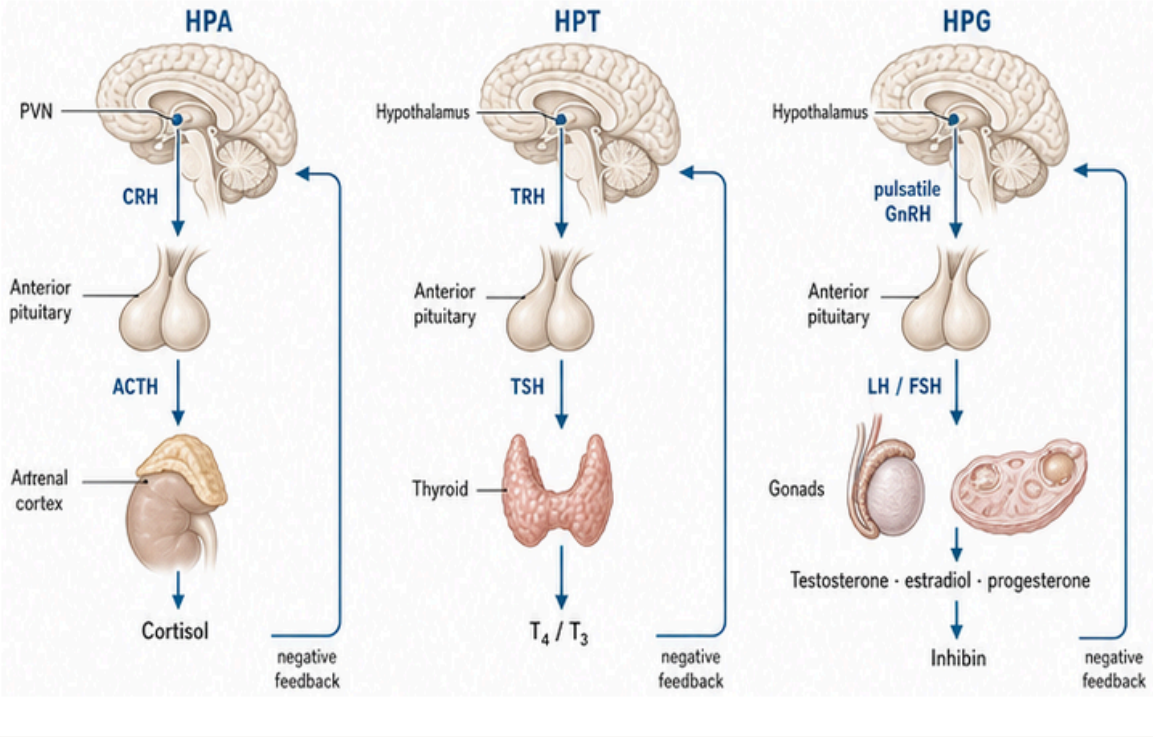


Fig 2.9 The three neuroendocrine axes.

The single organising idea is a three-tier hormonal relay under negative feedback: a stressor drives hypothalamic **CRH**, which drives pituitary **ACTH**, which drives adrenal **cortisol**, and cortisol then shuts the loop off by acting back on the pituitary, hypothalamus and hippocampus. Kaplan and Sadock frame cortisol as the transmitter of the endocrine stress response, sharpening arousal, vigilance and memory encoding acutely, but corrosive to the hippocampus when chronically elevated (Kaplan & Sadock 2024). Learn the cascade forward, the feedback backward, and the disease signatures (depression high, PTSD paradoxically low) as the payoff.

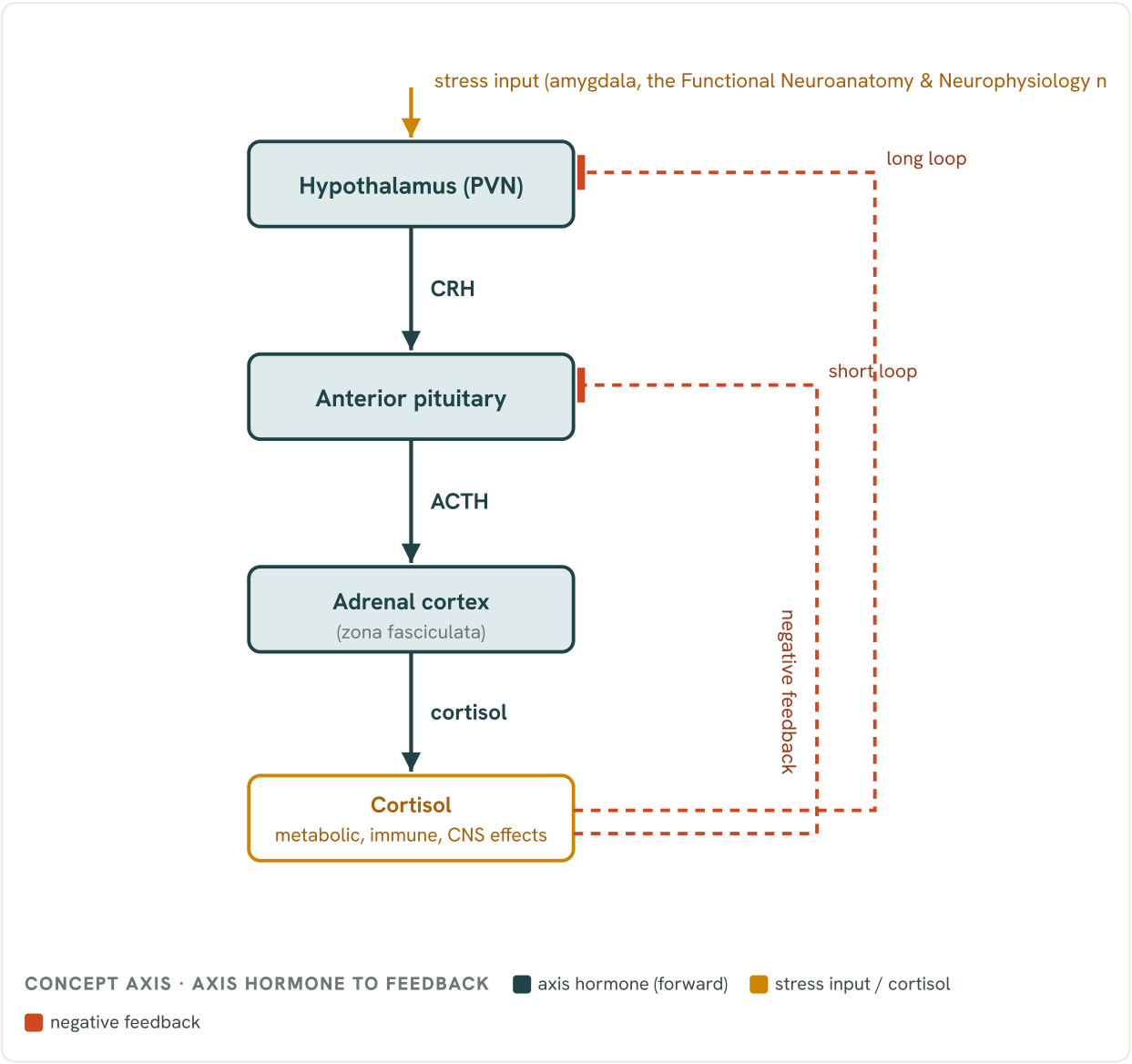


Fig 2.10 The HPA axis. A limbic stress signal (from the Functional Neuroanatomy & Neurophysiology circuit) drives the hypothalamic paraventricular nucleus to release CRH, which drives pituitary ACTH, which drives adrenal cortisol. Cortisol then closes two negative-feedback loops, a short loop onto the pituitary and a long loop onto the hypothalamus. The dexamethasone suppression test probes this feedback: failure to suppress cortisol (non-suppression) is the classic finding in melancholic depression.

13.1 The three-tier cascade: CRH to ACTH to cortisol

The anatomy of the relay. The axis is three glands in series, each secreting the signal for the next. Learn the source, the signal and the target at each tier.

Tier 1: hypothalamus (PVN)

Parvocellular neurons of the **paraventricular nucleus (PVN)** secrete **corticotropin-releasing hormone (CRH)**, a 41-amino-acid peptide, into the hypophyseal portal circulation. CRH is co-secreted with **arginine vasopressin (AVP)**, which is a weaker secretagogue on its own but strongly potentiates CRH at the pituitary (Kaplan & Sadock 2024).

Tier 2: anterior pituitary

CRH acts on corticotrophs of the **anterior pituitary** to release **adrenocorticotropic hormone (ACTH)**, cleaved from the precursor pro-opiomelanocortin (POMC). ACTH travels in the systemic circulation to the adrenal.

Tier 3: adrenal cortex

ACTH stimulates the **zona fasciculata of the adrenal cortex** to synthesise and release **cortisol**, the principal human glucocorticoid, from cholesterol. Cortisol is the effector hormone and the output that closes the loop.

MNEMONIC

CAP for the cascade, top to bottom

CRH (hypothalamic PVN) drives **A**CTH (anterior pituitary) drives cortisol from the adrenal **P**arenchyma (cortex, zona fasciculata). Read top-down for the forward cascade; the same three levels read bottom-up are exactly where cortisol feeds back.

13.2 The effector: what cortisol does acutely

Cortisol is adaptive in the short term and damaging when sustained, and the exam wants both faces. Acutely it increases arousal, vigilance and focused attention, mobilises energy (raising blood glucose via gluconeogenesis), contains the immune and inflammatory response, and facilitates the encoding of emotionally salient memory (Kaplan & Sadock 2024). This memory-enhancing effect is **contingent on noradrenaline**: glucocorticoid facilitation of emotional memory in the amygdala depends on concurrent arousal-driven noradrenergic activation, tying the endocrine arm back to the locus coeruleus circuit of the Functional Neuroanatomy & Neurophysiology notes.

PEARL

Cortisol has a **biphasic (inverted-U) effect** on hippocampal function and memory: a moderate rise sharpens memory consolidation, but high or sustained levels impair hippocampal-dependent cognition. This dose-dependence is why acute stress can sharpen recall while chronic stress dulls it, and it is the mechanistic bridge to the hippocampal atrophy seen with prolonged hypercortisolaemia.

13.3 Feedback: the two receptors, MR and GR

Two receptors, two thresholds. Cortisol closes its own loop through two intracellular corticosteroid receptors that differ critically in affinity, and this affinity difference is the single most examinable point in HPA feedback (Kaplan & Sadock 2024; Goodman & Gilman 2018).

FEATURE	MINERALOCORTICOID RECEPTOR (MR)	GLUCOCORTICOID RECEPTOR (GR)
Affinity for cortisol	**High affinity: occupied even at low, basal (trough) cortisol**	**Lower (moderate-to-low) affinity: recruited only when cortisol is high, at the diurnal peak and during stress**
Physiological role	Sets basal tone and maintains the circadian rhythm of the axis	Mediates the negative-feedback shut-off of the stress response and the return to baseline
Regional concentration	Dense in the hippocampus	Widespread; very high in hippocampus, also pituitary and hypothalamus
Feedback site	Tonic, permissive	**The main brake: GR at pituitary, hypothalamus and hippocampus terminates the surge**

The discriminator: MR is the high-affinity receptor that keeps the axis toned at rest, GR is the lower-affinity receptor that only engages when cortisol is high and is therefore the receptor that shuts stress off. Impaired GR feedback is the core lesion posited in melancholic depression.

RULE **MR is high-affinity and tones the axis at rest; GR is lower-affinity and only engages when cortisol is high, so GR is the brake that shuts stress off.** Impaired GR feedback is the posited melancholic lesion.

The **hippocampus** carries a very high density of both receptors and is the principal site of glucocorticoid negative feedback; this is why hippocampal damage both results from and worsens HPA dysregulation, a feed-forward loop of cortisol excess and hippocampal injury. Note also that MR responds to cortisol centrally because neurons lack the 11-beta-hydroxysteroid dehydrogenase type 2 that elsewhere protects MR from cortisol (Goodman & Gilman 2018).

13.4 Diurnal rhythm and the cortisol awakening response

Cortisol is not secreted flat: it follows a strong **diurnal (circadian) rhythm**, driven by the suprachiasmatic nucleus (cross-reference the circadian topic). Levels peak in the early morning, around waking, and fall to a nadir (trough) around midnight and the first hours of sleep. Superimposed on waking is the **cortisol awakening response (CAR)**, a sharp 50 to 75 percent rise in the 30 to 45 minutes after waking. The rhythm matters clinically for two reasons: it dictates *when* you must sample cortisol for any test to be interpretable, and its *flattening* (loss of the normal peak-to-trough amplitude) is itself a marker of chronic stress and HPA dysregulation.

COMMON TRAP

A single random cortisol is nearly uninterpretable because of the diurnal swing. The abnormality in depression is classically described not just as a raised mean but as an **elevated evening (nadir) cortisol with loss of the normal diurnal fall**, an earlier nadir and blunted amplitude. Always anchor a cortisol value to the time of day it was drawn.

13.5 Stress response and allostatic load

From adaptation to damage. The acute stress response is *allostasis*: the active process of achieving stability through change, mobilising the HPA axis and sympathetic system to meet a challenge, then switching off. **Allostatic load** (McEwen) is the cumulative physiological cost of this machinery when it is over-used or fails to shut off, that is, the wear-and-tear of a stress response that is too frequent, too prolonged, or inadequately terminated. Continuous high levels of hypothalamic and extrahypothalamic CRH are a strong contributor to allostatic load (Kaplan & Sadock 2024).

The four failure modes of the stress response that generate allostatic load are worth naming as a set: (a) too many stressors (repeated hits), (b) failure to habituate to a repeated stressor, (c) failure to shut off after the stressor ends (the GR-feedback problem), and (d) an inadequate response in one system leading to compensatory overactivity in another. The downstream cost of sustained cortisol is the peripheral syndrome of hypercortisolaemia (hypertension, insulin resistance, dyslipidaemia, osteoporosis, immunosuppression, visceral adiposity, procoagulant state) plus central hippocampal and prefrontal injury.

PEARL

Distinguish the terms cleanly. **Homeostasis** = keeping a fixed setpoint constant. **Allostasis** = achieving stability *through* change (the adaptive response itself). **Allostatic load** = the price paid for chronic or inefficient allostasis. **Allostatic overload** = the point where that load produces frank pathology. Examiners test the allostasis-versus-homeostasis distinction directly.

13.6 The dexamethasone suppression test (DST): protocol

The one test to know in full. The DST probes the integrity of glucocorticoid negative feedback. Dexamethasone is a potent synthetic glucocorticoid that suppresses pituitary ACTH (and hence cortisol) in a normal, feedback-intact axis. In the standard low-dose overnight protocol, **1 mg of dexamethasone is given orally at 11 PM**, and plasma cortisol is measured the next day, classically at 8 AM, 4 PM and 11 PM (Kaplan & Sadock 2024).

Normal (suppression)

Post-dexamethasone plasma cortisol falls and stays low, indicating an intact HPA feedback loop. This is the expected, healthy result.

Abnormal (non-suppression)

Plasma cortisol remains **above 5 micrograms/dL** (the classical cut-off), meaning the axis has escaped feedback: this is a positive test. Non-suppression reflects impaired GR-mediated feedback and is the finding of interest in depression (Kaplan & Sadock 2024).

COMMON TRAP

The DST is **not diagnostic of depression** and is not used clinically to make the diagnosis. Its low sensitivity, its escape as mood improves, and its non-specific positives (it is also positive in Cushing syndrome, and confounded by weight loss, alcohol, and enzyme-inducing drugs like carbamazepine and phenytoin that speed dexamethasone metabolism) mean it never entered routine practice. Know it as a historical and mechanistic marker, not a diagnostic test.

13.7 DST performance: melancholia, psychosis and the DEX/CRH refinement

The numbers are examinable and specific. In the pooled literature the 1 mg DST shows about **67 percent sensitivity and 96 percent specificity for melancholic depression** (Carroll's original claim), but sensitivity for major depression in general is only about **44 percent** (Contreras 2013). Non-suppression rates rise with biological severity: roughly **43 percent in MDD overall, but 67 percent in MDD with psychotic features** (Varghese 2001). Non-suppression is also **age-dependent**, climbing from about 34 percent in patients under 18 to 64 percent in those over 60, and correlates with the number of past depressive episodes.

The **combined dexamethasone/CRH (DEX/CRH) test** is the more sensitive research refinement: the axis is first suppressed with dexamethasone, then challenged with CRH. In dysregulated patients cortisol paradoxically rises despite pre-treatment, and the test reaches **sensitivity up to 90 percent** for detecting depression (Varghese 2001). Elevated CSF CRH is a fairly specific, *state* marker of depression (normal in mania, schizophrenia and dementia) that normalises with treatment.

67%	96%	44%	90%
1 MG DST SENSITIVITY IN MELANCHOLIA	SPECIFICITY FOR MELANCHOLIA	SENSITIVITY IN MDD OVERALL	DEX/CRH TEST SENSITIVITY

CLINICAL ANCHOR

Persistent non-suppression predicts relapse. DST non-suppression typically normalises as depression remits; a DST (or DEX/CRH) that *fails* to normalise despite symptomatic improvement flags a substantially higher risk of early relapse. This prognostic use, not diagnosis, is the clinically meaningful signal, and non-suppression also predicts better response to somatic (drug, ECT) than to placebo treatment.

13.8 HPA in depression: the hypercortisolaemic signature

Major depressive disorder (ICD-11 6A70-6A71; DSM-5-TR major depressive disorder), particularly the **melancholic** subtype, is the archetype of HPA *over*-activity. The composite signature (Varghese 2001; Kaplan & Sadock 2024) is: hypercortisolaemia with a flattened diurnal rhythm and raised evening cortisol; adrenal and pituitary hypertrophy on imaging; elevated CSF CRH with CRH-neuron overactivity in the PVN; a **blunted ACTH response to exogenous CRH** (from chronic CRH-driven pituitary downregulation); DST non-suppression; and reduced hippocampal volume. The mechanistic story is impaired GR-mediated feedback: the brake fails,

CRH drive is sustained, and the resulting cortisol excess is itself hippocampally toxic, a self-reinforcing loop.

COMMON TRAP

Atypical depression breaks the pattern. The hypercortisolaemia story is specific to *melancholic/endogenous* depression. Atypical depression (with hyperphagia, hypersomnia, leaden paralysis, mood reactivity) shows lower basal cortisol and a higher proportion of normal DSTs, closer to the *hypo*-cortisol pattern. Do not claim hypercortisolaemia across all depression.

13.9 HPA in PTSD: the low-cortisol paradox

The counter-intuitive case. Post-traumatic stress disorder (ICD-11 6B40; DSM-5-TR PTSD) is the examiner's favourite trap because, despite chronic stress, the classic finding is **low, not high, cortisol** (Yehuda). The paradox resolves through **enhanced negative feedback**: PTSD is associated with reduced urinary free cortisol, increased glucocorticoid-receptor density and sensitivity on lymphocytes, and consequently an over-active feedback brake that keeps cortisol low. CRH, by contrast, is *elevated* in CSF, so the abnormality is a hypersensitive GR feedback loop clamping down on the output, not a quiet axis (Contreras 2013).

The signature laboratory demonstration is **hypersuppression on a low-dose DST**: at **0.5 mg dexamethasone (half the usual dose)**, PTSD patients still suppress cortisol (indeed over-suppress) whereas depressed patients do not, a dissociation historically used to distinguish the two (Yehuda 2004).

MNEMONIC

Depression is HIGH and escapes; PTSD is LOW and over-suppresses

MDD: high cortisol, blunted feedback, DST *non*-suppression. PTSD: low cortisol, *enhanced* feedback (up-regulated, hypersensitive GR), *hyper*-suppression on the 0.5 mg DST. The two disorders sit at opposite poles of the same feedback axis.

HOLD THIS

Melancholic depression is high-cortisol and escapes feedback (DST non-suppression); PTSD is low-cortisol and hyper-suppresses on the 0.5 mg DST. Opposite poles of one feedback axis, driven by GR sensitivity.

13.10 HPA and suicide

HPA dysregulation carries independent prognostic weight for suicide. Across studies, DST non-suppression and evidence of HPA over-activity in depressed patients are associated with an **increased risk of completed suicide** (Varghese 2001). A widely cited meta-analytic finding is that DST non-suppressors have a substantially higher long-term risk of eventual suicide than suppressors, making persistent HPA dysregulation one of the few biological markers with replicated links to suicidal outcome. Post-mortem work adds convergent evidence of altered CRH signalling and reduced frontal-cortex CRH-binding in suicide, consistent with sustained central CRH hyperdrive.

13.11 Early-life programming of the axis

Where the setpoint is set. The HPA axis is developmentally plastic, and early-life stress durably resets its sensitivity, a central theme in the diathesis-stress and developmental-psychiatry literature. Preclinical work shows basal CSF CRH is persistently higher in primates that experienced early-life stress, and that excessive early CRH exposure produces hippocampal damage in later life (Kaplan & Sadock 2024). The best-characterised mechanism is **epigenetic**: early caregiving quality alters DNA methylation of the glucocorticoid-receptor (NR3C1) promoter in the hippocampus, changing lifelong GR expression and therefore feedback set-point (Meaney and Szyf, in the maternal-care model).

PEARL

Early-life adversity produces a **gene-environment interaction at the HPA axis**: the FKBP5 polymorphism (which regulates GR sensitivity) interacts with childhood trauma to predict adult depression and PTSD. This is the molecular embodiment of the diathesis-stress model and links the endocrine axis directly to developmental-psychiatry and epigenetics stems.

13.12 Therapeutics targeting the axis

Because the axis is a mechanism, it is a drug target, and current agents are examinable. **Mifepristone (RU-486)**, a glucocorticoid-receptor (GR) antagonist, has been trialled for **psychotic depression** (rapid reversal reported) and, in older adults with elevated cortisol, for cognitive and worry symptoms (Kaplan & Sadock 2024). Direct **CRH-1 receptor antagonists** were a rational strategy but have disappointed: no CRH-1 antagonist has shown efficacy in a phase III trial for a stress-related disorder, and pexacerfont failed against placebo in generalised anxiety disorder. Conceptually, standard antidepressants themselves partly work by *normalising* HPA feedback (restoring GR function and DST suppression) as mood improves, which is why persistent non-suppression on treatment signals inadequate response.

INDIA

The DST and DEX/CRH test are research and teaching instruments, not part of routine Indian (or international) clinical workup for depression: HPA-axis testing does not feature in IPS or NICE depression pathways, and diagnosis remains clinical. Know the axis for its mechanistic and viva value, and reserve endocrine testing for when a genuine endocrinopathy (Cushing syndrome, Addison disease) is in the differential.

14 · HPT and HPG axes in psychiatry

After the HPA axis, the two neuroendocrine loops most often examined in psychiatry are the **hypothalamic-pituitary-thyroid (HPT)** axis and the **hypothalamic-pituitary-gonadal (HPG)** axis. Both illustrate the same organising idea: a hypothalamic releasing hormone drives an anterior-pituitary trophic hormone, which drives a peripheral endocrine gland, whose product feeds back negatively on the two levels above it. Each axis touches psychiatric practice at three points: the endocrinopathy itself can present as a psychiatric syndrome (hypothyroid depression, menopausal mood change), the axis can be used diagnostically or therapeutically (the TRH

stimulation test, T3 augmentation), and psychotropic drugs perturb it (lithium and the thyroid, antipsychotics and prolactin). This topic also gathers the two remaining anterior-pituitary hormones of exam interest, **prolactin** (the antipsychotic problem) and **growth hormone** (the clonidine challenge test), because they share the same hypothalamic-pituitary anatomy.

The examiner reliably wants three things in this territory: the exact feedback logic of each axis, the numbers attached to the challenge tests and to lithium-induced thyroid disease, and a rational, prolactin-sparing approach to antipsychotic hyperprolactinaemia. The through-line is that dopamine is the hidden regulator of both prolactin (inhibitory) and TSH (inhibitory), which is why the neuroleptic that blocks dopamine raises prolactin, and why the axes are never fully separable from the transmitter pharmacology of these notes.

14.1 The HPT axis: TRH to TSH to T3/T4, and its feedback

Three hormones, one negative-feedback loop. Hypothalamic **thyrotropin-releasing hormone (TRH)**, a tripeptide from the paraventricular nucleus, drives the anterior pituitary to release **thyroid-stimulating hormone (TSH, thyrotropin)**, which drives the thyroid follicular cells to synthesise and release **thyroxine (T4)** and **triiodothyronine (T3)** from the thyroglobulin precursor. Low circulating thyroid hormone releases the brake on both TRH and TSH; high thyroid hormone suppresses them (Kaplan & Sadock 2024). Two facts have direct psychiatric relevance. First, **T4 is the main hormone reaching the brain, whereas T3 is the metabolically active hormone at peripheral tissues**, and much brain T3 is generated locally by deiodination of T4, which is part of the rationale for using T3 (not T4) in depression augmentation. Second, **central dopamine and glucocorticoids inhibit TSH secretion**, coupling the thyroid axis to the same monoamine and stress systems that dominate the rest of these notes.

Protein binding

T3 and T4 are tightly bound to thyroxine-binding globulin (TBG); only about 0.3% of T3 and 0.02% of T4 circulate free. Because oestrogen raises TBG, pregnancy and oral contraceptives raise *total* T4 without raising free hormone, whereas androgens lower TBG. This is why free-hormone indices, not total levels, are used to judge thyroid status (Kaplan & Sadock 2024).

Where the level points

An *elevated* TSH with low free T4 localises the lesion to the thyroid gland (primary hypothyroidism). A *low or normal* TSH with low free T4 points instead to the pituitary or hypothalamus (central hypothyroidism), the pattern to remember when a depressed patient has low thyroid hormone but an inappropriately unraised TSH.

Euthyroid sick syndrome

In serious non-thyroidal illness (myocardial infarction, chronic kidney disease, anorexia nervosa, cirrhosis) peripheral T4-to-T3 conversion falls, giving a low T3 with a normal TSH. It is a confound, not thyroid disease, and must not be treated as hypothyroidism (Kaplan & Sadock 2024).

TRAP A low T3 with a normal TSH in serious non-thyroidal illness is euthyroid sick syndrome, a confound, not hypothyroidism; do not start levothyroxine for it.

CLINICAL ANCHOR

Serum TSH is the single most useful screen and belongs in the initial workup of any new mood, cognitive or treatment-resistant presentation, alongside electrolytes, fasting glucose and calcium. Psychiatric symptoms arising from an endocrinopathy will not remit until the endocrine disturbance is corrected, and may worsen if psychotropics are added over an untreated axis.

14.2 Subclinical hypothyroidism, overt hypothyroidism and depression

The commonest endocrine mimic of depression. Overt hypothyroidism (raised TSH, low free T4) classically produces depressed mood, apathy, psychomotor retardation and a cognitive picture of slowed processing with prominent *verbal memory* and working-memory deficits (Kaplan & Sadock 2024). **Subclinical hypothyroidism (SCH)**, defined as a raised TSH with a still-normal free T4, is the more exam-relevant entity because it is easy to miss: it too is associated with cognitive impairment (mainly under age 75) and with depressive symptoms, and even *euthyroid but thyroid-antibody-positive* patients show a higher prevalence of depression. Worldwide the commonest cause of hypothyroidism is iodine deficiency; where salt is iodised, autoimmune **Hashimoto thyroiditis** (with anti-thyroglobulin and anti-thyroid-peroxidase antibodies) predominates.

Why it matters for treatment. Both overt hypothyroidism and SCH predict a *poorer antidepressant response* in major depressive disorder, and correcting the thyroid state does not always fully lift the neuropsychiatric symptoms, so thyroid disease is a genuine cause of apparent treatment resistance (Kaplan & Sadock 2024). In ICD-11 the correct label when a mood syndrome is driven by thyroid disease is a *secondary mood syndrome* (mood disorder due to thyroid disease), cross-mapped to DSM-5-TR "depressive disorder due to another medical condition"; the diagnosis of primary major depressive disorder should be withheld until the axis is corrected.

CLINICAL ANCHOR

Two named traps in one axis. **Hashimoto encephalopathy** is a rare autoimmune presentation with altered sensorium, delusions, auditory hallucinations, catatonia, seizures and even coma; it is steroid-responsive, with 90 to 98% responding to corticosteroids, and is the reason antithyroid antibodies belong in an atypical psychosis or catatonia workup. **Postpartum thyroiditis** occurs in roughly 5 to 9% of women after delivery, may cycle through a hyperthyroid then hypothyroid phase, and is a recognised organic contributor to postnatal mood disturbance (Kaplan & Sadock 2024).

14.3 Lithium and the thyroid (and parathyroid)

Lithium is itself a common cause of hypothyroidism. Lithium concentrates in the thyroid and inhibits the iodination of tyrosine and, principally, the *release* of thyroid hormone from the gland, driving a compensatory rise in TSH and often a goitre. The examinable figures: after long-term lithium, roughly **20% of patients develop overt hypothyroidism with goitre and a further ~20% develop subclinical hypothyroidism** (Kaplan & Sadock 2024). Risk is higher in

women, in patients with pre-existing **antithyroid antibodies**, and with **longer exposure**. Lithium can also raise serum calcium and parathyroid hormone (lithium-associated hyperparathyroidism), an easily forgotten cause of lethargy, cognitive change and renal effects in a lithium-treated patient.

~20%	~20%	25%
OVERT HYPOTHYROIDISM ON LONG-TERM LITHIUM	SUBCLINICAL HYPOTHYROIDISM	EUTHYROID DEPRESSED WITH BLUNTED TSH-TO-TRH

PEARL

Lithium-induced hypothyroidism is *not* a reason to stop a working mood stabiliser: it is managed by adding levothyroxine and continuing lithium. This is why baseline and periodic TSH (and calcium) monitoring is a hard rule of lithium prescribing, and why a new depressive relapse in a euthymic lithium-treated patient should prompt a TSH before it prompts an antidepressant.

14.4 The TRH stimulation test and the blunted-TSH finding

A historical biological marker of depression. In the **TRH stimulation test (TRH infusion test)** a baseline TSH is taken, TRH is given intravenously, and TSH is remeasured over the following half hour. The *normal* response is a rise in TSH of **at least 5 mIU/mL above baseline within 30 minutes**. The response is *exaggerated* in hypothyroidism and *blunted* in hyperthyroidism (Kaplan & Sadock 2024).

The psychiatric result. Around **25% of euthyroid patients with major depression show a blunted TSH response to TRH**, a finding widely reported as a putative state marker of depression, alongside the observation that many depressed patients have a subtly activated HPT axis (raised CSF TRH, blunting of the normal nocturnal TSH surge). The prevailing interpretation is that this thyroid activation is a *compensatory* response to the depressive process rather than its cause (Kaplan & Sadock 2024). With the arrival of highly sensitive TSH assays in the 1990s the test fell out of routine clinical use and is now essentially a viva-and-theory topic, paired with the dexamethasone suppression test (DST) as the two classic, non-specific "biological markers" of depression.

COMMON TRAP

Do not confuse the two blunting phenomena. A *blunted TSH response to TRH* is the depression marker (about a quarter of euthyroid depressed patients) and is not diagnostic. A blunted response in a non-depressed patient with normal T4 instead defines *subclinical hyperthyroidism*. Neither the TRH test nor the DST is sensitive or specific enough to diagnose depression, which remains a clinical diagnosis.

14.5 T3 augmentation and thyroid hormone in mood disorder

Using the axis therapeutically. Two distinct thyroid strategies appear in mood-disorder pharmacology, and the examiner wants them kept apart. First, **liothyronine (T3) augmentation** of an antidepressant: adding low-dose T3 (typically about 25 to 50 micrograms daily) to an SSRI or a tricyclic can convert non-responders to responders in unipolar depression, and this benefit is

seen even in *euthyroid* patients, with a particular signal where treatment resistance coincides with subclinical hypothyroidism (Kaplan & Sadock 2024). T3 is preferred over T4 here because T3 is the active hormone and acts faster. In the STAR*D programme T3 augmentation and lithium augmentation were compared at an equivalent step, with T3 at least as well tolerated. Second, in *bipolar* disorder, **high-dose (supraphysiological) thyroxine** has been used adjunctively for rapid-cycling and refractory illness, a separate and more specialist use.

Mechanistic thread. Thyroid hormone interacts with the serotonin system that dominates antidepressant pharmacology: hypothyroidism reduces brain 5-HT synthesis, and thyroid hormone reduces the sensitivity of inhibitory 5-HT1A autoreceptors in the raphe while increasing 5-HT2 sensitivity, an arrangement that plausibly disinhibits serotonergic output and rationalises T3 augmentation (Kaplan & Sadock 2024).

MNEMONIC

"T3 to Treat, T4 to the Thinker"

Use **T3** to **treat** (augment antidepressants; active, fast, peripheral). Remember **T4** reaches **the thinker** (T4 is the main hormone crossing into the brain, converted locally to T3). This keeps the augmentation choice and the brain-delivery fact straight.

14.6 The HPG axis: GnRH to LH/FSH to the sex steroids

A pulsatile axis unlike the others. Hypothalamic **gonadotropin-releasing hormone (GnRH)** is released in *pulses*, and it is this pulsatility, not a steady level, that drives the anterior pituitary gonadotrophs to secrete **luteinising hormone (LH)** and **follicle-stimulating hormone (FSH)** (Kaplan & Sadock 2024). LH and FSH act on the gonads: in the ovary they drive follicular oestradiol and, after ovulation, corpus-luteum progesterone; in the testis LH drives Leydig-cell testosterone and FSH supports Sertoli-cell spermatogenesis. The sex steroids feed back on the hypothalamus and pituitary, mostly negatively, with the mid-cycle oestrogen surge providing the one physiological example of *positive* feedback (triggering the LH surge and ovulation). Continuous, non-pulsatile GnRH agonism paradoxically *suppresses* the axis by desensitising the gonadotroph, the basis of GnRH-agonist "chemical castration" used in paraphilic and hypersexuality disorders.

Why psychiatry cares. Gonadal steroids are neuroactive. Oestradiol modulates dopaminergic, serotonergic and glutamatergic transmission and increases dopamine availability; this underlies the **oestrogen-protection hypothesis** of schizophrenia, which explains the later mean onset in women, the symptomatic worsening during low-oestrogen phases of the cycle, and the second incidence peak at menopause (Matuszewska 2023). Progesterone's metabolite **allopregnanolone** is a positive allosteric modulator of GABA-A receptors and dampens the HPA axis, linking the gonadal and stress axes and setting up the perinatal pharmacology below.

CLINICAL ANCHOR

The oestrogen-protection idea is now a therapeutic target. Adjunctive **selective oestrogen-receptor modulators (SERMs)**, notably *raloxifene*, have shown benefit for positive, negative and cognitive symptoms in some trials of postmenopausal women with schizophrenia, exploiting brain-oestrogenic action while avoiding the feminising and thromboembolic risks of oestrogen itself (Matuszewska 2023). Results are mixed, so this remains adjunctive and investigational rather than standard care.

14.7 Reproductive-cycle mood syndromes: PMDD, perinatal, menopause

Three windows where HPG shifts drive psychiatric risk. The shared principle is *sensitivity to change* in gonadal steroids rather than an abnormal absolute level.

Premenstrual dysphoric disorder (PMDD)

A luteal-phase disorder of affective, irritable and somatic symptoms that remit within a few days of menses, coded in ICD-11 in the gynaecological chapter and cross-listed, and given a discrete diagnosis in DSM-5-TR. Circulating oestrogen and progesterone are *normal*; the disorder reflects an abnormal central sensitivity to normal luteal-phase falls in these steroids and their neuroactive metabolites. SSRIs are first-line and, unusually, work rapidly and can be given *luteal-phase only*, consistent with a serotonergic rather than a slow neurotrophic mechanism; ovulation suppression is a second-line option.

Perinatal (postpartum) depression

The postpartum period carries the highest lifetime risk for a new or recurrent mood episode. The precipitous *fall* in oestrogen and progesterone (and in allopregnanolone) at delivery is the leading endocrine hypothesis, which motivated the allopregnanolone-based drugs below. Postpartum thyroiditis (14.2) is an organic differential that must be excluded.

Perimenopause and menopause

The menopausal transition, with its erratic then declining oestradiol, is a window of raised risk for depressive episodes and, in women with psychotic illness, the second peak of schizophrenia incidence (Matuszewska 2023). Transdermal oestradiol has antidepressant evidence for perimenopausal (but not established postmenopausal) depression, again pointing to change-sensitivity.

CLINICAL ANCHOR

The allopregnanolone story is the modern, examinable payoff of HPG-HPA cross-talk. **Brexanolone**, an intravenous allopregnanolone, and **zuranolone**, an oral neuroactive-steroid GABA-A positive modulator, are approved for postpartum depression with a rapid onset over days, directly replacing the neurosteroid that crashes after delivery. This is the clearest example of reproductive endocrinology yielding a novel psychiatric drug class.

14.8 Prolactin and antipsychotics: recognition and management

The one anterior-pituitary hormone under tonic dopamine inhibition. Prolactin is unique in being held *down* by hypothalamic dopamine acting on lactotroph D2 receptors (dopamine is the physiological prolactin-inhibiting factor). Any drug that blocks D2 in the tuberoinfundibular pathway therefore *raises* prolactin. The high offenders are the potent D2 blockers that bind

tightly and do not dissociate rapidly: **risperidone, paliperidone, amisulpride** and the typical antipsychotics (Maudsley 2021). The prolactin-sparing drugs are those that are partial agonists or dissociate rapidly from D2: **aripiprazole, brexpiprazole, cariprazine, quetiapine and clozapine**. Note that transient physiological rises also follow a generalised seizure, which is used clinically to distinguish an epileptic seizure from a psychogenic non-epileptic attack.

Recognition. Symptomatic hyperprolactinaemia causes *menstrual irregularity or amenorrhoea, galactorrhoea, gynaecomastia, reduced libido and sexual dysfunction*, and, through hypogonadism, longer-term **reduced bone mineral density**. Before ascribing a raised prolactin to the drug, exclude pregnancy, primary hypothyroidism (raised TRH also drives prolactin), a prolactinoma when the level is very high, and laboratory *macroprolactin*. Antipsychotics typically produce modest elevations; a markedly high prolactin unexplained by dose warrants pituitary imaging.

Management. The rational sequence is: confirm the elevation is symptomatic and drug-attributable, then either *reduce the dose*, *switch to a prolactin-sparing agent*, or add low-dose **aripiprazole**, whose partial D2 agonism at the lactotroph lowers antipsychotic-induced prolactin in placebo-controlled trials (Maudsley 2021). A dopamine agonist such as cabergoline is a last resort in psychosis because it can worsen the illness. Asymptomatic, modest elevations may simply be monitored.

PROLACTIN EFFECT	ANTIPSYCHOTICS	MECHANISM NOTE
High prolactin-raising	Risperidone, paliperidone, amisulpride, typicals (e.g. haloperidol)	**Potent, persistent D2 blockade; poor CNS-selectivity**
Prolactin-sparing	Aripiprazole, brexpiprazole, cariprazine	D2 partial agonism at the lactotroph
Prolactin-sparing	Quetiapine, clozapine	Low affinity and rapid D2 dissociation

Antipsychotics ranked by prolactin liability. The discriminator is D2 pharmacology: potent persistent antagonists raise prolactin, partial agonists and loose binders spare it.

HOLD THIS

Dopamine is the physiological prolactin-inhibiting factor, so any tuberoinfundibular D2 blocker raises prolactin. The rational fix is a prolactin-sparing switch or add-on aripiprazole (D2 partial agonism at the lactotroph), not a dopamine agonist.

INDIA

Risperidone is among the most-prescribed antipsychotics in Indian public and private practice on cost grounds, so antipsychotic hyperprolactinaemia is common and frequently missed, especially amenorrhoea and sexual dysfunction that patients do not volunteer. Switching to, or augmenting with, aripiprazole is usually affordable here and is the pragmatic first move; cabergoline needs cautious specialist use given psychosis-worsening risk.

14.9 Growth hormone and the clonidine challenge test

A probe of central noradrenergic (alpha-2) function. Growth hormone (GH) is released from the anterior pituitary under dual hypothalamic control: **growth hormone-releasing hormone (GHRH)** stimulates it and **somatostatin** inhibits it. GH secretion is driven partly by central alpha-2 adrenoceptor activation, which is the basis of the challenge test. In the **clonidine challenge test**, the alpha-2 agonist clonidine is given and the GH rise is measured; a *blunted GH response to clonidine* is the most consistent neuroendocrine finding in **major depression** and is interpreted as evidence of reduced sensitivity of post-synaptic hypothalamic **alpha-2 adrenoceptors** (Kaplan & Sadock 2024). A similar blunting has been reported in generalised anxiety disorder and panic disorder.

Reading the result. Like the TRH and dexamethasone tests, the clonidine-GH test is a research and viva instrument, not a clinical diagnostic: it is neither sensitive nor specific enough to diagnose depression, but it is the standard example when a question asks how the noradrenergic system is probed pharmacologically, and it complements the serotonergic fenfluramine challenge (which measures a prolactin or cortisol response). Growth-hormone regulation is also disturbed in eating disorders, where chronic undernutrition produces GH resistance with high GH but low IGF-1.

> **COMMON TRAP**
>
> Match each challenge test to the transmitter it probes. *Clonidine to GH* probes noradrenergic alpha-2 function and is blunted in depression; *fenfluramine to prolactin/cortisol* probes serotonergic function; *TRH to TSH* probes the thyroid axis; *dexamethasone to cortisol* probes HPA feedback. Confusing the agonist with the axis it interrogates is the classic marks-losing error here.

15 · Circadian rhythms and melatonin

A clock built from a gene loop, wired to the eye, read out through a hormone. The circadian system is the one piece of "basic" neuroscience the paper can turn into clinical questions from three directions at once: molecular biology (the clock-gene feedback loop), neuroendocrinology (melatonin and the cortisol rhythm), and psychopharmacology (the melatonin-agonist antidepressants and hypnotics). The examinable spine is a single causal chain. A self-sustaining transcription-translation loop in the suprachiasmatic nucleus keeps time with a near-24-hour period; light, sensed by a specialised retinal pathway, resets it each day; the reset clock drives an output rhythm of melatonin, cortisol and core temperature; and when that output drifts out of phase with the environment or the sleep-wake schedule, mood and psychotic disorders track the disruption. Get the loop, the light input and the melatonin output straight and the clinical material (seasonal depression, the bipolar phase-advance, agomelatine, ramelteon, tasimelteon) falls out of it.

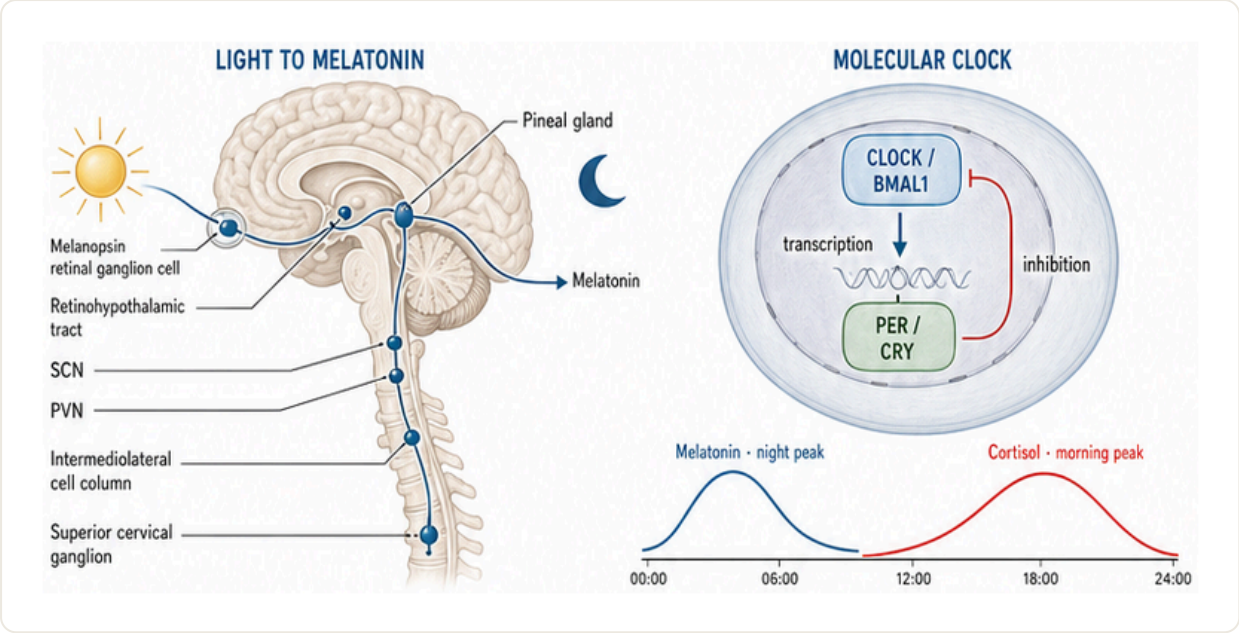


Fig 2.11 The circadian clock.

Two framing facts to carry into the detail. First, the endogenous human period is not exactly 24 hours: free-running, the suprachiasmatic clock runs at roughly 24.2 hours, so it must be actively re-entrained daily, and the direction a person's clock naturally drifts (long period gives an evening "owl", short period gives a morning "lark") is largely genetic (Kaplan & Sadock 2024). Second, melatonin is biochemically continuous with serotonin (it is synthesised from it), which is why the serotonergic and circadian systems are examined together and why the one drug that sits at their junction, agomelatine, is both a melatonin agonist and a 5-HT2C antagonist (Stahl 2021). This topic cross-references the the Functional Neuroanatomy & Neurophysiology notes material on sleep physiology and the two-process model of sleep regulation.

15.1 The suprachiasmatic nucleus: the master pacemaker

Location and anatomy. The primary circadian oscillator in mammals is the **suprachiasmatic nucleus (SCN)**, a paired nucleus in the anterior hypothalamus lying immediately dorsal to the optic chiasm (the name is literally "above the chiasm"). Its neurons are among the smallest in the brain, densely packed with short, sparsely branched dendrites. The SCN is anatomically divided into a **core** (ventral, calbindin-positive, receiving the main retinal input) and a surrounding **shell** (Kaplan & Sadock 2024).

Master and slave clocks. The circadian system is a hierarchy. The SCN is the master oscillator, but near-identical molecular clocks run autonomously in peripheral tissues (liver, kidney, lung, heart) and in other brain regions; the SCN's job is to keep these **peripheral oscillators** synchronised to each other and to environmental time. A key exam point is that the SCN is self-sustaining: an isolated SCN neuron, or even a dissociated SCN culture, continues to generate a circadian rhythm with no external cue, proving the clock is *endogenous* and not merely a passive response to the light-dark cycle.

15.2 The molecular clock: the transcription-translation feedback loop

The clock is a gene circuit that takes about a day to complete one cycle. The mammalian clockwork is a set of interlocking **transcription-translation feedback loops (TTFL)** built from a handful of core clock genes. The **positive limb** is a heterodimer of two transcriptional activators, **CLOCK** and **BMAL1**. This CLOCK-BMAL1 complex binds E-box enhancer elements in the promoters of the **Period (PER1, PER2, PER3)** and **Cryptochrome (CRY1, CRY2)** genes and drives their transcription.

The negative limb. The PER and CRY proteins accumulate in the cytoplasm, dimerise, and translocate back into the nucleus, where they *inhibit their own transcription* by repressing the CLOCK-BMAL1 complex that made them (Kaplan & Sadock 2024). As PER and CRY proteins are then degraded, the repression lifts, CLOCK-BMAL1 becomes active again, and the cycle restarts. This delayed negative feedback is the oscillator, and the delays (transcription, translation, protein complex formation, nuclear entry, degradation) are what set the roughly 24-hour period.

The stabilising secondary loop and post-translational timing. CLOCK-BMAL1 also drives the nuclear receptor genes **REV-ERBα** and **ROR**, whose products respectively repress and activate BMAL1 transcription; this second interlocked loop confers robustness and precision. Crucially, the period is fine-tuned not just by transcription but by **post-translational modification**: phosphorylation of PER proteins by **casein kinase 1 (isoforms epsilon and delta)** governs their nuclear entry and degradation rate, so a mutation here shortens the whole period. This is the mechanism of familial advanced sleep phase syndrome and the molecular reason casein kinase surfaces in exam stems.

MNEMONIC

"CB builds it, PC breaks it"

CLOCK and **B**MAL1 (positive limb) build the loop by activating transcription; **P**ER and **C**RY (negative limb) break it by repressing their own makers. The two pairs chase each other around a roughly 24-hour cycle. Bolt on the secondary loop (REV-ERB and ROR set BMAL1) and the tuner (casein kinase phosphorylates PER) and you have the whole clockwork.

HOLD THIS

The clock is a transcription-translation loop: CLOCK-BMAL1 build it, PER-CRY break it, over roughly 24 hours. Melatonin is biochemically made from serotonin, which is why agomelatine (MT1/MT2 agonist plus 5-HT2C antagonist) sits at their junction.

15.3 Light entrainment: the retinohypothalamic tract and melanopsin

The photic input pathway. Because the endogenous period is not exactly 24 hours, the clock must be reset daily, and the dominant resetting cue is light. Light is transduced not by rods and cones for this purpose but by a distinct population of **intrinsically photosensitive retinal ganglion cells (ipRGCs)** that express the photopigment **melanopsin** and are maximally sensitive to short-wavelength **blue light** (around 480 nm). These cells project directly to the SCN

via the **retinohypothalamic tract (RHT)**, whose neurotransmitter is **glutamate** (Kaplan & Sadock 2024).

Why blue light and screens matter clinically. The blue-light sensitivity of melanopsin is the mechanistic basis for the sleep-disrupting effect of evening screen exposure and for the therapeutic use of bright light and blue-enriched light. It also explains why totally blind individuals with no light perception lose entrainment: roughly 50 to 70 percent develop **non-24-hour sleep-wake rhythm disorder**, their clock free-running at its intrinsic period so their sleep drifts progressively later each day (Kaplan & Sadock 2024).

15.4 Zeitgebers: photic and non-photic time cues

Zeitgeber
German "time-giver": any external cue that entrains (resets) the endogenous clock to the 24-hour environmental day. The clock without zeitgebers free-runs at its intrinsic near-24.2-hour period.

Photic zeitgeber
Light, the strongest and dominant cue, acting through the melanopsin-RHT pathway to the SCN.

Non-photic zeitgebers
Feeding and meal timing, physical exercise and locomotor activity, social interaction (the basis of "social zeitgebers"), ambient temperature, and certain drugs (amphetamines). Non-photic signals reach the SCN largely via the thalamus and the midbrain raphe (Kaplan & Sadock 2024).

Entrainment
The process by which a zeitgeber locks the endogenous clock to the external cycle, holding a stable phase relationship rather than letting it free-run.

The phase-response curve. The direction in which a cue shifts the clock depends on *when* in the circadian cycle it arrives, described by the **phase-response curve (PRC)**. For light, exposure in the early biological night (evening) produces a **phase delay** (pushes the clock later), whereas exposure in the late night or early morning produces a **phase advance** (pulls it earlier). Melatonin has an almost mirror-image PRC: evening melatonin advances the clock, morning melatonin delays it. This is the pharmacological logic behind timing light and melatonin to treat delayed and advanced phase disorders and jet lag, and it is a favourite exam discriminator.

RULE **Evening light delays the clock, morning light advances it; melatonin has the mirror-image curve.** Evening melatonin advances, morning melatonin delays.

15.5 Melatonin synthesis: from serotonin in the pineal gland

The biosynthetic pathway. Melatonin (**N-acetyl-5-methoxytryptamine**) is synthesised in the pinealocytes of the **pineal gland** from serotonin in two enzymatic steps. Serotonin is first N-acetylated by **arylalkylamine N-acetyltransferase (AANAT)**, the rate-limiting enzyme whose activity rises steeply at night, to N-acetylserotonin; this is then O-methylated by **acetylserotonin O-methyltransferase (ASMT, formerly HIOMT)** to melatonin (Kaplan & Sadock 2024). Adding an acetyl group to serotonin's amine and a methoxy group in place of its hydroxyl makes

melatonin markedly more lipophilic than serotonin, so it crosses the blood-brain barrier and the placenta freely and is not stored but released as fast as it is made.

The neural drive is noradrenergic and dark-gated. The SCN controls melatonin through a multisynaptic efferent path: SCN to the hypothalamic paraventricular nucleus, then down to the spinal cord, out to the **superior cervical ganglion**, and finally by sympathetic fibres to the pineal. At the pinealocyte, **noradrenaline acts on beta-1 and alpha-1 adrenergic receptors** to switch on AANAT and drive melatonin synthesis. Because the SCN *inhibits* this pathway during the day and releases it at night, **melatonin synthesis rises when SCN activity falls**: light suppresses it, darkness permits it.

PEARL

Melatonin is the body's chemical signal for "biological night", not for sleep as such. It marks darkness and the timing of the internal clock to every organ, which is why it works better as a chronobiotic (a clock-shifter, taken in the early evening to advance the clock) than as a pure hypnotic. This distinction, phase-shifting versus sedating, separates melatonin and ramelteon from the benzodiazepine-receptor hypnotics.

15.6 Melatonin dynamics and the DLMO marker

The nocturnal profile. Plasma melatonin is low by day (around 40 pmol/L) and high at night, peaking near 2 to 3 a.m. (around 400 pmol/L), a roughly tenfold nocturnal rise, then falling to baseline by morning just as cortisol peaks (Kaplan & Sadock 2024). Its receptors are the G-protein-coupled **MT1** and **MT2** subtypes, both densely expressed in the SCN itself: broadly, MT1 mediates the acute suppression of SCN firing (the sleep-promoting, "opening the gate" effect) and MT2 mediates the phase-shifting (clock-resetting) effect, a mechanistic pairing worth naming.

Dim-light melatonin onset. The single most useful clinical marker of circadian phase is the **dim-light melatonin onset (DLMO)**, the evening time at which melatonin begins to rise measured under dim light (bright light would suppress it). DLMO normally precedes habitual sleep onset by about 2 to 4 hours; a *late* DLMO indicates a delayed clock (as in delayed sleep phase and much of adolescent and depressive presentation) and an *early* DLMO a phase-advanced clock (Kaplan & Sadock 2024).

15.7 Circadian output rhythms and the two-process model of sleep

What the clock drives. The SCN imposes a circadian rhythm on melatonin, on **core body temperature** (which reaches its nadir in the early morning, roughly 5 to 6 a.m., just before natural waking), and on the **HPA axis**: cortisol peaks in the early morning (about 6 to 8 a.m.) via an SCN to paraventricular-nucleus to CRH to ACTH pathway, and this early-morning cortisol surge is a robustly examinable output rhythm. The temperature minimum is the reference point around which sleep is best timed.

Interaction with the sleep homeostat (cross-reference the Functional Neuroanatomy & Neurophysiology notes). Sleep timing is the product of two processes (Borbely's model):

Process S, the homeostatic sleep drive that builds with time awake (adenosine accumulation is the leading substrate, and caffeine promotes wakefulness by antagonising adenosine), and **Process C**, the circadian drive for arousal that the SCN steadily raises across the day to oppose the mounting sleep pressure, peaking in the evening "wake-maintenance zone" before melatonin rises and it wanes. Chronotype (lark versus owl) is driven almost entirely by Process C, not Process S, because the homeostat is similar between people of similar age (Kaplan & Sadock 2024). See the the Functional Neuroanatomy & Neurophysiology notes sleep-physiology topic for sleep architecture and the two-process model in full.

15.8 Circadian disruption in depression and bipolar disorder

Circadian disturbance is a near-universal feature of mood disorder, and probably not just a symptom of it. In **depression** the most consistent circadian findings are a **phase advance** of several rhythms, classically expressed as *early-morning awakening* and a *shortened REM latency*, together with lower and phase-shifted nocturnal melatonin, loss of the normal nocturnal fall in core temperature, and the diurnal mood variation (worse in the morning) of melancholia. The **phase-advance hypothesis** of depression is the classical formulation the exam wants.

Bipolar disorder. Here circadian instability is arguably a trait, not just a state. Sleep loss is one of the most reliable triggers of a switch into mania, and mood episodes cluster with disruption of the sleep-wake and social rhythm. Polymorphisms in clock genes (including CLOCK, BMAL1, PER, CRY, TIMELESS, NR1D1 and CSNK1 isoforms) are associated with bipolar disorder, illness course and treatment response (Bunney 2015). Two mechanistic anchors are high-yield: the **ClockΔ19 mutant mouse** shows a mania-like phenotype (hyperactivity, reduced sleep, increased reward-seeking) driven by raised dopaminergic activity in the ventral tegmental area, a phenotype normalised by lithium; and **lithium inhibits GSK-3beta**, an enzyme that regulates the clock (it phosphorylates clock proteins and sets the period), giving a molecular link between the circadian system and the mood-stabilising action of lithium.

CLINICAL ANCHOR

Interpersonal and Social Rhythm Therapy (IPSRT) operationalises this biology for bipolar disorder: it targets the regularity of daily social zeitgebers (wake time, meals, activity, social contact) on the premise that stabilising social rhythms stabilises the underlying circadian clock and so reduces relapse. It is the therapy the exam pairs with the circadian model of bipolar disorder.

15.9 Seasonal affective disorder and the seasonal-pattern specifier

Nomenclature. What older texts call **seasonal affective disorder (SAD)** is, in current nosology, not a standalone diagnosis but a course specifier applied to a recurrent mood disorder: DSM-5-TR uses **"with seasonal pattern"** for major depressive disorder (recurrent) and for bipolar disorder, requiring a regular temporal relationship between episode onset and a particular time of year, most typically winter depression remitting in spring (DSM-5-TR 2022). ICD-11 similarly captures this as a seasonal pattern qualifier of a recurrent depressive or bipolar disorder rather than a separate entity.

Proposed mechanisms. The leading accounts are circadian: the **phase-shift hypothesis** holds that the shorter winter photoperiod delays the circadian clock relative to the sleep-wake cycle (a phase delay in most patients), which is why morning bright light, which phase-advances the clock, is therapeutic. Reduced light also lengthens the duration of nocturnal melatonin secretion in winter, and serotonergic hypofunction is implicated.

CLINICAL ANCHOR

Bright-light therapy is first-line for seasonal winter depression: typically **10,000 lux for about 30 minutes on waking**, timed in the early morning to phase-advance a delayed clock. Response is often faster than to antidepressants (within a week). The main cautions are precipitation of hypomania or mania in bipolar patients and, rarely, retinal considerations.

15.10 Chronotherapeutics: light, wake therapy and exogenous melatonin

Non-pharmacological. **Bright-light therapy** is used for seasonal depression, delayed sleep phase (morning light) and, in the evening, for advanced sleep phase, always exploiting the light PRC. **Total or partial sleep deprivation (wake therapy)** produces a rapid but transient antidepressant response in a substantial minority of patients, often lost after the next night's sleep; it is combined with sleep-phase advance and light to sustain the effect. **Chronotherapy** proper, the systematic timed shifting of the sleep schedule, treats circadian sleep-wake disorders.

Exogenous melatonin. Used in low physiological doses (often 0.5 to 5 mg) as a **chronobiotic**, timed in the early evening to phase-advance a delayed clock (delayed sleep phase disorder, jet lag travelling eastward, non-24 disorder), and as a mild hypnotic in older adults where endogenous melatonin is reduced. A prolonged-release preparation is licensed for insomnia in adults over 55 in several jurisdictions; melatonin is also widely used for insomnia in children with neurodevelopmental disorders (Maudsley Prescribing Guidelines).

15.11 Melatonin receptor agonists: ramelteon, agomelatine, tasimelteon

Three synthetic agonists, each defined by its receptor profile and its indication. All are structural analogues of melatonin, all are highly lipophilic, cross the blood-brain barrier, are metabolised principally by **CYP1A2** (a major interaction caveat: fluvoxamine, a potent CYP1A2 inhibitor, dramatically raises their levels and is contraindicated or cautioned with all three), and all have short elimination half-lives of under about two hours (Kaplan & Sadock 2024).

AGENT	RECEPTOR ACTION	LICENSED USE	KEY CAUTION
Ramelteon	MT1 / MT2 agonist	**Sleep-onset insomnia (no scheduled-drug / abuse liability)**	Avoid with fluvoxamine (CYP1A2)
Agomelatine	**MT1 / MT2 agonist plus 5-HT2C antagonist**	Major depressive disorder	Hepatotoxicity: monitor LFTs; contraindicated in hepatic impairment
Tasimelteon	MT1 / MT2 agonist	**Non-24-hour sleep-wake rhythm disorder (esp. totally blind)**	CYP1A2 / CYP3A4 metabolism
Melatonin (prolonged-release)	MT1 / MT2 agonist	Insomnia in adults over 55; paediatric neurodevelopmental insomnia	Generally well tolerated

The four melatonergic agents compared: the discriminators are agomelatine's added 5-HT2C antagonism (which gives it antidepressant efficacy and is why it is the one used for depression rather than insomnia) and tasimelteon's niche in non-24 disorder.

Agomelatine, the key drug. Its combination of MT1/MT2 agonism with **5-HT2C antagonism** is what distinguishes it: the 5-HT2C blockade disinhibits frontocortical dopamine and noradrenaline release, giving antidepressant and pro-sleep effects, while resynchronising disrupted circadian rhythms. It is notable for being relatively free of the sexual dysfunction, weight gain and discontinuation effects of SSRIs, but carries a dose-related risk of **hepatotoxicity** that mandates baseline and periodic liver function tests and precludes use in hepatic impairment (Stahl 2021).

COMMON TRAP

Do not lump the melatonin agonists with the benzodiazepine-receptor hypnotics. Ramelteon and melatonin act on MT1/MT2 with *no* action at the GABA-A benzodiazepine site, so they carry no meaningful dependence, tolerance, abuse or next-day psychomotor liability, and are not scheduled drugs. Their trade-off is a modest hypnotic effect confined largely to sleep *onset*. Agomelatine is an antidepressant, not a hypnotic, and its examinable hazard is hepatic, not sedative.

INDIA

Melatonin is inexpensive and widely available over the counter in India and is a pragmatic first choice for jet lag, delayed sleep phase and adjunctive insomnia. Agomelatine is marketed and used for depression, but the mandatory liver-function monitoring (baseline and periodic) is easily neglected in practice and must be counselled and arranged, particularly given variable follow-up. Ramelteon and tasimelteon are far less commonly available.

Neuroimaging

16 · Structural imaging (CT/MRI) findings in psychiatric disorders

Start at the scanner, not the syndrome. Before any disorder-specific finding means anything, you have to be able to look at a film and say *what* it is and *why it looks the way it does*. Structural imaging is the layer that shows the machinery the Functional Neuroanatomy & Neurophysiology notes mapped: it does not measure activity (that is the functional topic next door), it measures shape, tissue, and gross lesion. In psychiatry its role is almost entirely one of **exclusion** and correlation: no structural scan diagnoses a primary psychiatric disorder, but a scan can unmask the organic mimic hiding inside a first-episode presentation, and group-level structural signatures (enlarged ventricles in schizophrenia, white-matter hyperintensities in late-life depression, medial-temporal atrophy in Alzheimer disease) are examined precisely because they are reproducible.

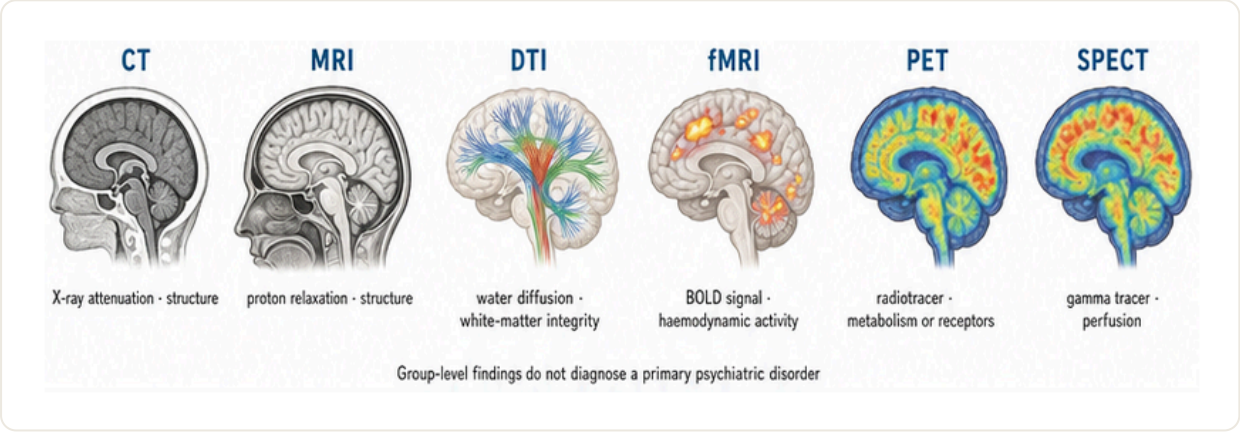
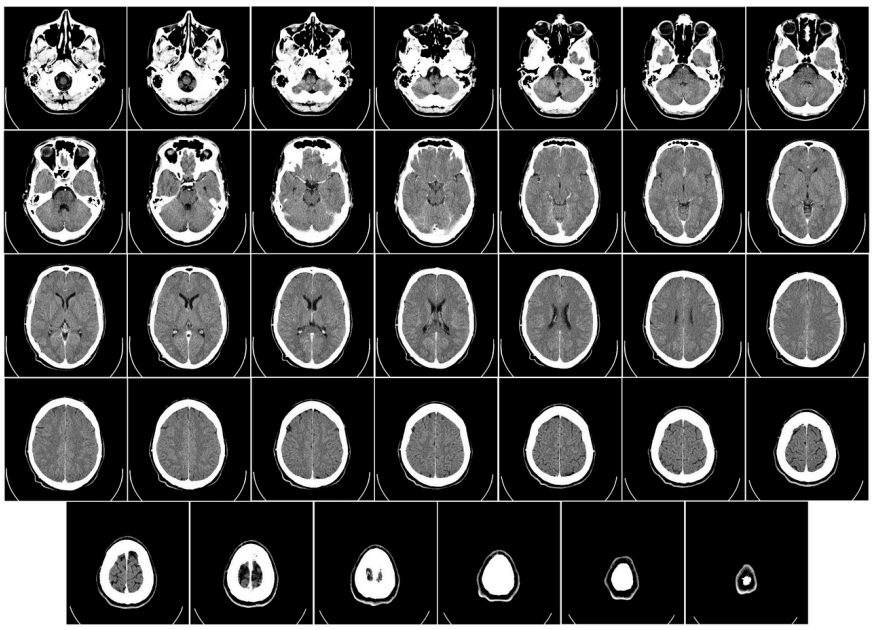
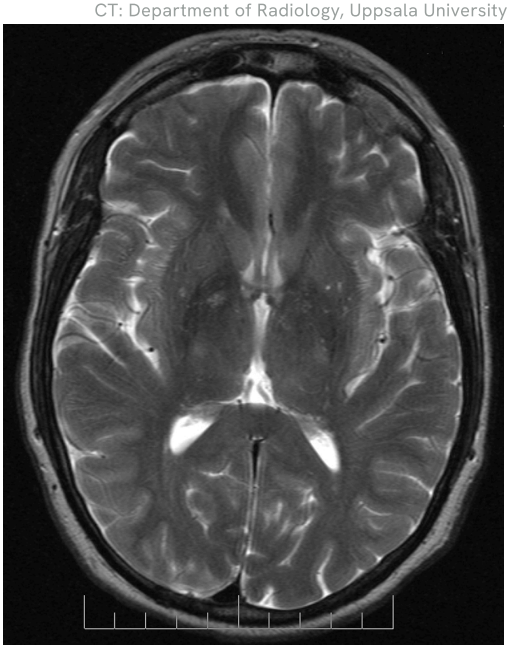


Fig 2.12 What each imaging modality measures.

The single most examinable skill is the one most easily skipped: telling a **CT** from an **MRI** at a glance, and knowing what is bright and dark on each MRI sequence and why. Get that physics right and every disorder finding below reads itself off the film. This topic is the imaging deep home for this material; it cross-references the Functional Neuroanatomy & Neurophysiology structures (hippocampus, ventricles, frontal and temporal cortex) rather than re-teaching them.



CT: Department of Radiology, Uppsala University Hospital, CC0, via Wikimedia Commons



MRI (T2): Afiller, CC BY-SA 3.0, via Wikimedia Commons

Fig 2.13 What a normal CT and MRI actually look like. On the CT series (top, skull base to vertex), bone is bright white, air and CSF are dark, and grey-white differentiation is modest; CT is fast and is the emergency scan for acute blood and bone. On the T2 MRI (below), CSF is bright, grey and white matter separate cleanly, and the soft-tissue detail is far greater; MRI carries the psychiatric yield. Read this real appearance alongside the sequence signal grid in Fig 2.7.

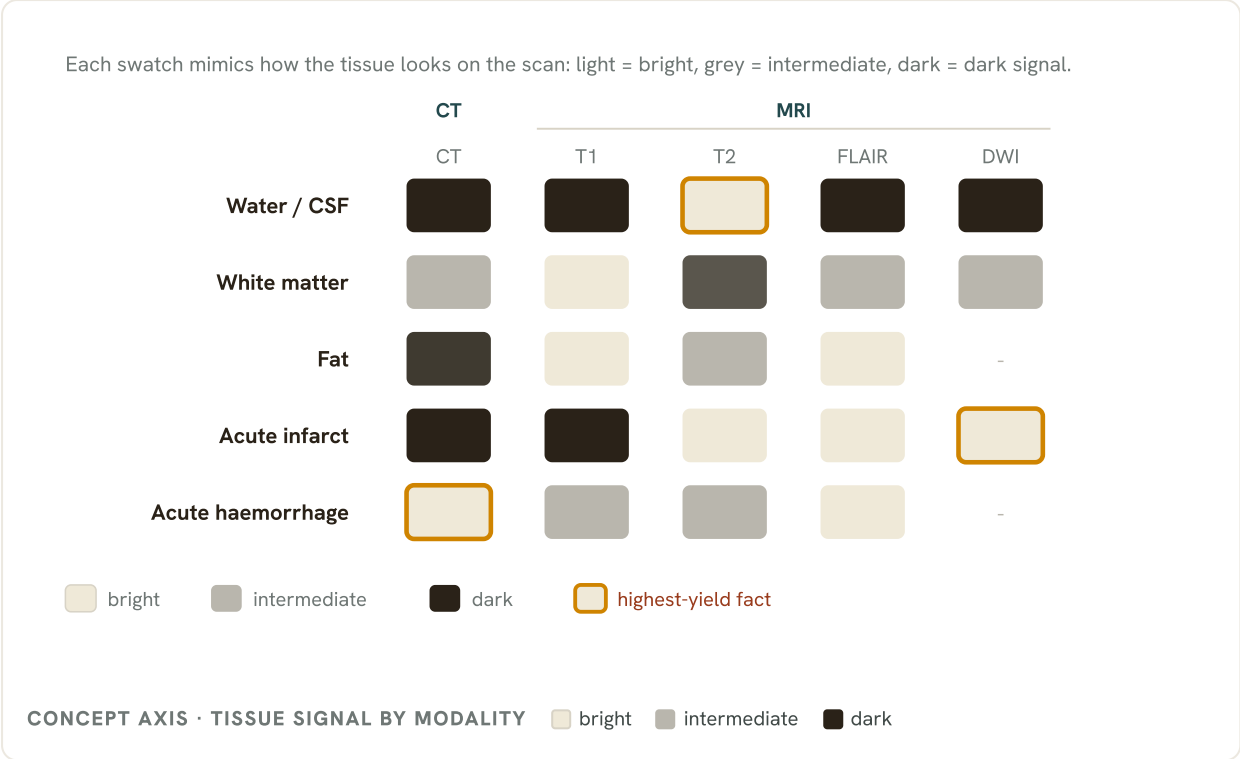


Fig 2.14 How to read the sequences at a glance. Anchor on water: CSF is bright only on T2, and FLAIR is a T2 with the CSF signal suppressed (so a periventricular lesion stands out). Fat is bright on T1. Acute haemorrhage is bright (hyperdense) on CT, which is why CT is the emergency scan; an acute infarct is bright on DWI before it shows anywhere else. The two one-liners: "water is white on T2" and "acute stroke is bright on DWI".

16.1 Telling a CT from an MRI at a glance, and in principle

The physics decides the picture. CT (computed tomography) is X-ray based: a rotating X-ray tube measures how much tissue attenuates the beam, and a voxel's brightness is its **density**, expressed in Hounsfield units. It uses ionising radiation, is fast (seconds), is widely available and cheap, and is the workhorse of the emergency setting. Dense things stop X-rays and appear white (**hyperdense**): bone and the skull vault, fresh clotted blood, and calcification. Water-like things appear dark (**hypodense**): CSF, oedema, and old infarct. On a plain CT the skull is brilliant white, CSF in the ventricles is black, and grey-white differentiation is only modest.

MRI (magnetic resonance imaging) uses no ionising radiation. A strong magnetic field aligns hydrogen protons and radiofrequency pulses tip them; the signal comes from how protons relax back (the T1 and T2 relaxation times) and from proton (water) density. This gives superb **soft-tissue contrast** and multiplanar imaging without moving the patient. The trade-off: it is slow, expensive, less available, contraindicated with many ferromagnetic implants and pacemakers, and cortical *bone* gives almost no signal (few mobile protons), so the skull is dark rather than white. The instant tell at the console: **if the skull is bright white, it is CT; if the skull is dark, it is MRI.**

PEARL

The one-line discriminator to carry into the exam and the ward: *bone bright, blood bright, fast, radiation, emergency* is CT; *bone dark, exquisite soft tissue, slow, no radiation, elective and definitive* is MRI. CT answers "is there acute blood or a fracture, right now?"; MRI answers "what exactly is the soft-tissue lesion?"

16.2 When each modality is chosen

The choice is not preference, it is the clinical question and the clock. **CT is chosen** when speed and blood detection matter: acute head trauma, suspected acute intracranial haemorrhage, the confused or newly seizing patient in the emergency room, screening before lumbar puncture, and any patient who cannot have an MRI (pacemaker, certain metallic implants, agitation, instability). Acute haemorrhage is the classic CT strength: fresh blood is reliably hyperdense on CT from the first minutes, whereas it is deceptively subtle on standard early MRI. **MRI is chosen** for the elective, definitive soft-tissue question: characterising a mass, demyelination, mesial temporal sclerosis, subtle cortical dysplasia, posterior-fossa and brainstem lesions (where CT bone-hardening artefact obscures the view), and the great majority of the psychiatric organic workup, where the yield is in grey-matter volume, white-matter change, and small structural lesions that CT would miss.

FEATURE	CT	MRI
Physical basis	X-ray attenuation (density, Hounsfield units)	**Proton relaxation in a magnetic field (T1/T2/proton density)**
Ionising radiation	**Yes**	No
Speed / availability	**Seconds; ubiquitous, cheap**	Minutes; scarcer, expensive
Skull / cortical bone	**Bright white (hyperdense)**	Dark (little signal)
Acute haemorrhage	**Reliably hyperdense from the outset (modality of choice)**	Subtle early on standard sequences
Soft-tissue / grey-white contrast	Modest	**Superb; multiplanar**
Best clinical question	**"Acute blood or fracture, now?"**	"What exactly is the soft-tissue lesion?"
Main contraindications	Radiation dose (pregnancy, repeated scans)	**Pacemaker, ferromagnetic implants, uncooperative patient**

The exam discriminator is the two-line summary: CT is the fast, radiation-based, blood-and-bone modality for the emergency; MRI is the slow, radiation-free, soft-tissue modality for the definitive elective workup that carries the psychiatric yield.

16.3 The MRI sequences, made concrete: what is bright and dark, and why

This is the load-bearing table of the topic. An MRI is not one image; it is a set of sequences, each weighted to make a different tissue property the source of contrast. The examiners want you to state, for a given sequence, what appears bright and what appears dark, and the single physical

reason. Anchor everything to **CSF**: it is the reference tissue that flips brightness across sequences, and reading CSF tells you which sequence you are looking at.

T1-weighted (anatomy)

The anatomy sequence. **Fat is bright, CSF is dark; white matter is brighter than grey matter** (myelin is fat-rich). Grey-white boundaries and gross morphology are crisp, so T1 is the volumetric and structural workhorse (and the sequence on which gadolinium contrast enhances). Memory hook: on T1 the picture looks "anatomical", water is black, and fat is white.

T2-weighted (pathology / water)

The pathology sequence. **Water is bright: CSF is bright, and most pathology (oedema, gliosis, demyelination, tumour, inflammation) is bright** because pathology increases tissue water. Grey matter is brighter than white matter (the reverse of T1). Memory hook: "WW2", *Water is White on T2*; if it is wet or diseased, it lights up.

FLAIR (fluid-attenuated inversion recovery)

A T2 image with the bright CSF signal deliberately nulled (inverted out). **CSF is dark, but pathology stays bright.** This is the trick that makes periventricular and cortical lesions visible: on plain T2 a bright lesion next to bright CSF is camouflaged; on FLAIR the CSF goes black and the lesion stands out. FLAIR is the go-to for white-matter hyperintensities, periventricular MS plaques, and cortical/juxtacortical lesions.

DWI (diffusion-weighted imaging)

The acute-ischaemia sequence. It maps the random (Brownian) motion of water. In acute infarction, cytotoxic oedema restricts water diffusion, so the infarct is **bright on DWI and dark on the ADC map** (restricted diffusion) within minutes to hours, long before CT or conventional MRI changes. "Bright on DWI, dark on ADC" is the signature of acute stroke; it also lights up the abscess core and, classically, cortical ribboning in Creutzfeldt-Jakob disease.

DTI (diffusion tensor imaging)

An extension of diffusion imaging that measures the *direction* of water diffusion. In white-matter tracts water diffuses preferentially along the axon (anisotropic diffusion), quantified as **fractional anisotropy (FA)**. DTI indexes the integrity and myelination of tracts and enables tractography; reduced FA is the standard readout of disrupted connectivity (Kaplan & Sadock 2024).

TISSUE / LESION	T1	T2	FLAIR	DWI (ACUTE)
CSF (ventricles, sulci)	Dark	**Bright**	Dark (suppressed)	Dark
White matter	**Bright (brighter than grey)**	Darker than grey	Intermediate	Intermediate
Grey matter	Intermediate (darker than white)	**Brighter than white**	Intermediate	Intermediate
Fat (scalp, marrow)	**Bright**	Intermediate/bright	Bright	Variable
Oedema / most pathology	Dark	**Bright**	Bright	Variable

TISSUE / LESION	T1	T2	FLAIR	DWI (ACUTE)
White-matter hyperintensity, MS plaque	Dark to iso	Bright	**Bright with CSF nulled (best seen)**	Usually iso
Acute infarct (cytotoxic oedema)	Iso early	Bright (hours later)	Bright	**Bright (restricts within minutes; dark on ADC)**

Read the table by anchoring on CSF: bright CSF means T2, dark CSF with bright lesions means FLAIR, dark CSF with bright fat and bright white matter means T1. The two highest-yield one-liners are "Water is White on T2" and "acute stroke is bright on DWI, dark on ADC".

MNEMONIC

WW2, and "T1 = anatomy, fat white; FLAIR = T2 minus water"

WW2 fixes the pivot: *Water (CSF) is White on T2*. From there T1 is simply the inverse for water (CSF black) and the sequence where *fat is white and white matter is white*, i.e. the anatomy scan. FLAIR is "T2 with the water taken out", so CSF turns black while disease stays bright. DWI is the odd one out and easiest to remember by its job: the acute-stroke sequence.

HOLD THIS

Bright skull means CT (blood and bone, the emergency); dark skull means MRI (soft tissue, the definitive scan). Anchor the sequences on water: Water is White on T2, FLAIR is T2 with the CSF nulled, acute stroke is bright on DWI.

16.4 When to image the psychiatric patient: red flags and the organic workup

Routine structural imaging is *not* indicated for every psychiatric presentation; the yield in an otherwise typical young patient with a classic picture is low. Imaging earns its place when the presentation carries features that raise the pre-test probability of an organic lesion. The examinable trigger list is the **first-episode psychosis red flags** and the broader organic-workup indications.

First-episode psychosis red flags for imaging

Atypical age of onset (very young or new onset in later life), any focal neurological sign, seizures, an abrupt or fluctuating course with clouding of consciousness (suggesting delirium rather than a primary psychosis), headache, rapid cognitive decline, focal or catatonic features, or any finding pointing to a space-occupying, inflammatory, or vascular cause.

Broader organic-workup indications

New cognitive impairment or suspected dementia (structural imaging is part of the standard dementia assessment), new personality change with frontal features, first psychiatric presentation in the elderly, head injury, focal deficit, and treatment-resistant or otherwise unexplained presentations where an occult lesion must be excluded before committing to a primary psychiatric label.

CLINICAL ANCHOR

The governing principle is exclusion, not diagnosis: a scan in psychiatry is ordered to *rule out* the organic mimic (tumour, subdural, demyelination, hydrocephalus, vascular lesion) that would change management, and to support a dementia workup, not to confirm schizophrenia or depression. A normal scan does not exclude a primary psychiatric disorder, and a group-level finding (enlarged ventricles) is never diagnostic in the individual patient.

16.5 Schizophrenia: enlarged ventricles, reduced grey matter, and the hippocampus

The oldest and most robust structural story in psychiatry. The landmark study was Johnstone and colleagues in 1976, who used the then-novel technique of CT and found significantly enlarged lateral ventricles in patients with schizophrenia (Semple & Smyth 2019), reviving a finding first hinted at by pneumoencephalography decades earlier. Modern MRI has confirmed and extended this into a reproducible signature.

Ventricular enlargement

Enlargement of the lateral and third ventricles is the single most replicated structural finding. The large meta-analysis by Haijma and colleagues (2013), pooling over 18,000 subjects, put the increase in ventricular volume at roughly **30%** (Semple & Smyth 2019).

Reduced brain and grey-matter volume

Total brain volume is reduced by about **2.6%** and intracranial volume by about **2%** in the same meta-analysis; the reduced intracranial volume argues that much of the change is neurodevelopmental and present early in life. Grey-matter loss exceeds white-matter loss, and cortical grey matter is thinner, especially in frontal and superior-temporal regions.

Hippocampus and thalamus

Effect sizes were largest for the **hippocampus and thalamus**, both smaller in schizophrenia. Reduced hippocampal volume is among the most consistent regional findings, and smaller superior temporal gyri have been associated specifically with formal thought disorder.

~30%	~2.6%	~2%
LARGER VENTRICULAR VOLUME IN SCHIZOPHRENIA	LOWER TOTAL BRAIN VOLUME	LOWER INTRACRANIAL VOLUME (DEVELOPMENTAL)

The pathology is neurodevelopmental, not neurodegenerative: there is an *absence of gliosis* and no neuronal loss of the degenerative kind, with reductions instead in synaptic and dendritic markers. Findings are broadly similar in antipsychotic-naive and medicated patients, which argues that the core changes are not simply a drug effect, though the contribution of progressive change versus medication over the illness course remains debated (Semple & Smyth 2019). Schizophrenia, in ICD-11, is classified under schizophrenia and other primary psychotic disorders (DSM-5-TR: schizophrenia spectrum and other psychotic disorders); the imaging is a research and exclusion tool, never a diagnostic test.

COMMON TRAP

Do not describe the schizophrenia changes as "atrophy" in the degenerative sense: there is no gliosis and no Alzheimer-type neurodegeneration. The changes are a neurodevelopmental shift in the whole distribution of ventricular and brain volumes, present in part before symptom onset. Equally, ventricular enlargement is a group finding; you cannot diagnose schizophrenia from an individual patient's ventricles.

16.6 Mood disorders: white-matter hyperintensities and hippocampal volume

The two examinable structural themes in mood disorder are **white-matter hyperintensities** (the vascular-depression story) and reduced **hippocampal volume** (the neurotrophic story).

White-matter hyperintensities (WMH)

Hyperintense signals on T2/FLAIR in the **deep and periventricular white matter**, seen in normal ageing but increased in major depression, especially late-onset illness. In depression, greater deep-WMH burden is associated with greater illness severity, poorer treatment response, late onset, apathy and psychomotor retardation, and vascular risk factors (Semple & Smyth 2019). This gave rise to the **vascular depression** hypothesis: that late-life depression with these clinical and radiological features is driven by cerebrovascular disease disrupting mood-regulatory pathways (Aizenstein and colleagues 2011).

Hippocampal volume

Decreased hippocampal volume is a consistent finding in recurrent major depression, more marked with longer and more recurrent illness, and in the elderly it correlates with cognitive deficits. The favoured explanation is the **neurotrophic hypothesis**: chronic stress and cortisol hypersecretion drive neuronal atrophy and downregulate adult hippocampal neurogenesis (Semple & Smyth 2019).

Bipolar disorder and the lithium effect

Volumetric findings in bipolar disorder are inconsistent and heavily confounded by illness stage and medication. The examinable nuance is lithium: in bipolar patients *not* taking lithium, hippocampal volumes are lower as in recurrent depression, but this reduction is **reversed in patients taking lithium**, consistent with lithium's neurotrophic and neuroprotective action (Hallahan and colleagues 2011). There is also evidence of cerebral volume reduction over the course of bipolar illness and DTI abnormalities in frontal and temporal white-matter tracts.

Depressive disorders sit under mood disorders in ICD-11 (DSM-5-TR: depressive disorders); bipolar type I and II are the bipolar and related disorders. As in schizophrenia, none of these findings is diagnostic; they are group-level correlates and, in the WMH case, a marker that flags a vascular subtype with prognostic weight.

PEARL

Two clean mood-disorder pairings for the exam: *white-matter hyperintensities to vascular depression* (late-onset, poor response, vascular risk) and *reduced hippocampus to the neurotrophic/cortisol hypothesis*. The lithium point is the high-value discriminator: lithium *reverses* the hippocampal volume loss in bipolar disorder, a rare instance where a drug's structural effect is neuroprotective rather than a confound to explain away.

16.7 Dementia subtypes: the atrophy pattern is the diagnosis

In dementia, structural imaging shifts from exclusion to positive pattern recognition: *where* the atrophy sits discriminates the subtype, and the regional pattern is the examinable content. Imaging is a formal part of the dementia workup, both to exclude reversible causes and to read the atrophy signature.

DEMENTIA	STRUCTURAL SIGNATURE	DISCRIMINATING FEATURE
Alzheimer disease	Medial-temporal-lobe atrophy (hippocampus, entorhinal cortex), later temporoparietal and generalised cortical atrophy with ventricular enlargement	**Early medial-temporal (hippocampal) atrophy is the imaging hallmark; disproportionate hippocampal loss out of keeping with age**
Frontotemporal dementia	Focal, often asymmetric atrophy of the frontal and anterior temporal lobes	**Frontal / anterior-temporal atrophy with relative posterior sparing; "knife-edge" gyri; matches behavioural or language onset**
Vascular dementia	Multiple infarcts, extensive deep and periventricular white-matter change (leukoaraiosis), lacunes	**Vascular lesion load and strategic infarcts rather than a single atrophy focus**
Dementia with Lewy bodies	Relative preservation of the medial temporal lobe (hippocampus) compared with Alzheimer disease	**Medial temporal lobe relatively spared, unlike AD (a useful negative discriminator)**
Late/advanced or unspecified	Generalised cortical atrophy with widened sulci and enlarged ventricles	Non-specific; must be read against age and clinical picture

The single highest-yield contrast is Alzheimer disease (early medial-temporal/hippocampal atrophy) versus frontotemporal dementia (frontal and anterior-temporal atrophy) versus dementia with Lewy bodies (medial temporal lobe relatively preserved). Generalised atrophy alone is non-specific and expected with age.

RULE **The atrophy pattern is the diagnosis: medial-temporal for Alzheimer, frontal/anterior-temporal for FTD, medial-temporal spared in dementia with Lewy bodies.**

COMMON TRAP

Generalised cortical atrophy and widened ventricles are common in normal ageing and cannot, by themselves, diagnose dementia: the atrophy must be disproportionate to age and matched to the clinical syndrome. The classic error is over-reading age-appropriate atrophy as pathology, or missing the specificity of a *focal* pattern (medial temporal for AD, frontal for FTD) by calling everything "generalised atrophy".

16.8 Normal-pressure hydrocephalus and the reversible mimic

The reason you scan the cognitively declining patient. **Normal-pressure hydrocephalus (NPH)** is the flagship reversible mimic that imaging catches. The clinical triad is the classic examinable trio: **gait apraxia** (typically first and most prominent, a magnetic, shuffling gait), **cognitive impairment**, and **urinary incontinence** ("wet, wobbly, and wacky"). The structural

signature is **ventricular enlargement out of proportion to sulcal (cortical) atrophy**: the ventricles are markedly dilated but the surface sulci are not correspondingly widened, which is the key that separates NPH from the ex-vacuo ventricular enlargement of generalised atrophy, where ventricles and sulci enlarge together.

CLINICAL ANCHOR

NPH matters because it is potentially treatable by CSF shunting, and gait typically responds best. The imaging discriminator is the mismatch: *big ventricles, normal-sized sulci* in NPH, versus *big ventricles and wide sulci together* in atrophy. Miss the mismatch and a reversible cause of the "dementia with gait disturbance" presentation is lost.

TRAP Big ventricles alone do not mean NPH. NPH is ventricles enlarged *out of proportion* to the sulci; when sulci widen too, it is ex-vacuo atrophy.

16.9 Organic mimics on structural imaging

Beyond NPH, a defined set of structural lesions can present with psychiatric or cognitive symptoms and is the reason the scan is ordered. Each has a characteristic look that the examiners may show.

Space-occupying lesions

Frontal and temporal tumours (gliomas, meningiomas) can present with personality change, apathy, disinhibition, or new psychosis before any focal sign; a mass with surrounding vasogenic oedema (bright on T2/FLAIR) and mass effect is the picture.

Chronic subdural haematoma

A crescent-shaped extra-axial collection over the convexity in an older or alcohol-dependent patient, presenting as fluctuating confusion or "dementia"; its density on CT evolves from hyperdense (acute) to isodense to hypodense (chronic).

Demyelination (multiple sclerosis)

Periventricular and juxtacortical FLAIR-bright ovoid white-matter plaques, classically presenting with mood disorder, euphoria, or cognitive change; FLAIR is the sequence that makes the periventricular lesions visible.

Vascular lesions

Strategic infarcts (thalamic, caudate) and extensive small-vessel white-matter disease can produce cognitive and mood syndromes; the vascular-depression and vascular-dementia links above are the psychiatric face of this.

Other

Herpes and limbic encephalitis (medial temporal T2/FLAIR signal), Wilson disease (basal-ganglia change), and the atrophy of chronic alcohol use and thiamine deficiency each have a structural face worth recognising as a mimic.

16.10 Voxel-based morphometry and the quantitative structural toolkit

The disorder findings above increasingly come not from a radiologist's eye on a single film but from automated group analysis of high-resolution MRI. Three methods are examinable.

Voxel-based morphometry (VBM)

An automated, whole-brain method that identifies voxels where grey-matter (or white-matter) volume or concentration differs between groups, inferred from signal-intensity differences on structural MRI (Kaplan & Sadock 2024). Its strength is that it is unbiased by prior region-of-interest choice: it surveys the whole brain and localises where differences fall, which is how the distributed grey-matter reductions of schizophrenia were mapped.

Volumetric MRI (vMRI)

Automated or semi-automated segmentation of specified regions of interest to obtain volumes, cortical thickness, and shape indices; the method behind the hippocampal and ventricular volume figures (Kaplan & Sadock 2024).

Diffusion tensor imaging (DTI)

Indexes white-matter tract integrity and myelination through anisotropic diffusion (fractional anisotropy), enabling tractography; reduced FA is the standard marker of disrupted connectivity in schizophrenia and mood disorder (Kaplan & Sadock 2024).

PEARL

Keep the toolkit paired to its output: *VBM* asks "where in the whole brain does grey matter differ?"; *vMRI* asks "how big is this specific structure?"; *DTI/FA* asks "how intact is this white-matter tract?". These three are how a modern structural paper turns anatomy into a group-level finding, and each is fair game as a short-note stem.

16.11 Cross-references to the Functional Neuroanatomy & Neurophysiology notes and the one-line synthesis

This topic deliberately does not re-teach the structures; it reads findings off the anatomy the Functional Neuroanatomy & Neurophysiology notes established. The **hippocampus and medial temporal lobe** (the Functional Neuroanatomy & Neurophysiology notes limbic system) are the shared site across schizophrenia, depression, and Alzheimer disease. The **lateral and third ventricles** (the Functional Neuroanatomy & Neurophysiology notes ventricular system) are the schizophrenia and NPH readout. The **frontal and temporal cortex** (the Functional Neuroanatomy & Neurophysiology notes lobar anatomy) carry the frontotemporal-dementia and thought-disorder signatures. The **white-matter tracts** (the Functional Neuroanatomy & Neurophysiology notes connectivity) are what DTI and the WMH story index.

MNEMONIC

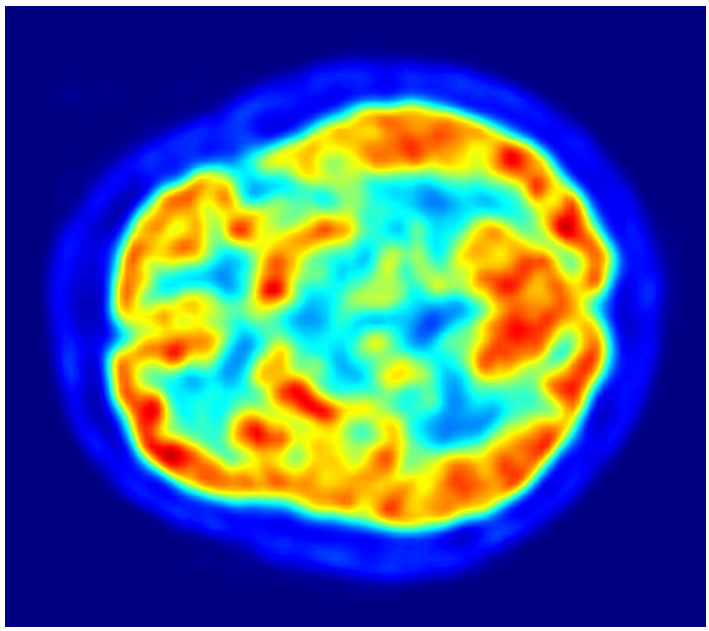
"Ventricles up, hippocampus down, white matter bright, atrophy where the syndrome lives"

The whole topic in one line. *Ventricles up*: schizophrenia (and NPH, but with spared sulci). *Hippocampus down*: schizophrenia, recurrent depression, and Alzheimer disease. *White matter bright*: FLAIR hyperintensities of vascular depression and demyelination. *Atrophy where the syndrome lives*: medial temporal for AD, frontal for FTD. Underneath it all sits the physics: CT for blood and bone in the emergency, MRI with "Water is White on T2" for the soft-tissue answer.

17 · Functional imaging (fMRI/PET/SPECT) principles and findings

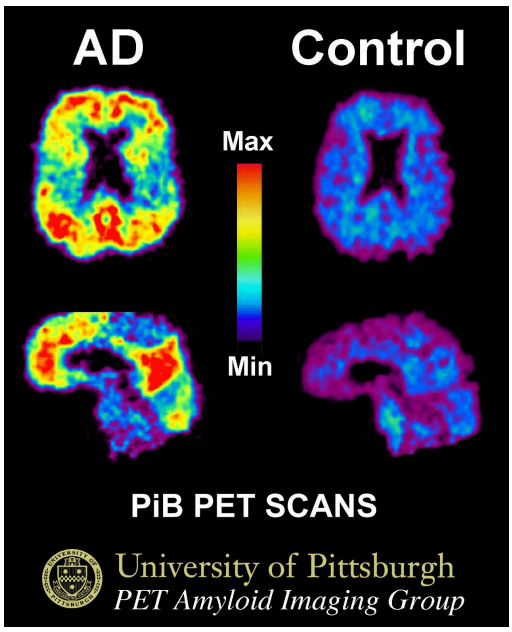
Functional imaging is where the molecular material of this paper meets the phenomenology of the clinical papers, and examiners exploit that junction relentlessly. Structural imaging shows what the brain *is*; functional imaging shows what the brain *is doing*, either through a haemodynamic surrogate for neural activity (**fMRI**) or through a radiotracer that reports metabolism, perfusion, or the density and occupancy of a named receptor (**PET and SPECT**). The single most useful mental move for the exam is to keep two questions apart: *what does the modality physically measure*, and *which finding maps to which syndrome*. Almost every Step-5 discrimination item is really the second question in disguise, "here is an imaging signature, name the disorder", and it rewards a clean lookup table more than any amount of prose.

Exam framing. Very little of this is clinical-grade. With three exceptions (FDG-PET and amyloid/tau PET in the dementia work-up, D2 occupancy PET as a pharmacological reference, and DAT-SPECT for parkinsonian syndromes), functional imaging in psychiatry remains a *research and group-level* tool: it separates cohorts, not individual patients, and no scan diagnoses schizophrenia, depression, or OCD. Say this explicitly in a viva before you recite findings; it is the discriminating maturity examiners look for. Cross-reference the the Functional Neuroanatomy & Neurophysiology notes material on resting-state networks: the default mode, salience, and central executive networks are the substrate on which most of the disorder findings below are now framed.



FDG-PET: Jens Maus, public domain, via Wikimedia Commons

Fig 2.15 A normal FDG-PET slice. 18F-fluorodeoxyglucose maps regional glucose metabolism, brightest in grey-matter cortex and deep grey. The *pattern of hypometabolism* then localises disease: temporoparietal in Alzheimer disease, frontal in frontotemporal dementia, occipital in dementia with Lewy bodies. In schizophrenia, reduced frontal activation on cognitive tasks is the hypofrontality finding.



PiB amyloid PET: Klunkwe, CC BY-SA 3.0, via Wikimedia Commons

Fig 2.16 Amyloid PET with Pittsburgh compound B. The Alzheimer brain (left) retains tracer diffusely across the cortex; the control (right) shows only non-specific white-matter signal. Amyloid and tau PET are molecular markers that can support an Alzheimer diagnosis in a living patient, distinct from the FDG metabolic map and from structural atrophy.

17.1 BOLD fMRI: what the signal actually is

Functional MRI does not measure neuronal firing directly. It measures the **blood-oxygen-level-dependent (BOLD)** signal, an indirect haemodynamic proxy discovered by Ogawa in 1990 (Kaplan & Sadock 2024).

The physical basis

Deoxyhaemoglobin is *paramagnetic* and distorts the local magnetic field, shortening T2*; oxyhaemoglobin is diamagnetic and does not. When a region becomes active, local blood flow rises out of proportion to the oxygen actually extracted, so the venous blood becomes *relatively more oxygenated*. The fall in deoxyhaemoglobin reduces field distortion and the T2*-weighted signal **rises**. The BOLD signal is therefore a report on the neurovascular coupling that follows neural activity, not on the spikes themselves.

Neurovascular coupling

BOLD tracks **local field potentials** (synaptic and dendritic input) more faithfully than output spiking, which matters when interpreting a "hyperactivity" finding: it may reflect greater afferent processing rather than more firing.

The haemodynamic response function

The signal lags the neural event by roughly 4 to 6 seconds and is sluggish, giving fMRI excellent *spatial* resolution (millimetres) but poor *temporal* resolution, the mirror image of EEG. This is the classic paired contrast in exams.

Task versus rest. Task-based fMRI contrasts BOLD during a cognitive or emotional challenge (an n-back for working memory, fearful faces for the amygdala) against a baseline. **Resting-state fMRI** requires no task: it measures spontaneous low-frequency (below 0.1 Hz) BOLD

fluctuations and infers **functional connectivity** from the correlation of these fluctuations between regions. Resting-state work is the engine behind the network models below and needs no patient cooperation, a practical advantage in psychosis and dementia.

COMMON TRAP

BOLD is a signal about *oxygenation*, and the counter-intuitive point examiners test is the sign: an active region ends up with *less* deoxyhaemoglobin and therefore a *higher* T2* signal, because the flow response overshoots the metabolic demand. Do not say activity "uses up oxygen and lowers the signal"; the net effect is the reverse.

17.2 PET and SPECT: three things a radiotracer can report

Both PET and SPECT inject a radiolabelled tracer and image where it accumulates; the difference is physics. **PET** uses positron-emitters (fluorine-18, carbon-11, oxygen-15) and detects the paired 511 keV photons of annihilation, giving higher resolution and quantification. **SPECT** uses single-photon emitters (technetium-99m, iodine-123), is cheaper and more available, but has lower resolution. What the tracer reports depends entirely on which tracer you choose (Kaplan & Sadock 2024).

WHAT IS MEASURED	REPRESENTATIVE TRACER	READS OUT
Glucose metabolism	**[18F]-FDG (fluorodeoxyglucose)**	Regional metabolic rate; the workhorse of dementia imaging
Cerebral perfusion	[99mTc]-HMPAO, [99mTc]-ECD (SPECT); [15O]-water (PET)	Regional blood flow, a proxy for activity
Presynaptic dopamine synthesis	**[18F]-FDOPA (FDOPA-PET)**	Dopamine synthesis and storage capacity in striatum
Presynaptic dopamine transporter	[123I]-FP-CIT (DaTSCAN, SPECT)	Nigrostriatal terminal integrity; parkinsonian syndromes
Postsynaptic receptor density / occupancy	[11C]-raclopride, [123I]-IBZM (D2)	Available D2 receptors and drug occupancy
Amyloid burden	**[11C]-PIB, [18F]-florbetapir/flutemetamol**	Cortical fibrillar amyloid-beta
Tau burden	[18F]-flortaucipir	Neurofibrillary tangle load

The tracer decides the question. The discriminator to fix: FDG reports metabolism, FDOPA reports presynaptic dopamine *synthesis*, raclopride/IBZM report postsynaptic D2 *availability and occupancy*, and DaTSCAN reports the presynaptic *transporter*. Confusing FDOPA (synthesis) with raclopride (receptor) is a standard trap.

PEARL

The two axes to keep straight are *presynaptic versus postsynaptic* and *synthesis versus transporter versus receptor*. FDOPA and DaTSCAN are presynaptic (synthesis capacity and transporter respectively); raclopride and IBZM are postsynaptic (D2 availability). This single grid answers most molecular-imaging single-best-answer items.

TRAP Schizophrenia does not show raised D2 receptors on PET. The durable finding is raised *presynaptic* dopamine synthesis on FDOPA-PET; do not swap FDOPA (synthesis) for raclopride (receptor).

17.3 Receptor occupancy and the therapeutic window

The most clinically anchored use of PET in psychiatry is measuring how much of a receptor pool a drug occupies. By comparing tracer binding before and after a drug, PET quantifies **receptor occupancy** as a percentage, and this reshaped antipsychotic dosing (Kapur 2000).

The D2 occupancy window

Kapur's double-blind PET work in first-episode schizophrenia established that antipsychotic response and side effects track striatal D2 occupancy on a threshold basis: clinical response emerges above roughly **65%** occupancy, while **extrapyramidal side effects** rise steeply above about **80%**. The practical *therapeutic window* is therefore approximately 65 to 80% D2 occupancy, and **hyperprolactinaemia** appears at the upper end (around 72% and above). This is the single most examinable number in the whole topic.

SERT occupancy

Antidepressant SSRIs occupy about 80% of the serotonin transporter at standard clinical doses, an occupancy reached at the bottom of the dose range, which is why pushing SSRI doses higher rarely adds efficacy (Maudsley Prescribing Guidelines).

The clozapine exception

Clozapine is antipsychotic at strikingly *low* D2 occupancy (often below 60%), one of the arguments that its efficacy in treatment resistance is not primarily D2-mediated. Occupancy imaging is the evidence base for that claim.

CLINICAL ANCHOR

The 65 to 80% window explains a common ward error: escalating an antipsychotic dose in a non-responder who is already at 80% occupancy adds no benefit and only buys EPS and prolactinaemia. If a patient is fully occupied and still psychotic, the problem is unlikely to be more D2 blockade; consider adherence, the non-dopaminergic (glutamatergic) subgroup, and clozapine. Occupancy plateaus while dose keeps climbing, the pharmacological argument against reflexive dose increases.

HOLD THIS

The antipsychotic window is roughly 65 to 80% striatal D2 occupancy: response above 65%, EPS above 80%. Escalating a fully-occupied non-responder buys only EPS and prolactinaemia.

65%	80%	~80%
D2 OCCUPANCY FOR ANTIPSYCHOTIC RESPONSE	D2 OCCUPANCY WHERE EPS RISES	SERT OCCUPANCY AT STANDARD SSRI DOSE

17.4 Resting-state networks and the triple-network model

Resting-state connectivity reframed psychiatric findings from "which region" to "which network", and one framework recurs across disorders (Kaplan & Sadock 2024; Menon 2011).

Default mode network (DMN)

Precuneus/posterior cingulate, medial prefrontal cortex, and inferior parietal and lateral temporal regions. It is *more* active at rest and during self-referential thought, and deactivates during external tasks. Linked to rumination and self-focus.

Salience network

Anterior insula and dorsal anterior cingulate cortex. Detects behaviourally relevant stimuli and switches control between the DMN and the executive network.

Central executive network

Dorsolateral prefrontal cortex and posterior parietal cortex. Supports working memory and goal-directed cognition.

The triple-network model. Menon's synthesis holds that many disorders share a common architecture of dysfunction: aberrant salience-network gating fails to toggle correctly between an over-engaged DMN (self-referential, ruminative) and an under-engaged executive network. In depression this reads as DMN hyperconnectivity and rumination; in schizophrenia as failure to deactivate the DMN with a hyperactive salience system (the imaging correlate of aberrant salience). This is a research model, but it is the current language of the field and worth naming.

17.5 Schizophrenia: hypofrontality, the striatal window, and presynaptic dopamine

Schizophrenia carries three separable imaging signatures across three modalities, and the exam wants all three held apart (Companion to Psychiatric Studies; Howes & Kapur 2009).

- **Activation fMRI/perfusion, hypofrontality.** Reduced **dorsolateral prefrontal cortex** activation during executive tasks (the Wisconsin Card Sort, n-back), the classic *hypofrontality*, correlating with negative and cognitive symptoms. It is task-dependent and may follow an initial hyperactivity; a resting scan can look normal, which is why the finding is elicited with a cognitive challenge.
- **Postsynaptic D2 (raclopride/IBZM PET/SPECT).** The therapeutic window sits at **65 to 80% striatal D2 occupancy** (see 17.3). Baseline postsynaptic D2 density is *not* reliably raised once antipsychotic exposure is accounted for, which was the downfall of the crude receptor hypothesis.
- **Presynaptic dopamine (FDOPA-PET).** The robust, replicated positive finding is *elevated presynaptic striatal dopamine synthesis capacity*, present even in the prodrome and in unmedicated patients. This is the imaging cornerstone of the version III "final common pathway" hypothesis: the lesion is presynaptic, not at the receptor.

COMMON TRAP

Do not answer "schizophrenia shows increased D2 receptors on PET". The durable finding is raised *presynaptic dopamine synthesis and release capacity* on FDOPA-PET; postsynaptic D2 density is at best marginally and inconsistently elevated. FDOPA (synthesis) versus raclopride (receptor) is exactly the presynaptic/postsynaptic discrimination from 17.2, applied to the highest-yield disorder.

17.6 Depression: subgenual cingulate and prefrontal hypoactivity

Mood disorder imaging centres on a limbic-cortical imbalance, and one region has become the emblematic node (Kaplan & Sadock 2024; Mayberg 1997).

Subgenual anterior cingulate cortex (sgACC, Brodmann area 25)

Hyperactivity here (raised resting metabolism on FDG-PET, raised BOLD) is the signature finding of the depressed state, normalising with recovery. It is Mayberg's rationale for deep brain stimulation of area 25 in treatment-resistant depression, and appears across FDG-PET, task fMRI, and resting EEG, a rare convergence.

Dorsolateral prefrontal cortex (DLPFC)

Reduced dorsolateral prefrontal activity, the correlate of psychomotor retardation and cognitive slowing. The left DLPFC is the target of therapeutic repetitive TMS.

Amygdala

Exaggerated amygdala response to negative emotional stimuli (fearful faces), reflecting a negative processing bias that predates and predicts response to treatment.

The circuit summary. Depression reads as a *hyperactive ventral/limbic compartment* (subgenual cingulate, amygdala) with a *hypoactive dorsal/cortical compartment* (DLPFC), and treatments, whether SSRI, TMS, or DBS, act to rebalance the two. This dorsal-down, ventral-up shorthand is highly examinable.

MNEMONIC

"Ventral UP, Dorsal DOWN"

In depression the **ventral** limbic node (subgenual cingulate/BA25, amygdala) is **up** (hypermetabolic), and the **dorsal** cortical node (DLPFC) is **down** (hypoactive). Treatments push the balance back the other way. If you can only remember one region, remember subgenual cingulate hyperactivity.

17.7 Bipolar disorder: amygdala up, prefrontal down

Bipolar imaging shares the amygdala theme with unipolar depression but is defined by a *frontolimbic dysconnection* that is present across mood states (New Oxford Textbook of Psychiatry; Strakowski 2012).

- **Amygdala hyperactivity.** Heightened amygdala response to emotional (especially facial) stimuli, more state-independent than in unipolar depression, and a candidate trait marker.
- **Prefrontal (especially ventrolateral/ventromedial) hypoactivity.** Reduced ventral prefrontal engagement, read as failure of top-down cortical control over limbic drive, the imaging correlate of affective instability and impulsivity.
- **Reduced VLPFC-amygdala connectivity.** Weakened functional coupling between the medial/ventrolateral prefrontal cortex and the amygdala distinguishes the bipolar from the unipolar depressed brain in some studies.

Discriminator. The bipolar signature is best given as "amygdala hyperactivity with prefrontal hypoactivity and a failure of prefrontal-limbic modulation", which contrasts with depression's more specific subgenual-cingulate emphasis. All of this is research-grade; no scan diagnoses bipolar disorder.

17.8 OCD: the hyperactive cortico-striato-thalamo-cortical loop

OCD has the tightest, most reproducible circuit signature in the whole topic, and it is a favourite because the same loop explains the imaging, the surgery, and the treatment response (Kaplan & Sadock 2024; Saxena 1998).

The CSTC loop

A hyperactive **cortico-striato-thalamo-cortical (CSTC) circuit**: the *orbitofrontal cortex*, the *anterior cingulate cortex*, the *caudate nucleus* (head), and the *thalamus* show raised resting metabolism on FDG-PET. The model is a failure of the striatal "brake", so an excitatory orbitofronto-thalamic drive runs unchecked, generating the intrusive urge.

Treatment normalisation

The distinguishing feature is that this hypermetabolism *normalises* with successful treatment, whether SSRI or cognitive-behavioural therapy, and the degree of orbitofrontal/caudate reduction predicts response. Few functional findings in psychiatry are so cleanly state-dependent.

> **CLINICAL ANCHOR**
>
> The CSTC model is the rationale for neurosurgery and neuromodulation in refractory OCD: anterior *cingulotomy* and *capsulotomy*, and deep brain stimulation of the ventral capsule/ventral striatum, all interrupt the same overactive loop the imaging identifies. Symptom relief tracks reduced orbitofrontal-caudate metabolism, closing the loop between the scan and the intervention.

17.9 Anxiety and PTSD: amygdala up, ventromedial prefrontal down

The fear-circuit disorders share a two-node signature that is the direct imaging translation of extinction failure (Kaplan & Sadock 2024; Rauch 2006).

- **Amygdala hyperactivity.** Exaggerated amygdala response to threat and trauma cues, the substrate of hypervigilance and the exaggerated startle of PTSD, seen across anxiety disorders.
- **Ventromedial prefrontal cortex hypoactivity.** Reduced **vmPFC** activity, the region that normally exerts top-down inhibitory control over the amygdala and mediates extinction of conditioned fear. Its underactivity leaves the amygdala disinhibited.
- **Hippocampal changes (PTSD).** Reduced hippocampal volume and function, linked to contextual (mis)appraisal of safe situations as dangerous. This is the finding most specific to PTSD within the group.

Discriminator. The clean pairing to hold is *amygdala hyper- plus vmPFC hypoactivity* (failed prefrontal inhibition of fear), which recurs for panic, social anxiety, specific phobia, and PTSD. PTSD adds the hippocampal element.

COMMON TRAP

Depression, bipolar, anxiety, and PTSD all feature amygdala hyperactivity, so "amygdala hyperactivity" alone cannot discriminate them. The *partner cortical region* is the discriminator: subgenual cingulate for unipolar depression, ventrolateral/ventromedial prefrontal for bipolar, and specifically the *ventromedial* prefrontal (extinction) node plus hippocampus for anxiety/PTSD. Always name the second node.

17.10 Dementia subtypes: the FDG-PET metabolic map and the ATN framework

This is the one area where functional imaging is genuinely **clinical-grade** and diagnostically deployed. FDG-PET distinguishes the dementias by the *location* of hypometabolism, and molecular PET now anchors the biological diagnosis of Alzheimer disease (Kaplan & Sadock 2024; Stahl 2021).

DEMENTIA	FDG-PET HYPOMETABOLISM PATTERN	MOLECULAR / DISTINGUISHING MARKER
Alzheimer disease	**Temporoparietal and posterior cingulate/precuneus, later frontal**	Amyloid PET positive; tau PET in medial temporal to neocortex
Frontotemporal dementia	**Frontal and anterior temporal (asymmetric)**	Amyloid PET typically negative; helps separate from AD
Dementia with Lewy bodies	**Occipital hypometabolism; posterior cingulate "island sign" spared**	Reduced DaTSCAN uptake (nigrostriatal loss); MIBG cardiac
Vascular dementia	Patchy, multifocal, following vascular territories	Structural infarcts on MRI

The metabolic map of the dementias. The three highest-yield discriminators: AD is temporoparietal, FTD is frontotemporal, and DLB is occipital with the cingulate island sign (relative sparing of posterior cingulate against reduced occipital and precuneus metabolism). Amyloid-negative PET argues against AD.

The A/T/N biomarker framework

Alzheimer biology is now defined biologically: **A** (amyloid, by amyloid PET or CSF Abeta42/Abeta40), **T** (tau, by tau PET or CSF phospho-tau), and **N** (neurodegeneration, by FDG-PET, structural MRI, or CSF total tau). FDG-PET is an *N* marker, not specific to AD; amyloid and tau PET are the specific molecular markers.

DLB and DaTSCAN

Reduced striatal dopamine transporter uptake on *DaTSCAN* (SPECT) is a supportive DLB criterion, reflecting nigrostriatal degeneration and separating DLB from AD, where DaTSCAN is normal.

Currency (through 2026)

The *anti-amyloid monoclonal antibodies* (lecanemab, donanemab) require *amyloid PET or CSF confirmation of amyloid positivity* before treatment, so molecular imaging has moved from research tool to a gatekeeper for disease-modifying therapy, and treatment response is now monitored by falling amyloid PET signal.

PEARL

The **cingulate island sign** is the DLB pearl: on FDG-PET the posterior cingulate is *relatively preserved* (an "island") against surrounding occipital and precuneus hypometabolism, the reverse of AD, where the posterior cingulate is among the first to fail. Occipital hypometabolism plus a preserved cingulate island points to Lewy bodies.

17.11 ADHD: fronto-striatal hypoactivation

ADHD imaging maps onto the dopaminergic hypofunction model from the dopamine topic (Kaplan & Sadock 2024; Cortese 2012).

- **Fronto-striatal hypoactivation.** Reduced activation of the *prefrontal cortex* (especially inferior frontal and dorsolateral) and the *striatum* during inhibitory-control and attention tasks (go/no-go, stop-signal), the correlate of impaired response inhibition and executive control.
- **Fronto-parietal and ventral attention networks.** Under-recruitment of the networks that sustain and reorient attention, with failure to deactivate the default mode network during tasks (DMN intrusion, linked to lapses of attention).
- **Stimulant normalisation.** Methylphenidate and amphetamine tend to *increase* the deficient fronto-striatal activation toward control levels, consistent with raising synaptic dopamine and noradrenaline.

Grade. Research-only. There is no imaging diagnosis of ADHD, and a scan cannot confirm or exclude it in an individual; the diagnosis remains clinical.

17.12 The finding-to-syndrome discrimination table

This is the Step-5 anchor for the whole topic: given an imaging signature, name the syndrome. Read it in both directions, and note the clinical grade in the final column.

IMAGING SIGNATURE	MODALITY	SYNDROME	GRADE
Hypofrontality (DLPFC) on activation	Task fMRI / perfusion SPECT	Schizophrenia (negative/cognitive symptoms)	Research
Raised presynaptic striatal dopamine synthesis	FDOPA-PET	Schizophrenia (final common pathway)	Research
65 to 80% striatal D2 occupancy = therapeutic window	Raclopride/IBZM PET-SPECT	Antipsychotic dosing reference	**Clinical (pharmacology)**
Subgenual anterior cingulate (BA25) hyperactivity	FDG-PET / fMRI	Major depression	Research
Reduced dorsolateral prefrontal activity	Task fMRI	Major depression (retardation)	Research

IMAGING SIGNATURE	MODALITY	SYNDROME	GRADE
Amygdala hyper- + prefrontal hypoactivity	Task fMRI	Bipolar disorder	Research
Hyperactive orbitofrontal-caudate-thalamus (CSTC), normalises with treatment	FDG-PET / fMRI	OCD	Research
Amygdala hyper- + ventromedial prefrontal hypoactivity (± small hippocampus)	Task fMRI	Anxiety disorders / PTSD	Research
Temporoparietal + posterior cingulate hypometabolism	FDG-PET	Alzheimer disease	**Clinical**
Frontal + anterior temporal hypometabolism	FDG-PET	Frontotemporal dementia	**Clinical**
Occipital hypometabolism + cingulate island sign; low DaTSCAN	FDG-PET / DaTSCAN	Dementia with Lewy bodies	**Clinical**
Cortical amyloid tracer retention	Amyloid PET	Alzheimer disease (gates anti-amyloid mAbs)	**Clinical**
Fronto-striatal hypoactivation on inhibitory tasks	Task fMRI	ADHD	Research

The master discrimination grid. When two syndromes share amygdala hyperactivity, the partner cortical node discriminates them: subgenual cingulate (unipolar depression), ventrolateral prefrontal (bipolar), ventromedial prefrontal plus hippocampus (anxiety/PTSD). The clinical-grade rows (D2 occupancy, the three dementia FDG patterns, amyloid PET) are the only ones used in individual patients.

INDIA

Functional and molecular imaging remain scarce and expensive in Indian practice: PET is confined to metropolitan tertiary centres, and FDOPA, amyloid, tau, and DaTSCAN tracers are rarely available or affordable outside research and a handful of private centres. The exam-relevant consequence is that the dementia work-up in most Indian settings still leans on clinical criteria plus structural MRI, with FDG-PET or DaTSCAN reserved for genuinely ambiguous cases (AD versus FTD, or DLB versus AD). Know the findings for the exam, but frame their availability realistically in a viva.

Basic psychopharmacology

18 · Pharmacokinetics (ADME)

What the body does to the drug. Pharmacokinetics is the mirror-image of pharmacodynamics: dynamics is what the drug does to the body, kinetics is what the body does to the drug. Every psychotropic decision you make, the dose, the interval, whether to load, when to check a level, whether to halve it in the elderly, is a kinetic decision. The four processes are packaged in one acronym, **ADME** (absorption, distribution, metabolism, excretion), and the exam rewards you for knowing not just the definitions but the three or four equations that tie them together and the handful of psychiatric drugs where getting the kinetics wrong is dangerous.

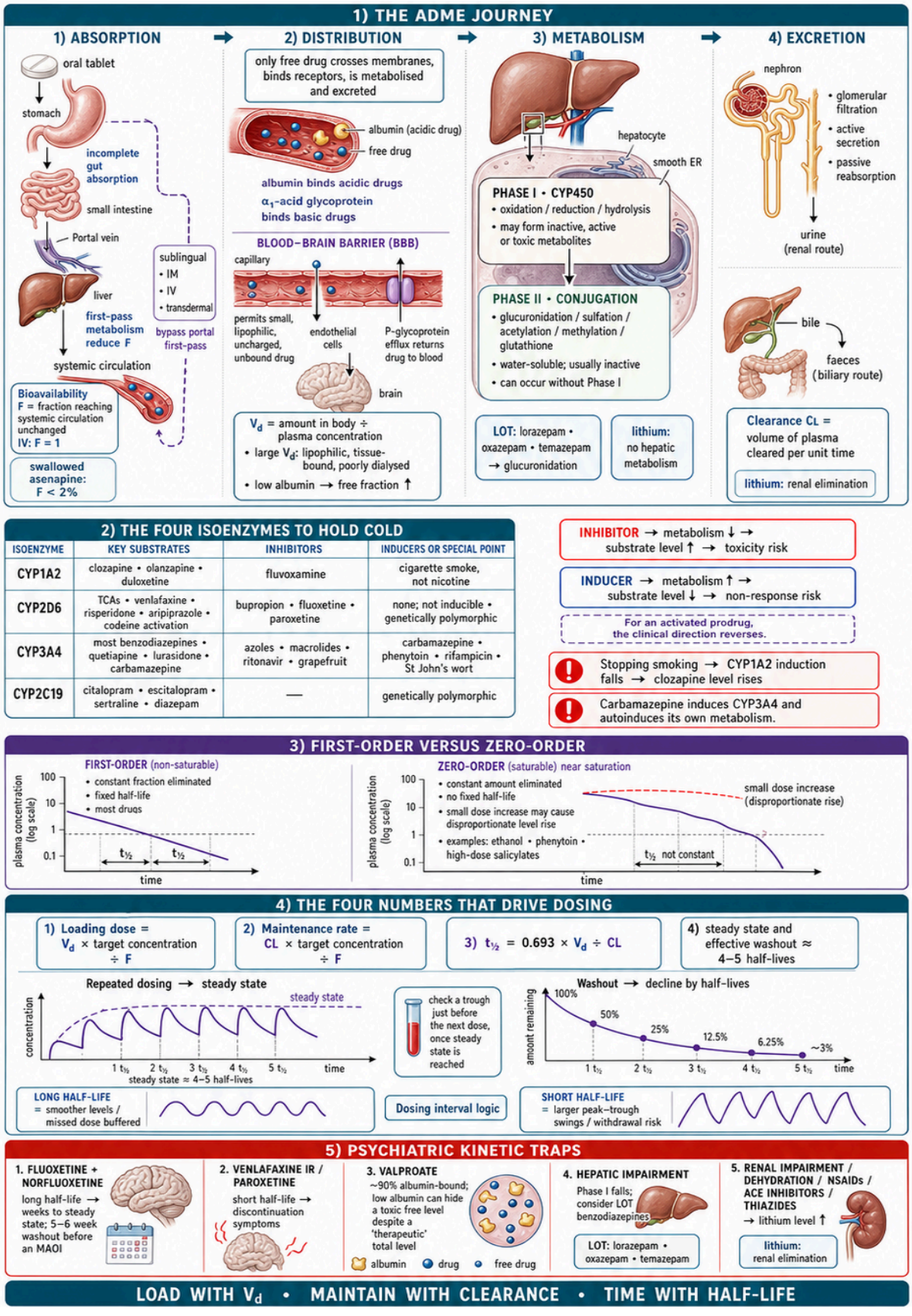


Fig 2.17 ADME and CYP450: the journey of a psychotropic.

Frame the whole topic as a journey of a single molecule (Kaplan & Sadock 2024). It is swallowed and must survive the gut and the first pass through the liver to reach the blood (absorption); it is

carried by plasma proteins and must be lipophilic enough to cross the blood-brain barrier to reach its target (distribution); the liver dismantles it in two phases (metabolism); and the kidney clears the water-soluble remains (excretion). Absorption and distribution set how fast and how much drug reaches the brain; metabolism and excretion set how long it stays and therefore the dosing interval. The one number that governs steady state, drug interactions and toxicity monitoring all at once is the **half-life**, so build toward it.

18.1 Absorption and the two things that erode oral dose

Bioavailability is the survivors. **Bioavailability (F)** is the fraction of an administered dose that reaches the systemic circulation in unchanged form (StatPearls 2023). Intravenous dosing is the reference: F is 1.0 (100%) by definition, because the drug is placed directly into the blood. Everything given by any other route is measured against that IV standard, quantified as the ratio of the areas under the plasma concentration-time curves (AUC-oral divided by AUC-IV). Two hurdles cut F for an oral psychotropic: incomplete absorption across the gut wall, and **first-pass metabolism**.

First-pass (presystemic) metabolism is the extraction of drug by the gut wall and, chiefly, the liver before it ever reaches the systemic circulation, because the entire venous drainage of the gut passes through the portal vein into the liver first (Tripathi/KDT 2019). A drug with heavy first-pass metabolism (the classic psychiatric example being the older tricyclics and beta-blockers such as propranolol) has a low and highly variable oral F, so oral and parenteral doses differ markedly and interindividual variation is large. Bypassing first-pass is precisely why some routes matter clinically: sublingual (asenapine, buprenorphine), intramuscular, intravenous and transdermal all skip the portal circulation.

> **CLINICAL ANCHOR**
>
> Route choice in psychiatry is a bioavailability decision. **Asenapine** is given sublingually because its oral (swallowed) bioavailability is under 2% from near-total first-pass metabolism, so a swallowed tablet is inert. Long-acting intramuscular antipsychotic depots deliberately trade a slow, complete absorption for months of steady levels. Intranasal **esketamine** is chosen to bypass hepatic first-pass and give rapid CNS entry.

RULE **Sublingual, intramuscular, intravenous and transdermal routes exist to bypass first-pass metabolism.** Swallowed asenapine is inert (oral bioavailability under 2%).

18.2 Order of kinetics: first-order versus zero-order, and why it is examined

The rate at which a drug is eliminated defines its kinetics, and the distinction is high-yield because a few dangerous psychiatric drugs are the exceptions. In **first-order kinetics** a constant *fraction* of the drug is eliminated per unit time; the absolute amount cleared is proportional to plasma concentration, so the half-life is constant regardless of dose. This is the ordinary case for most drugs. In **zero-order (saturation) kinetics** a constant *amount* is eliminated per unit time because the metabolising enzymes are saturated; there is no fixed half-life, and a small dose increase produces a disproportionately large rise in plasma level (StatPearls 2023).

COMMON TRAP

The examined zero-order drugs are **ethanol**, **phenytoin** and high-dose **salicylate**. Phenytoin is the psychiatry-adjacent trap: near the top of its range its kinetics flip from first- to zero-order, so a routine dose increase can push a patient into toxicity. Some sources add high-dose fluoxetine and fluvoxamine as showing non-linear (saturable) kinetics. Do not state these have a "fixed half-life."

18.3 Distribution: volume of distribution and what a high or low number tells you

A number that is not a real volume. The **apparent volume of distribution (Vd)** is the theoretical volume into which the total amount of drug in the body would have to be dissolved to give the measured plasma concentration (Vd = total drug in body divided by plasma concentration). It is not an anatomical space; it is an index of how widely a drug leaves the plasma for the tissues. A drug confined to plasma has a small Vd; a drug that partitions deeply into fat and tissue has a very large Vd, far exceeding total body water (StatPearls 2023).

Read Vd off two properties: lipophilicity and protein binding. A small, lipophilic molecule distributes into cells and adipose tissue and has a huge Vd (the non-psychiatric teaching example is chloroquine at around 140 L/kg); a large, charged or highly protein-bound molecule stays intravascular with a low Vd. In psychiatry the lipophilic psychotropics (most antipsychotics, TCAs, fluoxetine) have large volumes of distribution, which is why they are not effectively removed by haemodialysis and why lipophilic long-half-life drugs accumulate in body fat.

PEARL

Vd drives the loading dose; clearance drives the maintenance dose. Loading dose = Vd times target plasma concentration divided by F. This is why lithium, with a small Vd close to total body water, reaches a predictable level, and why a drug with a very large Vd cannot be cleared by dialysis. Half-life is the bridge between the two: it rises with Vd and falls with clearance.

18.4 Protein binding: the free-drug principle and its interaction traps

In plasma a drug exists as a protein-bound fraction and a free fraction, and only the **free (unbound) drug** is pharmacologically active: only free drug crosses membranes, reaches receptors, is metabolised and is excreted (StatPearls 2023). The two principal binding proteins are **albumin** (binds acidic drugs, for example valproate, phenytoin, diazepam) and **alpha-1-acid glycoprotein** (binds basic drugs, for example many antipsychotics and TCAs). A fall in albumin (malnutrition, hepatic or renal disease, the elderly, pregnancy) raises the free fraction of a highly bound drug and can produce toxicity at an apparently therapeutic total level.

CLINICAL ANCHOR

Valproate is the canonical psychiatric protein-binding trap. It is roughly 90% albumin-bound, but binding is saturable: as the total level rises, the free fraction rises disproportionately, and in hypoalbuminaemia (elderly, hepatic disease) a "therapeutic" total valproate level can conceal a toxic free level. Displacement interactions (valproate displacing warfarin, or aspirin displacing valproate) matter most for highly bound, narrow-index drugs.

18.5 Crossing into the brain: the blood-brain barrier and lipophilicity

A psychotropic can only work if it reaches the CNS, and the **blood-brain barrier (BBB)** is the gate. The BBB is formed by tight junctions between brain capillary endothelial cells that abolish the porous, fenestrated permeability seen elsewhere, so passive entry is restricted to small, lipophilic, uncharged, unbound molecules; hydrophilic and highly protein-bound drugs are largely excluded unless carried by a transporter (Nursing Pharmacology 2021). Efflux pumps, chiefly **P-glycoprotein**, actively push many drugs back out, further limiting brain penetration.

The design consequence runs both ways. Psychotropics are deliberately lipophilic to enter the brain, which is also why they have large volumes of distribution and cross the placenta. Conversely, unwanted CNS entry by a peripheral drug causes central side effects: sedating first-generation antihistamines (diphenhydramine) are the standard example of a drug crossing the BBB to cause drowsiness, whereas second-generation agents are engineered not to cross.

18.6 Metabolism: phase I and phase II, and the CYP450 system that matters most

Two phases, one goal. Hepatic metabolism converts lipophilic drugs into water-soluble metabolites the kidney can excrete, usually in two sequential phases (StatPearls 2023).

Phase I

Non-synthetic functionalisation reactions (oxidation, reduction, hydrolysis) that add or expose a reactive polar group. Oxidation by the **cytochrome P450 (CYP)** mono-oxygenase family is the dominant route. Metabolites may be inactive, active, or occasionally toxic.

Phase II

Synthetic conjugation reactions (glucuronidation by UGT, sulfation, acetylation, methylation, glutathione conjugation) that attach a large polar group to make the compound water-soluble for excretion. Products are almost always inactive. Phase II can occur without a prior phase I step.

The examined CYP isoenzymes in psychiatry are **CYP3A4** (the highest-abundance isoform, metabolises many antipsychotics and benzodiazepines), **CYP2D6** (metabolises risperidone, aripiprazole, many TCAs and SSRIs; genetically polymorphic), **CYP1A2** (clozapine and olanzapine; induced by tobacco smoke), and **CYP2C19** (citalopram, escitalopram, sertraline; polymorphic). An **inhibitor** raises the substrate's level (fluvoxamine and fluoxetine are potent inhibitors); an **inducer** lowers it (carbamazepine, and the polycyclic aromatic hydrocarbons in cigarette smoke induce CYP1A2). These are the mechanistic backbone of psychotropic drug interactions.

ISOENZYME	KEY PSYCHIATRIC SUBSTRATES	CLASSIC INDUCER / INHIBITOR WITH EXAM RELEVANCE
CYP1A2	Clozapine, olanzapine, duloxetine	**Induced by cigarette smoke (not nicotine): stopping smoking, or a smoking ban on admission, raises clozapine levels and can precipitate toxicity; fluvoxamine is a potent inhibitor**
CYP2D6	Risperidone, aripiprazole, TCAs, many SSRIs; codeine to morphine activation	**Highly polymorphic: poor and ultrarapid metaboliser phenotypes; paroxetine and fluoxetine are potent inhibitors of this pathway**
CYP3A4	Quetiapine, pimozide, many benzodiazepines, carbamazepine	**Inhibited by ketoconazole and grapefruit juice; carbamazepine is a strong inducer and also autoinduces its own metabolism**
CYP2C19	Citalopram, escitalopram, sertraline, diazepam	**Polymorphic; regulatory QTc-based dose caps on citalopram reflect concentration-dependent risk**

The four isoenzymes to hold cold are CYP1A2 (clozapine and smoking), CYP2D6 (polymorphism), CYP3A4 (highest abundance, most substrates) and CYP2C19. Two special metabolic behaviours are examined by name: carbamazepine autoinduction, and lithium being an outlier that undergoes no hepatic metabolism at all.

18.7 Excretion, clearance and the equations that link them

The kidney clears the water-soluble remains. Most metabolised drug is excreted by the kidney (glomerular filtration, active tubular secretion, passive reabsorption), with a biliary and faecal route for others. **Clearance (CL)** is the volume of plasma completely cleared of drug per unit time; it is the single best index of the body's efficiency at eliminating a drug and it sets the maintenance dose (maintenance rate = CL times target concentration divided by F).

The **elimination half-life (t-half)** is the time for the plasma concentration to fall by 50%. It is a derived parameter tying together the two primary ones: t-half = 0.693 times Vd divided by CL. So half-life lengthens if the drug distributes more widely (higher Vd) or is cleared more slowly (lower CL, as in renal or hepatic impairment or old age). Half-life governs two clinically decisive quantities (StatPearls 2023, Pharmaceutical Press 2023):

Time to steady state

On regular dosing, plasma level plateaus after approximately **4 to 5 half-lives**, independent of the dose or interval. This is when to check a trough level and when to judge full effect of a dose change.

Time to elimination

After stopping, a drug is effectively cleared (about 94 to 97% gone) after 4 to 5 half-lives; this sets safe washout before switching drugs.

CLINICAL ANCHOR

Fluoxetine's long half-life is the clinical exception you must know. Fluoxetine (1 to 4 days) and its active metabolite norfluoxetine (7 to 15 days) mean steady state takes weeks and washout takes about 5 to 6 weeks, which is why a long drug-free interval is needed before starting an MAOI. Conversely, the very short half-life of immediate-release venlafaxine or paroxetine explains their prominent discontinuation syndrome.

18.8 Loading, maintenance and the dosing interval

Two everyday decisions fall straight out of the parameters. The **loading dose** (Vd times target level divided by F) rapidly fills the volume of distribution to reach a therapeutic level without waiting the 4 to 5 half-lives, used when speed matters. The **maintenance dose and interval** replace what is eliminated each period and are set by clearance. The dosing interval is chosen relative to the half-life: an interval much longer than the half-life gives large peak-to-trough swings, while an interval near or shorter than the half-life gives smoother levels, which is the rationale for modified-release formulations and for once-daily dosing of long-half-life drugs.

PEARL

Because a long-half-life drug is self-buffering, once-daily dosing is rational and a single missed dose matters little (fluoxetine, aripiprazole). Because a short-half-life drug swings, it needs divided dosing or a modified-release form and punishes missed doses with withdrawal (venlafaxine IR, lithium in some regimens). Match the schedule to the half-life, not to habit.

18.9 Special populations: hepatic, renal, elderly, pregnancy and lactation

Every ADME step shifts in the populations you actually treat, and the exam tests the direction of change and the drug that is the exception.

POPULATION	DOMINANT KINETIC CHANGE	PRACTICAL RULE AND THE DRUG IT TURNS ON
Hepatic impairment	Reduced first-pass and phase I metabolism; low albumin raises free fraction; reduced clearance of hepatically cleared drugs	**Prefer drugs with minimal hepatic handling; among benzodiazepines choose lorazepam, oxazepam, temazepam (phase II glucuronidation only, no active metabolites, spared in liver disease)**
Renal impairment	Reduced excretion of renally cleared drugs and active metabolites	**Lithium is the critical one: it is renally excreted and unmetabolised, so any fall in GFR (dehydration, NSAIDs, ACE inhibitors, thiazides) raises the level toward toxicity; amisulpride and paliperidone are also renally cleared**

POPULATION	DOMINANT KINETIC CHANGE	PRACTICAL RULE AND THE DRUG IT TURNS ON
Elderly	Falling GFR and hepatic mass, reduced albumin, and increased fat-to-water ratio enlarging the Vd of lipophilic drugs, all prolonging half-life; increased BBB permeability and receptor sensitivity	**"Start low, go slow"; avoid long-half-life benzodiazepines (diazepam accumulates); anticholinergic load and orthostasis compound the kinetic risk**
Pregnancy	Increased plasma volume and GFR, increased hepatic metabolism (induction of some CYPs), fall in albumin; net effect often lowers plasma levels of some drugs as pregnancy advances	**Lithium clearance rises with GFR in pregnancy then falls abruptly at delivery, so the level must be tracked and the dose reduced around delivery to avoid postpartum toxicity; lamotrigine levels fall substantially and often need upward adjustment**
Lactation	Transfer into milk favours lipophilic, low-protein-bound, low-molecular-weight, unionised drugs; infant clearance is immature	**The relative infant dose (infant dose per kg as a percentage of the maternal dose per kg) under about 10% is generally considered acceptable; sertraline is a preferred SSRI on this metric, lithium is relatively contraindicated**

Lithium recurs in four of the five rows because it is the drug whose kinetics (renal, unmetabolised, narrow index, small Vd) leave no margin for a physiological shift. Learn the special-population section through lithium first, then generalise.

INDIA

Genetic variation in drug-metabolising enzymes is clinically relevant in Indian populations: **CYP2C19** poor-metaboliser frequency is appreciable, affecting escitalopram and clozapine handling, and slow-acetylator status affects isoniazid (relevant when co-prescribing with psychotropics in patients on antitubercular therapy). Formal pharmacogenomic testing is not yet routine in most Indian settings, so dose titration and clinical monitoring remain the practical safeguard.

18.10 Therapeutic drug monitoring: lithium, valproate and clozapine

When to measure the blood level. **Therapeutic drug monitoring (TDM)** is justified when a drug has a narrow therapeutic index, a clear concentration-effect (or concentration-toxicity) relationship, wide interindividual kinetic variability, and a level that is not easily read off the clinical picture (Maudsley 2021). In psychiatry the three drugs for which TDM is mandatory or strongly indicated are lithium, valproate and clozapine; sampling is standardised as a **trough level**, taken just before the next dose once steady state is reached.

Lithium

The archetypal narrow-index drug. Standard maintenance range approximately **0.6 to 0.8 mmol/L** (some target up to 1.0, and up to about 1.2 in acute mania); toxicity climbs above roughly 1.5 mmol/L

and is serious above 2.0. Sample a **12-hour post-dose trough**, check 5 to 7 days after any dose change (its half-life is around 18 to 24 hours), then routinely every 3 to 6 months with renal and thyroid function.

Valproate

Reference range approximately **50 to 100 mg/L (about 350 to 700 micromol/L)** in the epilepsy tradition; the concentration-response relationship in mania is weaker, so TDM is used more for adherence, toxicity and the free-fraction caveat than for titration. Trough sampling; watch the saturable protein binding described above.

Clozapine

A plasma **clozapine level around 350 to 600 ng/mL (micrograms/L)** is the usual therapeutic threshold, with response unlikely below about 350; seizure risk and toxicity rise steeply above roughly 600 to 1000. Because CYP1A2 drives its metabolism, levels swing with smoking status and interacting drugs, and the clozapine-to-norclozapine ratio helps flag adherence and metabolic changes (Maudsley 2021, Stahl 2020).

0.6-0.8	50-100	350-600
LITHIUM MAINTENANCE MMOL/L (12H TROUGH)	VALPROATE MG/L	CLOZAPINE NG/ML

COMMON TRAP

A lithium level is meaningful only as a standardised **12-hour trough**; a random or peak sample is uninterpretable and a common error. For clozapine, the highest-yield trap is the **smoking-cessation surge**: cigarette smoke induces CYP1A2, so a patient stabilised on clozapine who stops smoking (planned quit, hospital admission, or a ward smoking ban) can see plasma levels rise by 50% or more into the toxic range within days. Reduce the dose and monitor when smoking status changes.

18.11 Pharmacogenomics: the modern kinetic frontier (currency to 2026)

The 2020s addition to this topic is **pharmacogenomic (PGx)** testing, which reads the genotype of drug-metabolising enzymes to predict phenotype before dosing. The best-evidenced psychiatric applications are the polymorphic CYP2D6 and CYP2C19 loci: a **poor metaboliser** accumulates a substrate (risk of toxicity at a standard dose), while an **ultrarapid metaboliser** subtherapeutically clears it (risk of non-response). International consortia (CPIC and DPWG) publish genotype-guided dosing guidance for several antidepressants, and regulators have added PGx information to the labels of drugs such as the CYP2D6-metabolised agents. The examinable principle is that PGx individualises the metabolism step of ADME, converting population dosing into genotype-informed dosing, though clinical uptake, and cost-effectiveness, remain uneven and it is not yet standard of care in most settings including India.

MNEMONIC

ADME, and "Load with Vd, Maintain with Clearance"

The four steps are **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion. The two dosing rules hang off two parameters: the **loading dose fills the Vd** (loading dose = Vd times target level divided by F) and the **maintenance dose replaces what clearance removes**. Half-life, t-half = 0.693 times Vd divided by CL, is the bridge, and 4 to 5 half-lives is the answer to both "when is it at steady state" and "when is it washed out."

HOLD THIS

Loading dose fills the Vd, maintenance dose replaces what clearance removes, and steady state (or washout) takes 4 to 5 half-lives. Half-life is the bridge: t-half = 0.693 times Vd divided by clearance.

19 · Pharmacodynamics, receptor theory and dose-response

Pharmacodynamics is "what the drug does to the body": the quantitative relationship between a drug at its molecular target and the biological effect that follows, as distinct from pharmacokinetics ("what the body does to the drug"). For psychiatry this is the grammar underneath every prescription, because almost all psychotropics act by occupying a **receptor** (or a transporter or enzyme, covered elsewhere) and shifting its output up or down. The examiner tests this topic as a set of clean, high-yield definitions plus their drug exemplars: the difference between affinity and efficacy, the agonist spectrum from full agonist to inverse agonist, the two flavours of antagonism, and the numbers that describe a dose-response curve. Get these right and a large slice of clinical pharmacology (why aripiprazole is not just another D2 blocker, why buprenorphine has a ceiling, why flumazenil reverses a benzodiazepine) falls out for free (Stahl 2021, Kaplan & Sadock 2024).

This fragment builds from the binding event outward: first receptor occupancy and the two independent properties a ligand can have (affinity, efficacy); then the full agonist spectrum and the two-state model that makes sense of inverse agonism; then the dose-response curve and its landmark numbers (EC50, therapeutic index); then the competitive/non-competitive distinction, spare receptors and allosteric modulation; and finally the three canonical worked examples. It cross-references the receptor-transduction machinery (GPCRs, ion channels) from the transporters-and-receptors topic of these notes. A concept figure of the agonism spectrum overlaid on log dose-response curves is flagged in metadata.

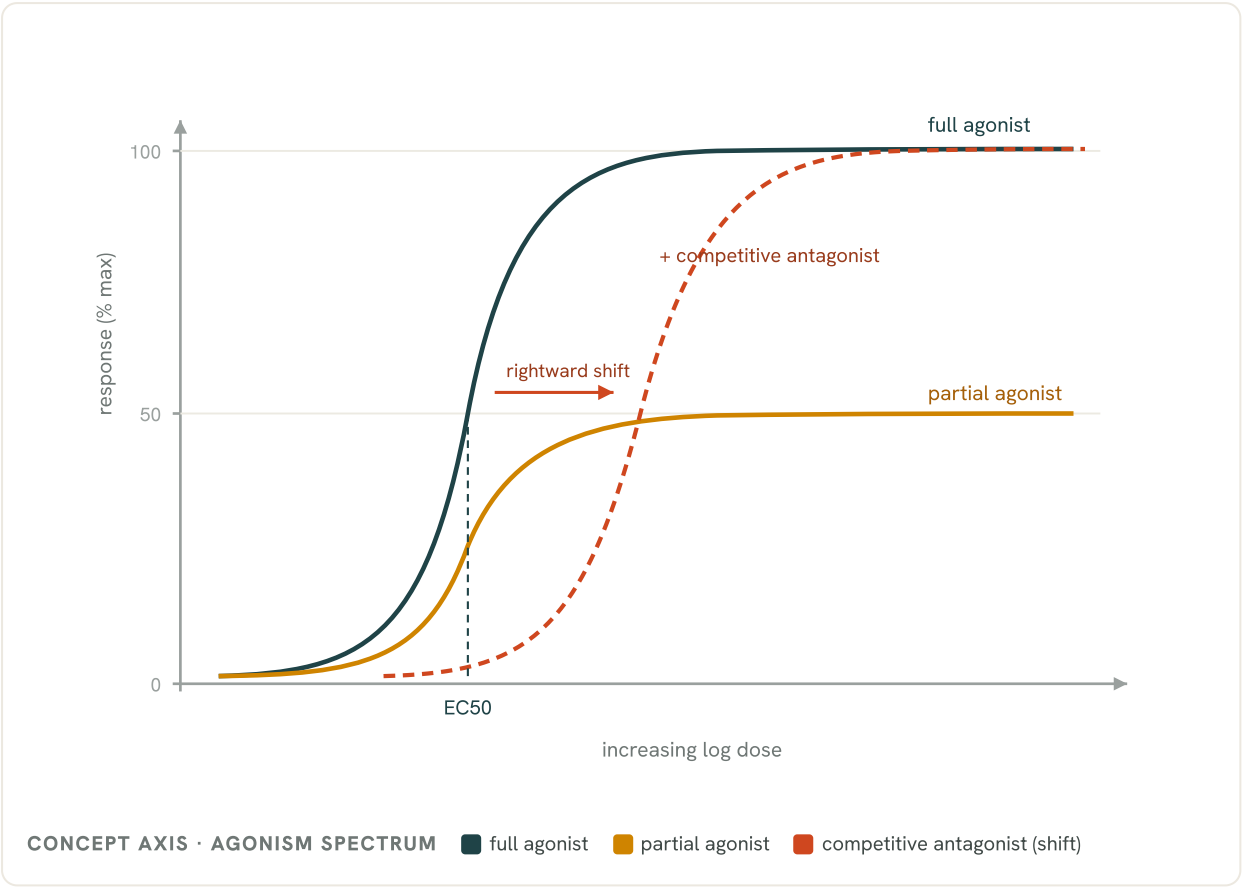


Fig 2.18 The log dose-response curve and the agonism spectrum. A full agonist reaches the maximal response; a partial agonist has lower intrinsic activity and plateaus below maximum (aripiprazole at D2, buprenorphine at mu); a competitive antagonist shifts the agonist curve rightward without lowering its maximum (surmountable). EC50, the dose giving half-maximal response, indexes potency; the plateau height indexes efficacy.

19.1 Receptor binding: occupancy, affinity and the two independent properties

Two things a ligand does, and they are separable. A drug that acts at a receptor has two logically distinct properties. **Affinity** is the tendency to bind, the strength of the drug-receptor association, and it determines what fraction of the receptor population a given concentration will occupy; it is captured by the dissociation constant **Kd** (the concentration occupying half the receptors), so a lower Kd means higher affinity. **Efficacy** (intrinsic efficacy, older term *intrinsic activity*) is a separate property: once bound, does the ligand change receptor activity, and by how much? Agonists have both affinity and non-zero intrinsic efficacy (they bind and produce a response); antagonists have affinity but *zero* intrinsic efficacy (they bind and do nothing themselves, but occupy the site) (Kenakin 2010).

Why the separation matters clinically. A drug can bind avidly yet do nothing (a high-affinity antagonist such as many antipsychotics), or bind and only partly activate (a partial agonist). This is the conceptual root of the whole agonist spectrum in 19.2: affinity puts the drug on the receptor, efficacy decides what happens next. In the classical framework the response of a tissue is a function of both the fraction occupied and the intrinsic efficacy of the occupying ligand.

Affinity

The strength of drug-receptor binding, indexed by Kd (lower Kd = higher affinity). Governs occupancy at a given concentration but says nothing about what the bound drug does.

Efficacy / intrinsic activity

The capacity of the bound ligand to change receptor activity and generate a response. Full agonist = maximal, partial agonist = submaximal, antagonist = zero, inverse agonist = negative.

Occupancy

The proportion of the receptor population bound at a given drug concentration; a function of affinity and concentration. Occupancy is necessary but, because of spare receptors (19.7), not always proportional to response.

19.2 The agonist spectrum: full, partial, antagonist, inverse

One continuum, four named positions. Stahl frames the ligands acting at a G-protein-linked receptor as sitting along a single **agonist spectrum**, ordered by their effect on signal transduction (Stahl 2021). At one end the naturally occurring neurotransmitter, or a drug mimicking it, is a **full agonist**: it drives the receptor to its maximal conformational change and the full downstream cascade (maximal second-messenger synthesis, maximal phosphorylation). A **partial agonist** ("stabilizer") produces a conformational change intermediate between the full agonist and the resting receptor, so it turns the signal up from baseline but not to maximum. A **silent antagonist** has affinity but no efficacy: alone it does nothing, it simply occupies the site and holds the receptor at its no-agonist conformation, blocking anything else. An **inverse agonist** is the true opposite of an agonist: it not only blocks but drives receptor output *below* the baseline, resting level (Stahl 2021).

The partial-agonist dual personality. The examiner-favourite property is that a partial agonist behaves differently depending on the prevailing tone. Where the endogenous full agonist is scarce (low dopaminergic tone, mesolimbic), the partial agonist acts as a *net agonist* and raises signalling; where the full agonist is abundant (high tone, mesocortical or with a full agonist present), it competes it off and acts as a *net antagonist*, dimming the excess. This is Stahl's rheostat/"Goldilocks" idea: a partial agonist finds a stable level "not too hot, not too cold." It is exactly why aripiprazole (19.8) stabilises dopamine rather than simply blocking it.

> **COMMON TRAP**
>
> An antagonist is *not* the opposite of an agonist. A silent antagonist has no action of its own in the absence of agonist; it is the **inverse agonist** that has the opposite action, reducing constitutive activity below baseline. Also do not call a partial agonist "weak" and stop there: partial agonism means a submaximal ceiling and dual behaviour, not simply reduced efficacy, and this distinction drives real clinical differences (Stahl 2021).

19.3 Constitutive activity, the two-state model and inverse agonism

Receptors work when no drug is present. Inverse agonism only makes sense once you accept that many receptors, especially GPCRs, have **constitutive activity**: even with no agonist bound, a fraction of the population spontaneously adopts the active conformation and generates a low baseline signal, most visibly where receptor density is high (Stahl 2021). The **two-state model** formalises this: receptors sit in equilibrium between an inactive state (R) and an active state (R*), and a ligand's behaviour depends on which state it prefers. A ligand with higher affinity for R*

enriches the active pool and acts as an agonist; a ligand with higher affinity for R depletes the active pool below baseline and acts as an **inverse agonist**; a ligand with equal affinity for both does not change the balance and behaves as a neutral antagonist, though it still blocks other ligands from binding (Costa & Herz 1989).

Why this is not academic. Many drugs historically labelled "antagonists" are, on careful testing, inverse agonists: the point is easy to miss because inverse agonism is only observable in a system with measurable constitutive activity; where constitutive activity is low, an inverse agonist looks like a plain competitive antagonist (Costa & Herz 1989). Pimavanserin, a 5-HT2A inverse agonist licensed for Parkinson-disease psychosis, is the clean psychiatric exemplar of a drug developed explicitly as an inverse agonist rather than a blocker.

PEARL

A useful three-line ladder: full agonist drives R toward R* (signal up to max); neutral antagonist locks the existing R/R* balance and blocks others (no change alone); inverse agonist pushes the balance toward R (signal below baseline). Constitutive activity is the hidden variable, and it is why the same molecule can read as "antagonist" in one tissue and "inverse agonist" in another (Stahl 2021).

19.4 Dose-response, the log curve and EC50

The sigmoid you must be able to read. Plot effect against drug concentration and you get a hyperbola; plot effect against the *logarithm* of concentration and it straightens into the familiar sigmoid, which is why dose-response curves are conventionally drawn on a log x-axis. The key landmark on the curve is the **EC50**, the concentration producing 50 percent of that drug's own maximal effect (the equivalent term for the fraction bound is the Kd; when measuring effect in a whole tissue it is the EC50). The **height** of the plateau reflects *efficacy* (the maximal attainable effect, Emax), and the **horizontal position** reflects *potency* (how much drug is needed to get there).

Potency versus efficacy, the classic discriminator. These are independent and constantly confused. **Potency** is a matter of dose: a more potent drug sits further left on the log axis (lower EC50), so less is needed, but potency alone says nothing about how good the drug is. **Efficacy** is the ceiling: the maximal effect the drug can produce however high the dose. A low-potency, high-efficacy drug given at the right dose can outperform a high-potency, low-efficacy one. In antipsychotics, haloperidol is high-potency (milligram doses) and chlorpromazine low-potency (hundred-milligram doses), yet their antipsychotic efficacy is broadly comparable: potency here reflects D2 affinity and daily dose, not clinical superiority (Kaplan & Sadock 2024).

HOLD THIS

Potency is horizontal position (EC50, the dose needed); efficacy is the ceiling (Emax). Haloperidol is more potent than chlorpromazine but not more efficacious; affinity puts a drug on the receptor, efficacy decides what it does there.

EC50

Concentration producing half of that drug's maximal effect; the standard index of potency for a graded (continuous) response. The steeper and further-left the curve, the more potent the drug.

ED50

The dose producing a specified effect (or the response of interest) in 50 percent of a population; used for quantal (all-or-none) responses and to derive the therapeutic index.

Emax

The maximal effect a drug can produce; the plateau of the curve. Reflects efficacy, not potency.

19.5 Therapeutic index and the safety window

How much room between working and harming. The **therapeutic index (TI)** is the ratio of the dose (or exposure) that produces toxicity to the dose that produces the therapeutic effect, classically TD50/ED50 in animals or LD50/ED50 for lethality. A large TI means a wide safety margin; a *narrow* TI means therapeutic and toxic doses are dangerously close, so the drug needs plasma-level monitoring and careful titration. In psychiatry this single concept explains the monitoring burden of **lithium** (narrow index, routine levels, toxicity just above the therapeutic range) and to a lesser degree some anticonvulsant mood stabilisers, versus the very wide index of the SSRIs, which are correspondingly hard to fatally overdose on their own (Kaplan & Sadock 2024).

CLINICAL ANCHOR

Narrow therapeutic index is the reason lithium is level-monitored (target trough roughly 0.6 to 0.8 mmol/L for maintenance, higher in acute mania), why dehydration, NSAIDs, thiazides and ACE inhibitors are dangerous (they raise lithium levels), and why lithium is a poor choice where adherence and monitoring cannot be assured. Contrast the SSRIs, whose wide index underlies their first-line status and relative overdose safety compared with the TCAs (narrow index, cardiotoxic in overdose).

INDIA

The wide-versus-narrow-index divide is directly practical here. Lithium remains cheap and widely used, but reliable serum-lithium assay access is uneven outside district and tertiary centres, which sharpens the case for SSRIs and low-toxicity agents where monitoring is impractical. Where TCAs are still prescribed for cost reasons, their narrow index and lethality in overdose warrant caution in patients at suicide risk and limited dispensing.

19.6 Competitive versus non-competitive antagonism

Can more agonist overcome the block, or not? A **competitive antagonist** binds reversibly at the same (orthosteric) site as the agonist, so the two compete; adding more agonist raises its probability of occupancy and eventually *surmounts* the block. On the dose-response curve this shifts the agonist curve to the right (higher EC50, reduced potency) but the same maximal effect (Emax) is still reachable at a high enough dose (Kenakin 2010). Most clinically used receptor antagonists are of this type, and it is why a benzodiazepine antagonist can be titrated and why beta-blocker effects can, in principle, be overridden by intense sympathetic drive.

Non-competitive / irreversible. A **non-competitive antagonist** either binds irreversibly to the orthosteric site or acts at a separate (allosteric) site to reduce the response in a way that added agonist cannot overcome. Here the curve is depressed downward: *Emax falls* and cannot be restored by more agonist (insurmountable block); potency (EC50) may be unchanged until spare receptors are exhausted. Phenoxybenzamine (irreversible alpha-blocker) is the standard general-pharmacology exemplar; in the CNS, channel-blocking NMDA antagonists such as ketamine and memantine act within the ion-channel pore, a use-dependent, non-competitive style of block.

FEATURE	COMPETITIVE ANTAGONIST	NON-COMPETITIVE / IRREVERSIBLE
Binding site	Same (orthosteric) site as agonist	Irreversible orthosteric, or a separate allosteric site
Effect of adding more agonist	**Block surmounted; response restored**	**Block insurmountable; response not fully restored**
Log dose-response curve	Parallel rightward shift	Downward depression of the curve
EC50 (potency)	Increased (curve shifts right)	Often unchanged until spare receptors exhausted
Emax (ceiling)	Unchanged	**Reduced**
Exemplar	Naloxone, flumazenil, propranolol	Phenoxybenzamine; ketamine/memantine (channel block)

Competitive versus non-competitive antagonism read off the dose-response curve. The single most testable discriminators are surmountability (does extra agonist win?) and whether Emax is preserved (competitive) or lowered (non-competitive).

RULE **Competitive block shifts the curve right but keeps Emax (surmountable); non-competitive block lowers Emax and cannot be overcome by more agonist.**

19.7 Spare receptors, receptor reserve and occupancy-response uncoupling

Maximal effect before full occupancy. Because postreceptor signalling machinery can saturate, an agonist can produce its maximal tissue response while occupying only a fraction of the receptor population; the unoccupied remainder are the **spare receptors** or *receptor reserve* (Kenakin 2010). The term is a mild misnomer, since all receptors participate and none are literally spare, but the phenomenon is real: one agonist might need only 25 percent occupancy for Emax where a lower-efficacy agonist needs 75 percent, the difference reflecting intrinsic efficacy. A large receptor reserve means the EC50 for effect lies well to the left of the Kd for binding, so occupancy and response are uncoupled.

Consequences worth knowing. A receptor reserve raises tissue sensitivity (small occupancy suffices) and buffers against a competitive or even a partial irreversible antagonist: the block must first consume the reserve before Emax starts to fall, which is one reason irreversible antagonists can leave potency intact until a threshold. It also underlies why receptor *occupancy* (from PET studies, for example the roughly 65 to 80 percent striatal D2 occupancy window associated with

antipsychotic efficacy without extrapyramidal side-effects) is a more useful clinical readout than plasma level alone (Kaplan & Sadock 2024).

19.8 Allosteric modulation and functional selectivity

Acting from the side, not the front door. An **allosteric modulator** binds at a site distinct from the orthosteric (agonist) site and changes the receptor's response to the endogenous agonist without necessarily activating the receptor on its own. A **positive allosteric modulator (PAM)** increases the agonist's effect, a **negative allosteric modulator (NAM)** decreases it. The archetype in psychiatry is the **benzodiazepine**, a PAM at the GABA-A receptor: it has no action without GABA but, when GABA is present, increases the frequency of chloride-channel opening, enhancing inhibition. This "only works in the presence of the natural transmitter" property gives allosteric drugs a ceiling and a generally safer profile than direct agonists, and is being pursued for muscarinic and metabotropic-glutamate targets.

Functional selectivity (biased agonism). A modern refinement of receptor theory: a single receptor couples to more than one downstream pathway (classically G-protein versus beta-arrestin), and a ligand can preferentially activate one over the other, so intrinsic efficacy is not a single fixed number but is pathway-dependent (Kenakin 2010). The mu-opioid receptor is the worked example: G-protein signalling mediates analgesia while beta-arrestin recruitment is linked to constipation and respiratory depression, motivating G-protein-biased agonists such as oliceridine that aimed to separate analgesia from those adverse effects. Aripiprazole's actions at D2 have likewise been attributed partly to functional selectivity, not partial agonism alone (de Bartolomeis 2015).

MNEMONIC

PAM Pushes, NAM Nixes; benzos are the PAM

Positive **A**llosteric **M**odulators *push* the transmitter's effect up, **N**egative ones *nix* it. Anchor the whole class to benzodiazepines at GABA-A: no GABA, no benzodiazepine effect, which is exactly why an allosteric drug has a self-limiting ceiling.

19.9 Worked examples: aripiprazole, buprenorphine, flumazenil

Three drugs that make the theory concrete. These are the canonical viva exemplars, one for each of partial agonism, ceiling-effect partial agonism, and competitive antagonism.

Aripiprazole: the D2 partial agonist

A high-affinity **partial agonist at the dopamine D2 receptor** (Burris 2002), and a partial agonist at 5-HT1A with 5-HT2A antagonism. As a "dopamine stabiliser" it dampens excess mesolimbic dopamine (net antagonist where tone is high, giving antipsychotic effect) while providing enough tone in mesocortical and tuberoinfundibular pathways to reduce parkinsonism and, characteristically, to spare or even lower prolactin. Its ceiling on D2 activation explains the low extrapyramidal and prolactin burden; functional selectivity at D2 is thought to contribute (de Bartolomeis 2015). Brexpiprazole and cariprazine share the D2 partial-agonist mechanism.

Buprenorphine: partial mu agonism with a ceiling

A **partial agonist at the mu-opioid receptor** (with kappa antagonism) and high mu affinity (Tripathi/KDT 2019). The partial agonism gives a *ceiling effect* on respiratory depression, making it far safer in overdose than full agonists and a mainstay of opioid-use-disorder maintenance (usually combined with naloxone to deter injection). Its high affinity means it can displace and block full agonists, which is why starting buprenorphine in a patient still opioid-dependent can precipitate withdrawal, the practical corollary of "high affinity, submaximal efficacy."

Flumazenil: the competitive benzodiazepine antagonist

A **competitive antagonist at the benzodiazepine binding site** of the GABA-A receptor, used to reverse benzodiazepine sedation and overdose (Kaplan & Sadock 2024). Because the block is competitive and surmountable, and because flumazenil's short half-life is briefer than most benzodiazepines, re-sedation can occur and repeat dosing may be needed. In the benzodiazepine-dependent patient it can precipitate withdrawal seizures, the mirror-image caution to buprenorphine.

> **PEARL**
>
> Line the three up against the spectrum: aripiprazole (partial agonist, stabiliser), buprenorphine (partial agonist with a safety ceiling), flumazenil (competitive antagonist). Add naloxone/naltrexone as the mu competitive antagonists and pimavanserin as the 5-HT2A inverse agonist, and you have one drug for every position on the agonist spectrum, a common single-best-answer pattern.

20 · CYP450 system and drug metabolism

The cytochrome P450 (**CYP450**) superfamily is the single most examinable pharmacokinetic topic in psychiatry, because almost every psychotropic drug is a substrate, inhibitor, or inducer of one or more of its isoenzymes, and because the resulting drug interactions are a leading cause of avoidable toxicity and treatment failure. **Why it matters.** A candidate who can name the five psychiatrically relevant isoenzymes, the flagship substrate for each, and the small set of high-yield inhibitors and inducers can predict and explain the majority of clinically significant interactions asked in vivas and MCQs. The examiner is rarely testing rote lists; the test is whether you can reason from "drug A inhibits enzyme X" and "drug B is a substrate of enzyme X" to "drug B accumulates and becomes toxic."

CYP450 enzymes are haem-containing mono-oxygenases concentrated in the hepatic endoplasmic reticulum and the enterocytes of the small intestine, where they mediate the bulk of oxidative **Phase I metabolism** (Kaplan & Sadock 2024). Nomenclature follows sequence homology: the number is the family (CYP2), the letter the subfamily (CYP2D), and the final number the specific gene (CYP2D6). Roughly 90% of clinically used drugs are handled by just six isoenzymes, of which CYP3A4, CYP2D6, CYP2C19, CYP1A2, and CYP2C9 dominate psychiatric practice.

20.1 Phase I versus Phase II, and where CYP450 sits

Biotransformation in two phases. **Phase I** reactions (oxidation, reduction, hydrolysis) introduce or unmask a functional group and are catalysed overwhelmingly by CYP450; they usually inactivate the drug but can also generate active metabolites (for example, fluoxetine to norfluoxetine, or risperidone to 9-hydroxyrisperidone/paliperidone). **Phase II** reactions

conjugate the drug or its Phase I metabolite with an endogenous moiety, most importantly glucuronidation by the UDP-glucuronosyltransferase (UGT) family, rendering it water-soluble for excretion. A drug that is cleared purely by Phase II conjugation (lorazepam, oxazepam, temazepam, lamotrigine) largely bypasses CYP450 and is therefore relatively protected from CYP-mediated interactions, a point of high clinical value in hepatic impairment and polypharmacy (Kaplan & Sadock 2024).

20.2 CYP3A4: the highest-volume isoenzyme

Substrates. CYP3A4 is the most abundant hepatic and intestinal CYP and metabolises the largest share of drugs, including most benzodiazepines (alprazolam, midazolam, triazolam), buspirone, most statins, quetiapine, ziprasidone, pimozide, carbamazepine, aripiprazole (with 2D6), and lurasidone. **Inhibitors.** The potent inhibitors are the azole antifungals (ketoconazole, itraconazole, fluconazole), macrolides (clarithromycin, erythromycin), protease inhibitors (ritonavir, indinavir), and grapefruit juice, which inhibits intestinal 3A4; among psychotropics, fluvoxamine and nefazodone are strong inhibitors. **Inducers.** Carbamazepine, phenytoin, phenobarbital, rifampicin, and St John's wort are the classic inducers. The magnitude can be dramatic: lurasidone exposure rises roughly 10-fold with ketoconazole, so potent 3A4 inhibitors are contraindicated, while potent inducers such as rifampicin can render it subtherapeutic (Spina 2015).

20.3 CYP2D6: the polymorphic workhorse

Substrates. CYP2D6 handles a disproportionate share of psychotropics relative to its modest hepatic abundance: most tricyclic antidepressants, many SSRIs (paroxetine, fluoxetine), venlafaxine, duloxetine, atomoxetine, vortioxetine, risperidone, aripiprazole, iloperidone, haloperidol, thioridazine, and the analgesic prodrugs codeine and tramadol (which require 2D6 to form their active opioid metabolites). **Inhibitors.** The strong psychiatric inhibitors are bupropion, fluoxetine, and paroxetine, with quinidine and terbinafine as potent non-psychiatric inhibitors; duloxetine is moderate. **A defining feature.** CYP2D6 is not inducible, so it has no clinically important inducers; interactions occur only through inhibition or genetic variation (Spina 2015). This makes 2D6 the isoenzyme most affected by pharmacogenetic phenotype (see 20.7).

> **CLINICAL ANCHOR**
>
> Paroxetine or fluoxetine added to a patient on a tricyclic antidepressant is a classic 2D6 interaction: the TCA level rises, risking anticholinergic delirium and cardiac conduction effects. Obtain a TCA level and reduce the dose. The same inhibition of 2D6 blocks codeine's conversion to morphine, so an analgesic dose of codeine may simply fail to work in a patient on paroxetine.

20.4 CYP2C19: benzodiazepines, PPIs, and citalopram

Substrates. CYP2C19 metabolises diazepam, citalopram and escitalopram, sertraline (partly), amitriptyline and clomipramine (demethylation), the proton pump inhibitors, and clopidogrel (activation). **Inhibitors and inducers.** Fluvoxamine and fluoxetine inhibit 2C19; omeprazole,

cimetidine, and ticlopidine also inhibit it; carbamazepine, phenytoin, phenobarbital, and rifampicin induce it (Spina 2015). **Genetics matter here too.** 2C19 is highly polymorphic, and the FDA advises a maximum citalopram dose of 20 mg/day in CYP2C19 poor metabolisers because of QT-prolongation risk from elevated exposure.

20.5 CYP1A2: clozapine, olanzapine, and the smoking effect

Substrates. CYP1A2 metabolises clozapine and its active metabolite norclozapine, olanzapine, asenapine, duloxetine, caffeine, and theophylline. **The key inhibitor is fluvoxamine,** a potent 1A2 inhibitor that can multiply clozapine levels several-fold and precipitate toxicity; fluoroquinolones (ciprofloxacin) and oral contraceptives also inhibit 1A2. **The key inducer is tobacco smoke,** specifically the polycyclic aromatic hydrocarbons (not nicotine), which increase olanzapine clearance by about 98% and comparably reduce clozapine levels (Spina 2015). This is the highest-yield induction fact in the syllabus.

> **CLINICAL ANCHOR**
>
> A stable smoker on clozapine who is admitted to a smoke-free ward, or who quits smoking abruptly, loses 1A2 induction over about a week: clozapine levels rebound and can reach toxic, seizure-provoking or myocarditis-associated concentrations. Anticipate a dose reduction of roughly 30 to 40% and monitor levels. The reverse (a non-smoker who starts smoking) needs an upward adjustment. Charcoal-grilled meat is a weaker dietary inducer of the same enzyme.

20.6 CYP2C9: warfarin and the anticonvulsants

Substrates and interactions. CYP2C9 metabolises warfarin (the active S-isomer), phenytoin, several NSAIDs, and sulfonylureas. It is inhibited by valproate and fluoxetine and by fluconazole and amiodarone, and induced by carbamazepine and rifampicin. The examinable interaction is valproate or fluoxetine plus warfarin, which raises the INR and bleeding risk, mandating INR monitoring (Spina 2015). Carbamazepine, conversely, induces 2C9 and lowers warfarin effect.

20.7 Genetic polymorphism: poor and ultrarapid metabolisers

Four metaboliser phenotypes. For polymorphic enzymes (2D6, 2C19, 2C9) the population divides into **poor metabolisers** (PM, two non-functional alleles, minimal enzyme activity), **intermediate metabolisers** (IM), **extensive/normal metabolisers** (EM, the reference), and **ultrarapid metabolisers** (UM, gene duplication or multiduplication with supranormal activity). **Consequences depend on the drug.** For a drug inactivated by the enzyme, a PM accumulates the parent drug and risks toxicity, whereas a UM sub-therapeutically clears it and may fail treatment. For a prodrug activated by the enzyme (codeine, tramadol, clopidogrel), the logic inverts: the PM fails to form the active metabolite and gets no effect, while the UM over-activates and risks toxicity (the basis of codeine-related opioid deaths in ultrarapid children). **Population frequencies.** Across world populations the predicted CYP2D6 PM frequency ranges from about 0.4% to 5.4%, highest in Europeans (about 5.4%) and lowest in East Asians (about 0.4%); 1 to 21% of individuals are UM depending on ancestry (Gaedigk 2017, cited in Kaplan & Sadock 2024). CYP2C19 PM status is notably more common in East Asian populations. This cross-

population variability makes pharmacogenetics directly relevant to Indian practice; the mechanism is developed further in the the Psychiatric Genetics notes pharmacogenetics topic.

COMMON TRAP

Do not assume "poor metaboliser equals low drug level." That is true only for prodrugs. For the far more common situation of a drug inactivated by the enzyme, the poor metaboliser has a HIGH level and is the one at risk of toxicity. Read the stem carefully for whether the drug is the active moiety or a prodrug.

PEARL

Enzyme inhibition is immediate (competition at the active site, effect within a day or two) whereas induction is delayed and gradual (it requires new enzyme protein synthesis, taking one to two weeks to develop and a similar time to wane after the inducer stops). This asymmetry explains both the delayed fall in clozapine levels when smoking starts and the delayed rebound when it stops.

20.8 P-glycoprotein: the efflux transporter

A transport-level determinant, not a metabolising enzyme. **P-glycoprotein** (P-gp; MDR1, gene ABCB1) is an ATP-dependent efflux pump expressed at the intestinal wall, the biliary and renal canaliculi, and the blood-brain barrier, where it pumps substrates back out of cells and limits their absorption and CNS penetration (Tasman 2015). Many psychotropics (TCAs, SSRIs, atypical antipsychotics, carbamazepine, lamotrigine) and digoxin are substrates. Inhibitors such as verapamil, clarithromycin, and ciclosporin reduce efflux and raise systemic and central exposure; inducers such as rifampicin and St John's wort lower it. P-gp substrate and inhibitor profiles overlap substantially with CYP3A4, so the two frequently act together at the enterocyte to shape first-pass exposure.

20.9 UGT and glucuronidation: lamotrigine and valproate

The Phase II axis with its own interactions. The UGT family conjugates lamotrigine, lorazepam, oxazepam, morphine, and many antipsychotics. **The flagship interaction is valproate plus lamotrigine.** Valproate inhibits UGT (specifically the glucuronidation of lamotrigine), roughly doubling lamotrigine levels and prolonging its half-life; this is why the lamotrigine titration schedule is halved when it is co-prescribed with valproate, to reduce the risk of serious rash including Stevens-Johnson syndrome. Conversely, **enzyme-inducing anticonvulsants** (carbamazepine, phenytoin, phenobarbital) induce UGT and roughly halve lamotrigine levels, requiring a higher target dose (Spina 2015). Carbapenem antibiotics induce UGT-mediated glucuronidation and can precipitously drop valproate levels, a well-recognised inpatient interaction. The polymorphism *UGT1A1*28* reduces glucuronidation capacity and is associated with Gilbert syndrome and reduced lamotrigine clearance (Kaplan & Sadock 2024).

CLINICAL ANCHOR

When adding lamotrigine to valproate, start lower and go slower (typically half the usual lamotrigine titration), because valproate's UGT inhibition doubles lamotrigine exposure and the rash risk is dose- and titration-rate-dependent. When adding it to an enzyme inducer such as carbamazepine, expect to need a higher maintenance dose.

RULE **Valproate inhibits UGT and roughly doubles lamotrigine, so halve the lamotrigine titration when they are combined.** The Stevens-Johnson risk is titration-rate-dependent.

20.10 Master inhibitor and inducer table

ISOENZYME	KEY PSYCHIATRIC SUBSTRATES	IMPORTANT INHIBITORS	IMPORTANT INDUCERS
CYP1A2	Clozapine, olanzapine, asenapine, duloxetine, caffeine, theophylline	**Fluvoxamine (potent), ciprofloxacin, oral contraceptives, cimetidine**	**Tobacco smoke (PAHs), carbamazepine, phenytoin, charcoal-grilled meat, modafinil**
CYP2C9	Warfarin (S-isomer), phenytoin, NSAIDs, sulfonylureas	Valproate, fluoxetine, fluconazole, amiodarone	Carbamazepine, rifampicin
CYP2C19	Diazepam, citalopram, escitalopram, clopidogrel (activation), PPIs, amitriptyline	**Fluvoxamine (potent), fluoxetine, omeprazole, cimetidine, ticlopidine**	Carbamazepine, phenytoin, phenobarbital, rifampicin
CYP2D6	TCAs, paroxetine, fluoxetine, venlafaxine, duloxetine, risperidone, aripiprazole, haloperidol, codeine and tramadol (activation)	**Bupropion, fluoxetine, paroxetine (all potent), quinidine, terbinafine, duloxetine**	**None (not inducible)**
CYP3A4	Most benzodiazepines, buspirone, statins, quetiapine, ziprasidone, pimozide, lurasidone, carbamazepine	**Ketoconazole, itraconazole, clarithromycin, ritonavir, grapefruit juice, fluvoxamine, nefazodone**	**Carbamazepine, phenytoin, phenobarbital, rifampicin, St John's wort**
UGT (Phase II)	Lamotrigine, lorazepam, oxazepam, morphine, many antipsychotics	Valproate (raises lamotrigine)	Carbamazepine, phenytoin, phenobarbital (lower lamotrigine); carbapenems (lower valproate)
P-glycoprotein (ABCB1)	Digoxin, TCAs, SSRIs, atypical antipsychotics, carbamazepine, lamotrigine	Verapamil, clarithromycin, ciclosporin, itraconazole	Rifampicin, St John's wort, phenytoin

High-yield inhibitor and inducer map for the five psychiatric CYP isoenzymes plus the UGT and P-glycoprotein axes; discriminators highlighted are the facts most often tested (fluvoxamine as pan-inhibitor, smoking as the 1A2 inducer, 2D6 as non-inducible).

HOLD THIS

Tobacco smoke (not nicotine) induces CYP1A2, so quitting raises clozapine and olanzapine levels toward toxicity. Inhibition is immediate; induction and its reversal take one to two weeks.

MNEMONIC

SICKFACES.COM (inhibitors) and CRAP GPS (inducers)

For broad-spectrum CYP inhibitors: **S**odium valproate, **I**soniazid, **C**imetidine, **K**etoconazole, **F**luconazole/fluvoxamine, **A**miodarone, **C**iprofloxacin, **E**rythromycin/clarithromycin, **S**ulfonamides, **C**hloramphenicol, **O**meprazole, **M**etronidazole/grapefruit. For inducers: **C**arbamazepine, **R**ifampicin, **A**lcohol (chronic), **P**henytoin/phenobarbital, **G**riseofulvin, **P**henobarbital, **S**t John's wort/smoking. In psychiatry the four you must never forget are fluvoxamine (inhibits everything, especially 1A2 and 3A4), fluoxetine and paroxetine (2D6), and smoking plus carbamazepine (inducers).

INDIA

Two interactions recur in Indian practice. First, rifampicin from antitubercular therapy is a powerful pan-inducer (3A4, 2C9, 2C19, P-gp) and will lower levels of most psychotropics, so a patient started on ATT may need upward dose adjustment and closer monitoring. Second, the high prevalence of smoking and bidi use in male psychiatric inpatients makes the clozapine/olanzapine-smoking interaction a frequent real-world problem on admission to smoke-restricted wards.

21 · Receptor up/down-regulation, tolerance and sensitisation

Receptors are not fixed hardware. When a receptor is chronically over-stimulated or chronically blocked, the neuron re-tunes itself to defend a set-point, altering the *number*, *affinity*, and *coupling efficiency* of its receptors over hours to weeks. This **adaptive receptor regulation** is the single unifying concept behind four apparently separate clinical phenomena: the delayed onset of antidepressants, the tolerance and withdrawal that define substance dependence, the sensitisation that drives stimulant addiction, and the tardive movement disorders and supersensitivity psychosis that follow long-term antipsychotic exposure (Kaplan and Sadock 2024). The rule of thumb is homeostatic and directional: chronic agonism (or a chronic surplus of transmitter) tends to **down-regulate** and desensitise receptors, while chronic antagonism (or a chronic deficit of transmitter) tends to **up-regulate** and supersensitise them.

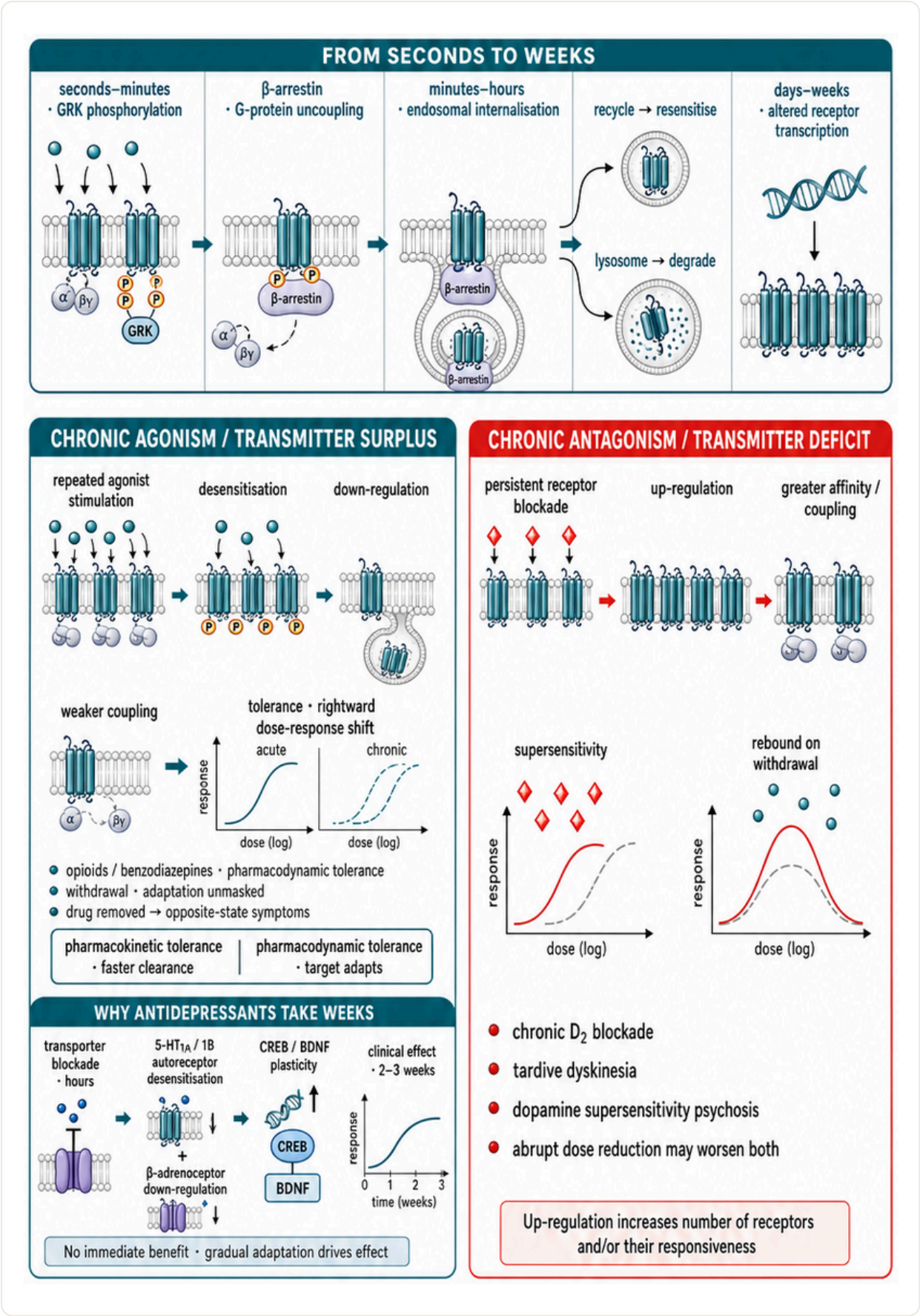


Fig 2.19 Receptor adaptation over time: regulation, trafficking and chronic exposure.

Why it recurs. Almost every long-latency or long-term drug effect in the paper resolves at this level. A candidate who can state that antidepressants occupy their transporter within hours but

take two to three weeks to change receptor density, and can extend the same adaptive logic to why benzodiazepines cause dependence, why cocaine sensitises, and why stopping a high-potency antipsychotic can precipitate rebound movements or psychosis, has one mechanism that answers a dozen questions. The examiner is testing whether you can distinguish the immediate pharmacology of a drug from the slow neuroadaptation the brain mounts against it.

21.1 Up-regulation and down-regulation: the homeostatic direction rule

The core principle. Receptor sensitivity is under continuous regulatory and homeostatic control, so that the same drug concentration can produce a greater or lesser response depending on the receptor state (Companion to Psychiatric Studies). Two directions matter. **Down-regulation and desensitisation** follow prolonged agonist stimulation: the cell becomes refractory, receptor number falls, and coupling to G proteins weakens. **Up-regulation and supersensitivity** follow prolonged loss of stimulation, whether from denervation, transmitter depletion, or chronic antagonist blockade, and the cell responds by increasing receptor number and affinity.

Fast versus slow mechanisms. The earliest change is **homologous desensitisation**: the agonist-occupied receptor is phosphorylated by a G-protein-coupled receptor kinase (GRK), which recruits **beta-arrestin** to uncouple the receptor from its G protein within seconds to minutes, then to internalise it into endosomes (Kaplan and Sadock 2024). Internalised receptors may be recycled back (resensitisation) or trafficked to lysosomes for degradation, the latter producing true **down-regulation** (a fall in total receptor number) over hours. The slowest limb is **altered synthesis**: long-term negative feedback suppresses new receptor transcription, or induces a structurally modified receptor, changing receptor density over days to weeks (Companion to Psychiatric Studies). This three-tier timescale, phosphorylation to internalisation to transcription, is why some drug adaptations are minutes-fast and others take weeks.

Homologous desensitisation

Loss of response confined to the receptor that was occupied by agonist; mediated by GRK phosphorylation and arrestin recruitment at that receptor specifically.

Heterologous desensitisation

Loss of response spreading to other, unoccupied receptors sharing a downstream pathway; mediated by second-messenger kinases (PKA, PKC) phosphorylating receptors or shared effectors.

Down-regulation

A true reduction in receptor *number* (not just coupling), from lysosomal degradation or reduced synthesis; the slow structural correlate of chronic agonism.

Up-regulation (supersensitivity)

An increase in receptor number or affinity after chronic understimulation or antagonism; the substrate of denervation supersensitivity, withdrawal, and tardive phenomena.

HOLD THIS

Chronic agonism down-regulates and desensitises; chronic antagonism up-regulates and supersensitises. One homeostatic direction rule answers antidepressant latency, tolerance, tardive dyskinesia and supersensitivity psychosis.

21.2 Tolerance defined: the rightward shift of the dose-response curve

The operational definition. **Tolerance** is a reduced effect from a given dose after repeated exposure, so that a higher dose is needed to reproduce the original effect. Graphically it is a **parallel rightward shift of the dose-response curve** (Goodman and Gilman 2018). It is a normal, expected adaptation of the nervous system to a drug and is not in itself evidence of addiction; DSM-5-TR is explicit that tolerance and withdrawal to a prescribed CNS medication taken as directed are normal physiological responses and do not by themselves indicate a substance use disorder (DSM-5-TR 2022).

Tolerance is effect-specific, not drug-specific. A single drug develops tolerance to its different effects at different rates, a fact that is clinically lethal with opioids. Tolerance to euphoria and analgesia develops rapidly, but tolerance to respiratory depression develops slowly; a dependent user chasing the fading high can therefore reach a dose that stops their breathing, which is the pharmacological basis of the opioid overdose epidemic (Goodman and Gilman 2018). By contrast, with opioids there is minimal tolerance to constipation and miosis, so pinpoint pupils and constipation persist even in a heavily tolerant user, a useful examination discriminator.

> **COMMON TRAP**
>
> Tolerance, dependence, and addiction are three separate axes and must not be conflated. **Tolerance** is a shifted dose-response curve. **Physical dependence** is the emergence of a withdrawal syndrome on cessation. **Addiction (substance use disorder)** is a behavioural syndrome of compulsive use despite harm. A patient on chronic morphine for cancer pain is tolerant and physically dependent but is not addicted; a binge stimulant user can be addicted while showing sensitisation rather than tolerance and little physical withdrawal.

21.3 Pharmacokinetic versus pharmacodynamic tolerance (and tachyphylaxis)

The mechanisms of tolerance divide into two families that examiners routinely ask to be contrasted. **Pharmacokinetic (dispositional) tolerance** is a reduction in the *concentration* of drug reaching the target, most often through **induction of metabolising enzymes**. Chronic alcohol, barbiturates, and carbamazepine induce hepatic cytochrome P450 enzymes so the drug is cleared faster and less reaches the brain; the dose-response curve shifts right because less drug arrives, not because the receptor has changed (Goodman and Gilman 2018). **Pharmacodynamic (functional) tolerance** is an adaptation at or beyond the receptor despite unchanged drug concentration: receptor down-regulation, desensitisation, or compensatory changes in downstream signalling and opposing circuits. Most tolerance of psychiatric interest, and most cross-tolerance, is pharmacodynamic.

Special forms. **Tachyphylaxis** is very rapid tolerance developing over minutes to hours with closely spaced doses, classically to indirectly acting sympathomimetics such as ephedrine and tyramine, which act by displacing stored noradrenaline: once the readily releasable vesicular pool is exhausted, further doses have little effect (Goodman and Gilman 2018). **Acute tolerance** is tolerance developing within a single episode of use, such as declining effect across a cocaine binge. **Cross-tolerance** is tolerance to one drug conferring tolerance to a pharmacologically

related drug, which is exploited therapeutically: heroin-dependent patients can be detoxified with any mu-opioid agonist such as methadone or buprenorphine, and alcohol withdrawal is managed with cross-tolerant benzodiazepines (Goodman and Gilman 2018). **Learned or conditioned tolerance** adds a behavioural layer, in which environmental cues that reliably precede the drug trigger anticipatory compensatory responses; loss of those cues in a novel setting can unmask the drug's full effect and precipitate overdose at a previously tolerated dose.

TYPE	LOCUS / MECHANISM	PROTOTYPE EXAMPLE
Pharmacokinetic	**Faster clearance (enzyme induction); drug level falls**	Barbiturates, carbamazepine, alcohol inducing P450
Pharmacodynamic	**Receptor down-regulation / desensitisation; level unchanged**	Benzodiazepine, opioid receptor adaptation
Tachyphylaxis	Depletion of a releasable transmitter pool over minutes	**Ephedrine, tyramine (indirect sympathomimetics)**
Acute tolerance	Within a single exposure / binge	Cocaine across a binge
Cross-tolerance	Shared receptor or pathway	**Alcohol to benzodiazepines; heroin to methadone**
Learned / conditioned	Cue-triggered compensatory response	Setting-dependent opioid tolerance

The discriminating question is always whether less drug is reaching the target (pharmacokinetic) or the target has adapted to the same amount of drug (pharmacodynamic); tachyphylaxis is distinguished by its speed and its mechanism of transmitter-pool depletion.

21.4 Sensitisation (reverse tolerance): when repetition amplifies

The opposite adaptation. **Sensitisation**, also called **reverse tolerance**, is the progressive *increase* in a drug effect with repeated intermittent dosing, a leftward shift of the dose-response curve (Goodman and Gilman 2018). It is characteristically seen with **psychostimulants** (amphetamine, cocaine) and depends critically on an **intermittent, spaced dosing schedule**; continuous exposure tends instead to produce tolerance. The behavioural readout in animal models is escalating locomotor activation and stereotypy to a fixed dose, and the neural substrate is progressive enhancement of dopamine release and responsiveness in the mesolimbic pathway, particularly the nucleus accumbens and ventral tegmental area, with lasting changes in glutamatergic synaptic strength.

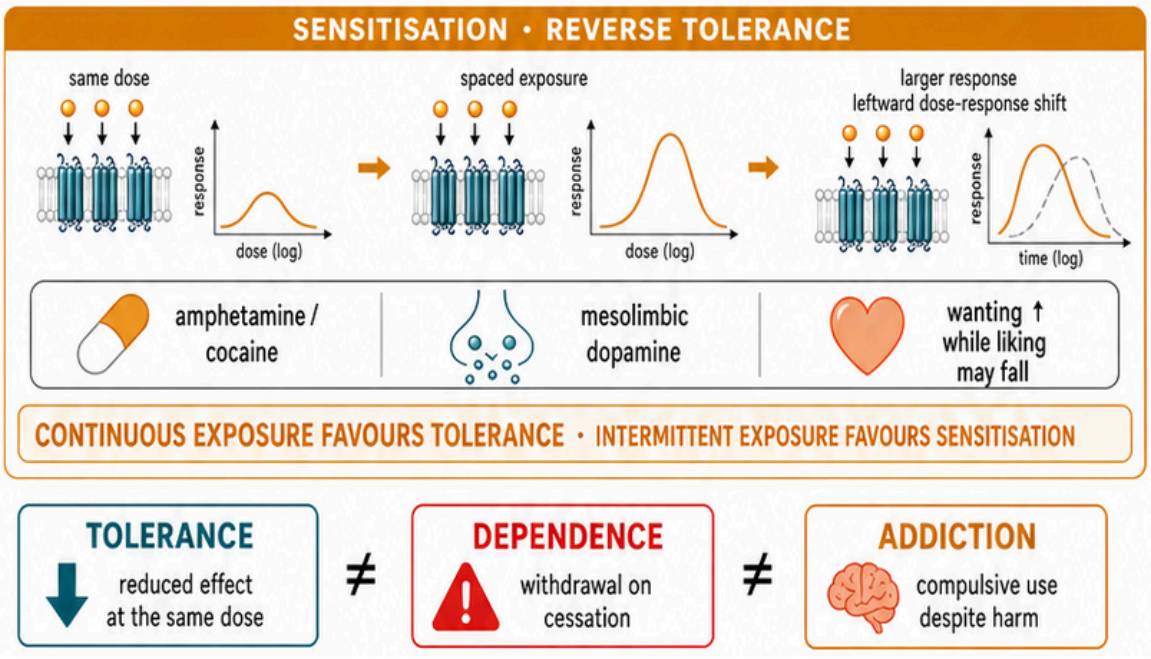


Fig 2.20 Sensitisation, reverse tolerance, dependence and addiction.

Why it matters clinically. Sensitisation is the leading neurobiological account of the **incentive-salience** theory of addiction (Robinson and Berridge): repeated drug use sensitises the "wanting" system so that drug cues acquire escalating motivational pull even as the drug's pleasurable "liking" effect wanes, dissociating craving from enjoyment. It is also invoked to explain **stimulant-induced psychosis** and its tendency to recur faster and at lower doses on re-exposure, and it offers a candidate mechanism for the **kindling** model, in which repeated affective episodes or repeated withdrawals become progressively easier to trigger. The exam-critical contrast is that the *same* drug can produce tolerance to some effects and sensitisation to others depending on the dosing schedule.

PEARL

Schedule is the switch. **Continuous or closely-spaced dosing favours tolerance; intermittent, spaced dosing favours sensitisation.** This is why a steady therapeutic infusion behaves differently from binge use of the same stimulant, and why the behavioural sensitisation paradigm in the lab is deliberately built on spaced injections. Whenever a question pairs a stimulant with "reverse tolerance" or "increasing response," sensitisation is the answer.

21.5 Dependence and withdrawal: the opponent-process and allostasis model

Withdrawal is adaptation unmasked. Physical dependence is the state in which the brain's compensatory adaptations have grown to oppose the drug so completely that removing the drug leaves those adaptations unopposed, producing a **withdrawal syndrome** that is characteristically the mirror image of the drug's acute effects. Thus opioid withdrawal (a CNS depressant) produces autonomic arousal, insomnia, anxiety, mydriasis, piloerection, cramps and rhinorrhoea, and alcohol or benzodiazepine withdrawal (also depressants) produces hyperarousal, tremor, and seizures (Companion to Psychiatric Studies; Goodman and Gilman 2018).

Withdrawal proves dependence, but dependence and withdrawal alone cannot explain the compulsive relapse that defines addiction (Companion to Psychiatric Studies).

The theoretical frame. Solomon's **opponent-process theory** formalises this: every drug-induced hedonic state (the a-process) recruits an opposing b-process that grows with repetition, so that with chronic use the opponent process comes to dominate and defines both tolerance and the negative-affect withdrawal state. Koob and Le Moal extended this to an **allostatic** model in which repeated cycles reset the hedonic set-point downward, recruiting anti-reward systems (CRF and dynorphin in the extended amygdala) and driving negatively-reinforced compulsive use. At the cellular level, opioid tolerance is now understood to involve not only classical receptor desensitisation and down-regulation but wider **allostatic and opponent processes**, including a compensatory up-regulation of the cAMP pathway (superactivation of adenylyl cyclase) in locus coeruleus neurons that becomes overtly hyperactive on drug removal, and pass-forward adaptations propagated to downstream circuitry and glia (Cahill et al 2016).

21.6 The delayed antidepressant onset and the beta-adrenoceptor down-regulation story

The classic paradox, and its resolution. Monoamine reuptake inhibitors and MAO inhibitors raise synaptic noradrenaline and serotonin within hours, yet clinical antidepressant benefit takes two to three weeks. Acute pharmacology cannot explain a two-week latency, so the effect must be a slow adaptation, and the historically pivotal observation was that chronic (not acute) antidepressant treatment, and electroconvulsive therapy, **down-regulate postsynaptic beta-adrenoceptors** and their coupled cAMP response in cortex, on a timescale that matches the therapeutic lag (Kaplan and Sadock 2024; Companion to Psychiatric Studies). This **beta-adrenoceptor down-regulation hypothesis** reframed the therapeutic action as a receptor adaptation to sustained excess transmitter rather than the acute rise in transmitter itself, and became the textbook answer to "why do antidepressants take weeks to work."

The modern extension. The receptor-adaptation story now sits within a broader plasticity account. Alongside beta-adrenoceptor down-regulation, chronic antidepressants **desensitise inhibitory 5-HT1A and 5-HT1B/1D autoreceptors**, which initially restrain firing; over one to two weeks these autoreceptors desensitise, disinhibiting raphe firing and increasing forebrain serotonin transmission, again on a timescale matching onset (Stahl 2021). Both threads feed downstream into the CREB and BDNF plasticity cascade (subtopic on second messengers), so the fully current answer is that antidepressant latency reflects a sequence of adaptive receptor changes, autoreceptor desensitisation and postsynaptic beta down-regulation, that translate a fast transmitter change into slow synaptic remodelling.

> **COMMON TRAP**
>
> Do not present the raw monoamine hypothesis as the explanation for antidepressant onset. A simple deficit-of-monoamines model predicts an *immediate* response once reuptake is blocked, which is exactly what does not happen. The examinable point is that the **delay is itself the evidence against the naive monoamine theory** and in favour of an adaptive receptor and plasticity mechanism.

21.7 Antipsychotic dopamine supersensitivity, tardive dyskinesia and supersensitivity psychosis

Chronic blockade breeds supersensitivity. The mirror-image case is chronic *antagonism*. Sustained D2 receptor blockade by antipsychotics drives a compensatory **up-regulation and supersensitivity of striatal D2 receptors**, demonstrable as increased D2 density after chronic antipsychotic exposure (Kaplan and Sadock 2024). Two clinical consequences follow. **Tardive dyskinesia** is the classic late motor syndrome of involuntary orofacial and limb movements, attributed in the traditional model to nigrostriatal D2 supersensitivity, and it is characteristically worsened transiently by dose reduction or withdrawal (which further disinhibits the supersensitive receptors) and masked by dose increase; it is more associated with prolonged first-generation antipsychotic use and can be irreversible (Maudsley Prescribing Guidelines). The current disease-specific treatments are the **VMAT2 inhibitors valbenazine and deutetrabenazine**, which deplete presynaptic dopamine rather than blocking the supersensitive postsynaptic receptor.

TRAP Tardive dyskinesia is transiently *worsened* by dose reduction and masked by a dose increase, because withdrawal disinhibits the supersensitive D2 receptors; raising the dose is not a treatment.

Supersensitivity in the mesolimbic system. The same adaptation in the mesolimbic pathway underlies **dopamine supersensitivity psychosis** (Chouinard's neuroleptic-induced supersensitivity psychosis): tolerance to the antipsychotic effect, rebound or breakthrough psychosis on dose reduction or switching, and an association with tardive dyskinesia are its features (Chouinard and Jones 1980; Yin et al 2017). This is the mechanistic caution behind never stopping a high-potency antipsychotic abruptly, and behind the observation that apparent "relapse" immediately after discontinuation may in part be a supersensitivity rebound rather than the natural course of illness.

CLINICAL ANCHOR

The supersensitivity concept has a practical corollary in polydipsia and hyponatraemia: one proposed mechanism is that chronic postsynaptic D2 blockade produces receptor supersensitivity with increased presynaptic dopamine release, driving hypothalamic thirst, and reducing the number and dose of antipsychotics can lessen dopamine supersensitivity and its adverse effects (Maudsley Prescribing Guidelines). It is the same adaptive up-regulation, read out in a different circuit.

21.8 Discontinuation and withdrawal syndromes across psychotropic classes

A shared logic, class-specific faces. Every discontinuation syndrome is the unmasking of an adaptation that opposed the drug, so its features are broadly the reverse of the drug's action and its severity tracks the drug's **half-life** (shorter half-life means faster fall in level and more abrupt, more severe withdrawal). **Antidepressants.** The SSRI/SNRI **discontinuation syndrome** is captured by the mnemonic **FINISH** (Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances including the characteristic "electric shock" or brain-zap sensations, and Hyperarousal). It is worst with short-half-life, high-potency agents such as paroxetine and

venlafaxine, minimal with long-half-life fluoxetine, typically begins within days of stopping, and is distinguished from relapse by its early onset, physical symptom profile, and rapid resolution on reinstatement (Maudsley Prescribing Guidelines). It is now emphasised that a subset of patients experience severe and protracted withdrawal, mandating slow, often hyperbolic, tapering (Maudsley Deprescribing Guidelines).

Sedative-hypnotics and others. **Benzodiazepine withdrawal** reflects GABA-A down-regulation and glutamatergic up-regulation and can produce anxiety, insomnia, perceptual disturbance, and, dangerously, seizures and delirium, again worse with short-acting agents such as alprazolam; management is a gradual taper, often after switching to a long-acting agent such as diazepam. Tolerance to benzodiazepines and z-drugs is well recognised and is itself a reason the initial benefit fades (Maudsley Deprescribing Guidelines). **Lithium** discontinuation, especially if abrupt, carries a rebound risk of mania and is associated with loss of prophylactic efficacy. **Antipsychotic** discontinuation can produce cholinergic rebound (nausea, insomnia, agitation) from muscarinic receptor up-regulation, plus the dopaminergic supersensitivity phenomena of subtopic 21.7.

MNEMONIC

FINISH

Flu-like, **I**nsomnia, **N**ausea, **I**mbalance (dizziness), **S**ensory disturbance (paraesthesiae, brain zaps), **H**yperarousal (anxiety, agitation). The six-domain picture of SSRI/SNRI discontinuation; onset within days of stopping, tied to short half-life, resolves on reinstatement, which is what separates it from a depressive relapse.

21.9 Exam integration: one adaptation, four syndromes

The reward for this topic is a single decision tree. Ask first whether the drug is a chronic *agonist*/transmitter-surplus (expect down-regulation, tolerance, and a hyperactive withdrawal) or a chronic *antagonist*/transmitter-deficit (expect up-regulation, supersensitivity, and rebound on removal). Then ask whether the schedule is continuous (favours tolerance) or intermittent (favours sensitisation). This maps every case: antidepressants down-regulate beta-adrenoceptors and desensitise autoreceptors, explaining their two-to-three-week latency; benzodiazepines and opioids down-regulate their inhibitory systems, explaining tolerance and mirror-image withdrawal; intermittent stimulants sensitise mesolimbic dopamine, explaining reverse tolerance and craving; and chronic antipsychotics up-regulate D2 receptors, explaining tardive dyskinesia and supersensitivity psychosis. Current agents fit the same frame: the muscarinic antipsychotic **xanomeline-trospium** acts through M1/M4 GPCRs subject to the same desensitisation biology, and rapid-acting antidepressants (esketamine, zuranolone) bypass the slow receptor-adaptation route by driving plasticity directly.

INDIA

In settings where laboratory monitoring and continuity of supply can be intermittent, the adaptive-receptor concepts translate into concrete safety rules worth voicing in a viva. Abrupt stoppage of a high-potency antipsychotic or lithium, whether through non-adherence or a supply gap, risks rebound psychosis, cholinergic rebound, or rebound mania, not merely "relapse." Short-half-life SSRIs such as paroxetine and short-acting benzodiazepines such as alprazolam, both widely prescribed, carry the sharpest discontinuation and dependence profiles and warrant deliberate tapering and patient counselling about missed doses.

Apply and consolidate

22 · Apply: four mechanism-to-bedside vignettes

The whole chapter converges here. Neurochemistry earns its place in the exam only when a receptor, an enzyme or a pathway is made to *predict* a clinical event and then a first move. These four vignettes are deliberately drawn from four different systems, so the discriminator in each is a different piece of machinery: a dopamine pathway, a serotonergic toxidrome, a cytochrome P450 isoenzyme, and a glutamate receptor cascade. Each runs to the same three-beat rhythm the examiners reward: the **presentation**, then the **mechanism** that alone explains it, then the **first drug choice or interpretation** that the mechanism forces. Where a management step belongs to clinical practice rather than basic science, the pointer is to the clinical psychiatry chapters (Paper II), not a full protocol here.

Read each as a reasoning drill, not a fact to memorise. If you can name the pathway, isoenzyme or receptor the moment the stem lands, the answer is already written; the drug simply follows from the biology. Numbers that carry weight are given only where a canonical source verifies them, and any figure you should confirm against a current formulary before quoting is flagged (Stahl 2021; Kaplan & Sadock 2024; Meyer & Stahl 2019; Taylor 2021).

HOLD THIS

Name the mechanism first and the answer writes itself: presentation, then the one mechanism that explains it, then the first move it forces. Galactorrhoea to tuberoinfundibular D2; clonus to 5-HT2A; smoking-cessation sedation to lost CYP1A2 induction; rapid antidepressant response to NMDA-to-AMPA-to-BDNF.

22.1 Vignette 1: galactorrhoea on a D2 antagonist, and the tuberoinfundibular logic

CLINICAL ANCHOR

A young man with a first episode of psychosis (ICD-11 6A20 schizophrenia; DSM-5-TR schizophrenia) is started on risperidone and responds well over three weeks. He then returns distressed, reporting breast tenderness and a milky nipple discharge; a woman on the same drug might present with galactorrhoea, amenorrhoea or loss of libido. Serum prolactin is raised.

Reasoning. Dopamine tonically *inhibits* prolactin release: it is the prolactin-inhibiting factor, travelling from the hypothalamus down the **tuberoinfundibular pathway** to act on D2 receptors on the lactotrophs of the anterior pituitary. A D2 antagonist blocks that brake, so prolactin rises unopposed, producing hyperprolactinaemia and its downstream galactorrhoea, menstrual disturbance and hypogonadism. This is the one classic dopamine pathway that lies largely *outside* the blood-brain barrier, which is why even a drug that raises prolactin need not be the most sedating or extrapyramidal-prone one: risperidone, amisulpride and the typical antipsychotics are the notable prolactin-raisers because they occupy pituitary D2 heavily and, unlike quetiapine or olanzapine, bind tightly without the offsetting rapid dissociation from D2 (Stahl 2021; Kaplan & Sadock 2024).

Management pointer. After excluding other causes of a raised prolactin (pregnancy, a prolactinoma, hypothyroidism), the mechanistically clean move is to switch to an agent that does not lock the tuberoinfundibular D2 receptor. **Aripiprazole** is the archetype: a D2 *partial agonist*, it supplies enough intrinsic dopamine tone at the lactotroph to hold prolactin down while still antagonising the overactive mesolimbic signal, which is why aripiprazole is described as prolactin-sparing and is used both as a switch target and as an add-on to lower antipsychotic-induced hyperprolactinaemia. The full switching and monitoring protocol belongs to the clinical psychiatry chapters (Paper II).

COMMON TRAP

Do not reach for a dopamine agonist such as bromocriptine or cabergoline as the reflex answer in a psychotic patient: adding a dopaminergic drug can destabilise the psychosis it is meant to sit alongside. The receptor-level fix is a partial agonist that raises tone *at the pituitary* without flooding the mesolimbic system, which is exactly the aripiprazole solution.

22.2 Vignette 2: agitation, hyperreflexia and fever on SSRI plus tramadol, the serotonin toxidrome

CLINICAL ANCHOR

A woman on a stable dose of an SSRI for depression (ICD-11 6A70 single episode depressive disorder; DSM-5-TR major depressive disorder) is prescribed tramadol for back pain. Within hours she becomes agitated and restless, then develops tremor, brisk lower-limb reflexes with inducible clonus, sweating, a rising temperature and a racing pulse.

Reasoning. This is **serotonin syndrome (serotonin toxicity)**, an excess-serotonin state that evolves over hours rather than days, driven here by a two-drug additive load on serotonergic transmission. The SSRI blocks the serotonin transporter (SERT), raising synaptic 5-HT; tramadol adds to the same pool by *two* routes, weak SERT inhibition and, importantly, an examinable pharmacokinetic twist, so the combination pushes serotonergic tone past threshold. The clinical picture is the Hunter triad and maps directly onto over-stimulation of postsynaptic serotonin receptors, chiefly **5-HT2A** (and 5-HT1A): *neuromuscular excitation* (clonus, hyperreflexia, tremor, rigidity, with a lower-limb predominance), *autonomic instability* (hyperthermia, diaphoresis, tachycardia, mydriasis, diarrhoea) and *altered mental state* (agitation, delirium). Spontaneous or

inducible clonus, especially ocular and lower-limb, is the single most useful discriminator (Kaplan & Sadock 2024).

Management pointer. The mechanism dictates the moves: stop every serotonergic agent, then supportive care with cooling and benzodiazepines for agitation and rigidity, escalating to the 5-HT2A antagonist **cyproheptadine** in more severe cases; hyperthermia above roughly 41 degrees Celsius with rigidity is the critical-care threshold and mandates aggressive cooling, sedation and consideration of paralysis (confirm the exact figure and dosing on the clinical psychiatry chapters (Paper II)). The take-home for the science paper is that naming the receptor (5-HT2A) tells you the antidote (a 5-HT2A blocker).

COMMON TRAP

Serotonin syndrome versus neuroleptic malignant syndrome. Both give hyperthermia and altered mental state, but serotonin toxicity is *hyperkinetic* (clonus, hyperreflexia, rapid onset over hours, a serotonergic drug or combination) whereas NMS is *hypokinetic* (lead-pipe rigidity *without* clonus, bradyreflexia, slower onset over days, a dopamine antagonist or dopaminergic withdrawal). If the stem gives clonus, it is serotonin syndrome; tramadol added to an SSRI is a stock precipitant, alongside MAOIs, linezolid and triptans.

22.3 Vignette 3: a stabilised clozapine patient quits smoking and turns toxic, the 1A2 induction story

CLINICAL ANCHOR

A man with treatment-resistant schizophrenia (ICD-11 6A20; DSM-5-TR schizophrenia) has been stable for a year on a fixed dose of clozapine. He is a heavy smoker. He is admitted for an unrelated reason, the ward is smoke-free, and he stops smoking abruptly. Over the next several days he becomes increasingly sedated and drowsy, with hypersalivation and, in the worst case, myoclonic jerks or a seizure.

Reasoning. Clozapine is metabolised predominantly by the hepatic isoenzyme **CYP1A2**. It is the *polycyclic aromatic hydrocarbons* in tobacco smoke, not the nicotine, that are the relevant **CYP1A2 inducers**, so a chronic smoker runs an up-regulated enzyme and clears clozapine faster; his stable dose is in fact a dose calibrated to induced metabolism. When smoking stops, induction fades over roughly a week to ten days, CYP1A2 activity falls back to baseline, clearance drops, and plasma clozapine climbs into the toxic range at an unchanged dose, producing dose-dependent sedation, hypersalivation, and a seizure risk that is itself concentration-dependent. The magnitude is examinable: for any given dose, nonsmokers reach plasma clozapine levels around 50 percent higher than smokers (Meyer & Stahl 2019). Nicotine replacement does *not* prevent this, because nicotine is not the inducer, a favourite distractor.

Management pointer (TDM/dose logic). This is the paradigm case for **therapeutic drug monitoring**: check a clozapine level and pre-emptively reduce the dose on cessation, guided by the level rather than by symptoms alone, and warn every clozapine patient at initiation to tell the prescriber before they start, stop or change smoking. The reciprocal trap is the patient who

resumes smoking and loses efficacy as levels fall. Target-range figures and the reduction schedule sit on the clinical psychiatry chapters (Paper II); verify the current recommended plasma range against your formulary (Taylor 2021).

MNEMONIC

SMOKE INDUCES 1A2; STOP AND YOU RISE

Smoke (the tar, not the nicotine) *induces* CYP1A2, so smokers need *more* clozapine (or theophylline, olanzapine, caffeine, all 1A2 substrates). Stopping removes the inducer, levels rise, toxicity follows. The direction is the whole point: induction lowers levels, so losing the inducer raises them.

TRAP Nicotine replacement does not prevent the clozapine surge on quitting: the polycyclic aromatic hydrocarbons in smoke, not the nicotine, are the CYP1A2 inducer.

22.4 Vignette 4: IV ketamine in treatment-resistant depression, the NMDA to BDNF to mTOR cascade

CLINICAL ANCHOR

A patient with treatment-resistant depression (ICD-11 6A70/6A71; DSM-5-TR major depressive disorder), having failed several adequate antidepressant trials, is given a single sub-anaesthetic intravenous infusion of ketamine at 0.5 mg/kg over about forty minutes. Mood improves within hours, well ahead of any monoamine timeline, with a transient dissociative experience during the infusion (Berman 2000; Zarate 2006).

Reasoning. Ketamine is a non-competitive **NMDA-receptor antagonist**, and its speed is the tell that this is not a monoamine mechanism. The leading account is a disinhibition cascade: by blocking NMDA receptors preferentially on GABAergic inhibitory interneurons, ketamine lifts inhibitory tone on glutamatergic pyramidal neurons, producing a **glutamate surge**. That surge drives postsynaptic **AMPA receptors**, and the downstream signalling, blockade of spontaneous NMDA activation relieving inhibition of eEF2 kinase to permit **BDNF** translation, together with suppression of extrasynaptic-NMDA-driven restraint of **mTOR**, converges on TrkB and the mTOR complex to trigger rapid protein synthesis, synaptogenesis and synaptic potentiation in prefrontal cortex. The active metabolite (2R,6R)-hydroxynorketamine is implicated in the AMPA-dependent, possibly NMDA-independent, limb of the effect (Kaplan & Sadock 2024). The final common path, BDNF and synaptic plasticity, is the same endpoint the delayed monoamine antidepressants reach slowly; ketamine reaches it in hours.

Management pointer (monitoring). The mechanism also frames the risks: the same NMDA antagonism that lifts mood produces the *dissociative and psychotomimetic* effects and a transient rise in blood pressure and heart rate, so infusions are given in a monitored setting with blood-pressure and mental-state observation during and after, and abuse potential is respected. The intranasal S-enantiomer esketamine is the licensed formulation for treatment-resistant depression and is dispensed under a supervised, monitored protocol with post-dose observation.

Full monitoring schedules, eligibility and the observation window belong to the clinical psychiatry chapters (Paper II).

PEARL

Keep the three fast-acting mechanisms mechanistically separate, because the exam pairs them. Ketamine and esketamine work at the *glutamate/NMDA* receptor; the neuroactive steroids brexanolone and **zuranolone** are positive allosteric modulators at *GABA-A*; the classical psychedelics (psilocybin) are *5-HT2A* agonists. Three different receptors, one shared clinical promise of rapid antidepressant action, and three different monitoring profiles.

22.5 The four vignettes at a glance: system, discriminator, first move

The consolidating grid. Read the discriminator column first: in each stem it is the single feature that names the mechanism and therefore writes the answer.

VIGNETTE	SYSTEM / MECHANISM	DISCRIMINATOR IN THE STEM	FIRST MOVE
1. Galactorrhoea on a D2 antagonist	Tuberoinfundibular dopamine pathway; loss of the prolactin-inhibiting brake	**Raised prolactin with galactorrhoea, on a prolactin-raising antipsychotic (risperidone, amisulpride, typicals)**	Switch to / add aripiprazole (D2 partial agonist, prolactin-sparing)
2. Agitation, hyperreflexia, fever on SSRI + tramadol	Serotonin excess at 5-HT2A/1A; serotonin toxicity	**Clonus (inducible, ocular, lower-limb) and hyperreflexia, rapid onset over hours**	Stop serotonergics, benzodiazepines, cyproheptadine (5-HT2A antagonist) if severe
3. Sedation and seizure after quitting smoking on clozapine	Loss of CYP1A2 induction; rising clozapine level	**Recent smoking cessation in a previously stable clozapine patient (tar, not nicotine, was the inducer)**	Check level, pre-emptively reduce dose (TDM-guided)
4. Rapid response to IV ketamine in TRD	NMDA antagonism to glutamate surge to AMPA to BDNF/mTOR plasticity	**Antidepressant effect within hours plus transient dissociation, ahead of any monoamine timeline**	Monitored setting: BP, heart rate, mental state during and after

Four systems, four discriminators: a dopamine pathway, a serotonergic toxidrome, a cytochrome P450 isoenzyme, and a glutamate-receptor cascade. In every row the discriminator names the mechanism and the mechanism forces the first move.

23 · Consolidate: mnemonic total, retrieval and synthesis

This closing block is not new material; it is a **consolidation device** for the whole of these notes. This material has run one long circuit, from molecule to syndrome: the transmitter systems and their receptors, the neuropeptides and gasotransmitters, the second-messenger cascades that carry the signal inward, the three neuroendocrine axes, the neurotrophic and neurodevelopmental machinery, and the structural imaging that reads all of it out at the level of

the whole brain. **Study by producing, not by re-reading.** Durable learning comes from spaced *active recall* (self-testing from memory) rather than repeated passive review, the testing effect that Roediger and Karpicke (2006) demonstrated directly. The three subtopics below give you the loop to run it: one master mnemonic that chains the smaller topic mnemonics into a single spine, a set of answer-free retrieval prompts, and a one-page synthesis map to redraw from memory.

Use them in that order. Recite the mnemonic spine to confirm the scaffold is intact, close the notes and work the retrieval prompts aloud, then take a blank sheet and rebuild the whole-day circuit from transmitter through receptor to drug to clinical effect. Where a limb of the map will not come, that gap is the prediction error naming the exact topic to reopen, which is the entire point of the exercise.

HOLD THIS

Learn by producing, not re-reading: spaced active recall beats passive review (the testing effect). Every limb of the map that will not come is the prediction error naming the exact topic to reopen.

System	Receptor	Drug acting here	Clinical read-out
Dopamine	D2	antipsychotic (D2 block)	positive symptoms down; EPS
Serotonin	5-HT2A, SERT	SSRI; atypical antipsychotic	mood up; anxiety down
Noradrenaline	alpha-2, beta	SNRI; alpha-2 agonist	arousal, attention
Glutamate	NMDA	ketamine (open-channel block)	rapid antidepressant
GABA	GABA-A	benzodiazepine	anxiolysis, sedation
Acetylcholine	M, nicotinic	cholinesterase inhibitor	memory (Alzheimer)
HPA axis	CRH, cortisol	dexamethasone (DST probe)	stress; melancholia
Imaging	D2 occupancy	PET, 65 to 80%	antipsychotic window

Cover the right three columns and rebuild each row from the system name alone.

CONCEPT AXIS · SYSTEM TO RECEPTOR TO DRUG TO EFFECT ■ the chapter in one grid

Fig 2.21 The whole synthesis map. Every system here reduces to one line: a transmitter or axis, the receptor that reads it, the drug that acts there, and the clinical effect that follows. This is the retrieval device for the chapter, redraw it from memory and the gaps are your revision list.

23.1 Master mnemonic total: chaining the chemistry into one spine

Every topic today already carries its own mnemonic. The problem at revision is not recalling any single one but retrieving the correct one under time pressure and in the right order. The device below is a *mnemonic of mnemonics*: a spine that indexes the transmitter systems, the three

endocrine axes, the imaging rules and the pharmacology principle, so that recalling the spine pulls each sub-mnemonic up with it. Walk it from the outside in, transmitters and their receptors first, then the cascade inside the cell, then the slow endocrine and trophic loops, then the picture the scanner returns.

MNEMONIC

"DA-SANG Signals, Peptides and Gases Whisper, Q Cuts the DIP, CAP the Three Axes, Stress Bends and Treatment Mends, Ventricles Up and Hippocampus Down"

DA-SANG fixes the six classical transmitter systems as an ordered set: *DA* dopamine, then *S*erotonin, *A*cetylcholine, *N*oradrenaline, *G*ABA and glutamate as the paired inhibition-excitation backbone. Each expands to its own device. Dopamine runs on "Limbic Lights up, Cortex Cools, Nigra Numbs, Tubero Talks (prolactin)": the four pathways as mesolimbic (positive symptoms, hyperdopaminergic), mesocortical (negative and cognitive, hypodopaminergic), nigrostriatal (extrapyramidal side effects) and tuberoinfundibular (hyperprolactinaemia). Serotonin runs on "1 is Inhibitory / auto, 2 is Excitatory / cortical, 3 is a Channel": 5-HT1A as the somatodendritic autoreceptor and anxiolytic target, 5-HT2A as the cortical excitatory receptor blocked by atypical antipsychotics, 5-HT3 as the one ionotropic (ligand-gated channel) serotonin receptor, the antiemetic target. Acetylcholine runs on "ACh WAKES you to LEARN and to DREAM": basal-forebrain projections for arousal and memory (the cortex that degenerates in Alzheimer), and brainstem groups driving REM. Noradrenaline runs on "A-VATS": Arousal, Vigilance, Attention, Threat-response, Stress-memory, all from the locus coeruleus. GABA runs on "FRequency vs duRation: Benzos are FRequent, Barbs enduRe": benzodiazepines raise the frequency of GABA-A channel opening, barbiturates prolong its duration, the single fact that explains the wider therapeutic index of the benzodiazepines. Glutamate runs on MEMANTINE = "MEMory, MEek block": the low-affinity uncompetitive NMDA blocker of the hypofunction model, the same receptor whose blockade by ketamine yields the rapid antidepressant effect.

Peptides and Gases Whisper chains the slow and unconventional signals. The opioid peptides run on "END-en-DYN to mu-delta-kappa; Kappa = Krummy": endorphin, enkephalin and dynorphin mapping to their receptors, with kappa activation dysphoric. The gasotransmitters run on "NO-CO-H2S: Not stored, no receptor, just diffuse": nitric oxide, carbon monoxide and hydrogen sulphide, made on demand, not vesicle-packaged, acting through diffusion rather than a membrane receptor. "Whisper" flags the theme: these are modulators layered on top of fast transmission (substance P and neurokinin-1 in pain and mood, CRF driving the stress axis, oxytocin in affiliation), not the fast synaptic signal itself.

Q Cuts the DIP is the second-messenger spine, "Q cuts PIP2 into a DIP": Gq activates phospholipase C, which cuts PIP2 into DAG and IP3 (the DAG-IP3 pair), IP3 releasing intracellular calcium and DAG activating protein kinase C. Hold it beside the Gs-cyclic-AMP-PKA arm and the Gi arm that lowers cyclic AMP, and the whole transduction layer that converts a metabotropic receptor event into a slow intracellular consequence sits in one line. This is where lithium acts, inside the cell on the phosphoinositide cycle, not at a receptor.

CAP the Three Axes encodes the neuroendocrinology. "CAP for the cascade, top to bottom" is the HPA axis: CRF from the hypothalamus, ACTH from the pituitary, and cortisol (the P for the adrenal *p*roduct) from the adrenal cortex, restrained by hippocampal negative feedback. Add the thyroid axis on "T3 to Treat, T4 to the Thinker" (T3 the active augmentation agent, T4 the storage form crossing to the brain) and the gonadal axis as the third HPx loop, and the trio of endocrine cascades is fixed. The exam discriminator for the stress axis is the direction: "Depression is HIGH and escapes; PTSD is LOW and over-suppresses" on the dexamethasone suppression test.

Stress Bends and Treatment Mends is the neurotrophin line, "Stress Bends, Treatment Mends: BDNF": chronic stress and hypercortisolaemia lower BDNF and shrink the hippocampus, while antidepressants, lithium and exercise raise it, the neurotrophic hypothesis of depression. It chains straight into neurodevelopment on "Nervous Programmers Make Dozens, Synapse Away, Myelinate" (proliferation, migration, differentiation, synaptogenesis, apoptosis/pruning, myelination) and the "two hits" model of a first insult in utero and a second trigger in adolescence.

Ventricles Up and Hippocampus Down closes the chapter on the imaging readout: "Ventricles up, hippocampus down, white matter bright, atrophy where the syndrome lives", paired with the sequence rule "T1 = anatomy, fat white; FLAIR = T2 minus water". Ventricular enlargement is the single most replicated structural finding in schizophrenia; hippocampal volume loss tracks depression, PTSD and early Alzheimer; white-matter hyperintensities mark vascular and late-life illness. The toolkit that produces these findings is VBM (where does grey matter differ across the brain), volumetric MRI (how big is this one structure) and DTI or fractional anisotropy (how intact is this tract).

The table restates the spine so you can quiz yourself on any single link. Cover the right two columns and recall the sub-mnemonic and its content from the cue phrase alone.

SPINE LINK	SUB-MNEMONIC	WHAT IT UNLOCKS
DA (dopamine)	Limbic Lights, Cortex Cools, Nigra Numbs, Tubero Talks	**Four pathways: mesolimbic, mesocortical, nigrostriatal, tuberoinfundibular, each to its clinical syndrome**
S (serotonin)	1 inhibitory/auto, 2 excitatory/cortical, 3 a channel	5-HT1A autoreceptor, 5-HT2A cortical, 5-HT3 the one ionotropic receptor
A / N (ACh, NA)	ACh WAKES-LEARN-DREAM; NA is A-VATS	**Cholinergic arousal, memory and REM; noradrenergic arousal, vigilance, threat, stress-memory**
G (GABA / glutamate)	FRequency vs duRation; MEMANTINE MEek block	Benzos raise frequency, barbiturates prolong duration; low-affinity NMDA blockade in hypofunction
Peptides and gases	END-en-DYN to mu-delta-kappa; NO-CO-H2S diffuse	**Opioid peptide-receptor map (kappa dysphoric); gasotransmitters unstored, receptorless, diffusing**
Second messenger	Q cuts PIP2 into a DIP	Gq to PLC to DAG plus IP3 to calcium and PKC, beside the Gs-cAMP-PKA arm; lithium acts here
Three axes (CAP)	CRF-ACTH-cortisol; T3 to Treat, T4 to Thinker	**HPA cascade with hippocampal feedback, HPT and HPG loops; DST direction in depression vs PTSD**

SPINE LINK	SUB-MNEMONIC	WHAT IT UNLOCKS
Trophic and development	Stress Bends, Treatment Mends; N-P-M-D-S-A-M; two hits	BDNF down with stress, up with treatment; developmental sequence; neurodevelopmental model
Imaging	Ventricles up, hippocampus down; T1 anatomy, FLAIR T2 minus water	**Replicated structural findings and the sequence rules; VBM, volumetric MRI, DTI toolkit**

The nine-link master spine for this chapter, each row a cue phrase pointing to a topic mnemonic; recall the middle and right columns from the left cue alone.

23.2 Active-recall prompts: cover the page and answer aloud

These are retrieval questions, not a summary. They are deliberately answer-free, so that they force you to generate the answer from memory, which is where the testing effect does its work; printing a model answer here would defeat the device. Cover everything below the label, answer each aloud in a full sentence, then reopen the relevant topic only for the prompts you could not complete.

RETRIEVAL PRACTICE, COVER THE ANSWERS

1. Name the four dopamine pathways, state whether each is hyper- or hypodopaminergic in schizophrenia, and give the clinical consequence of blocking the tuberoinfundibular pathway.
2. Distinguish 5-HT1A, 5-HT2A and 5-HT3 by location, signalling class and one drug that targets each, and say which is the only ionotropic serotonin receptor.
3. State the single biochemical fact that terminates acetylcholine differently from the monoamines, and explain why that dictates the drug class used to raise it in Alzheimer disease.
4. Give the five functions of the noradrenergic locus coeruleus and name the receptor an alpha-2 agonist acts on to reduce sympathetic outflow.
5. Contrast how benzodiazepines and barbiturates act on the GABA-A channel, and explain from that difference why one has the wider therapeutic index.
6. Explain the NMDA hypofunction model of psychosis, and state why memantine is tolerated as a chronic NMDA blocker while ketamine is not.
7. Map the three opioid peptides to their receptors and say which receptor produces dysphoria; then give the three defining features that separate a gasotransmitter from a classical transmitter.
8. Trace the Gq cascade from receptor to intracellular calcium, naming each intermediate, and state where in this pathway lithium is thought to act.
9. Recite the HPA cascade from hypothalamus to cortisol, name the structure providing negative feedback, and give the opposite dexamethasone-suppression-test directions of depression and PTSD.
10. Explain lithium-induced hypothyroidism, how it is managed, and why a depressive relapse in a euthymic lithium-treated patient should prompt a thyroid test before an antidepressant.
11. State the neurotrophic hypothesis of depression in terms of BDNF and the hippocampus, and name three interventions that raise BDNF.
12. List the developmental sequence from proliferation to myelination, and explain the "two-hit" neurodevelopmental model of schizophrenia.
13. Give the single most replicated structural imaging finding in schizophrenia, the structure that shrinks in depression and PTSD, and what white-matter hyperintensities signify.
14. Distinguish VBM, volumetric MRI and DTI or fractional anisotropy by the exact question each answers about brain structure.
15. State the T1, T2 and FLAIR sequence rules in one line each, and say which sequence nulls cerebrospinal fluid to reveal periventricular disease.
16. Explain the KarXT (xanomeline-trospium) strategy of exploiting the blood-brain barrier for selectivity, and name the analogous older strategy used with levodopa in Parkinson disease.

If more than a third of these will not come cleanly, do not push through the list a second time the same day; space the next attempt, because retrieval spaced across days is what builds durable memory (Roediger and Karpicke 2006).

23.3 Synthesis map: the one page to redraw from memory

The final consolidation step is to build a single **synthesis map** and *redraw from memory* the whole of this chemistry along one axis: **transmitter to receptor to drug to clinical effect**. On a blank sheet, place the six transmitter systems down the left as a column of nuclei of origin, carry each rightward to its principal receptor (ionotropic or metabotropic), then to the drug that acts there, then to the clinical effect that follows, so that dopamine reads across as mesolimbic to D2 to antipsychotic to reduced positive symptoms, serotonin as raphe to 5-HT1A/2A to SSRI or atypical to mood and antipsychotic effect, GABA and glutamate as the inhibition-excitation pair with their channel drugs, and acetylcholine and noradrenaline as the arousal modulators. Below the transmitter block, draw the three neuroendocrine axes as vertical cascades (HPA with its hippocampal feedback loop, HPT and HPG beside it), and to the right of them the trophic and developmental line (stress lowering BDNF, treatment raising it, feeding the neurodevelopmental two-hit model). Across the top, run the imaging readout as a banner: ventricles up, hippocampus down, white matter bright, annotated with the T1, T2 and FLAIR rules and the VBM, volumetric-MRI and DTI toolkit. Redraw it once from memory, then check it against the figures in this chapter and fill only the gaps; the act of reconstructing the map, not admiring a finished one, is what fixes the arc from molecule through receptor and drug to syndrome. The figure to rebuild is a four-column flow, transmitter to receptor to drug to clinical effect, with the three axes and the imaging findings drawn as the endocrine and structural frame around it.

Previously asked

Real long-essay (25-mark) and short-note (10-mark) questions from this territory.

LONG ESSAYS (25 MARKS)

- Q CSF / Neuropeptide Y / Post ictal psychoses / Prosopagnosia. MUHS 2012
- Q Describe Neuropsychiatric manifestations of Thyroid Disorder. MUHS 2016, 2018
- Q Describe physiological and psychological aspects of stress. MUHS 2017
- Q Describe the anatomy of monoamine neurotransmitter system. MUHS 2011
- Q Difference between neuropeptides and other neurotransmitters. Discuss BDNF and its role in neuroscience. MUHS 2017
- Q Discuss neurotransmitters in detail. MUHS 2011
- Q Merits of available neuroimaging techniques and their application in psychiatry. MUHS 2012, 2014
- Q Neuropeptides / Working memory. MUHS 2012, 2018
- Q Neuropsychiatric Manifestations of thyroid disorder and its management. MUHS 2016
- Q Organic Hallucinosis / Ablative neurosurgery / Circadian sleep wake rhythm. MUHS 2012, 2015
- Q What are the principles of Functional MRI and its use in Psychiatry?. MUHS 2013

SHORT NOTES (10 MARKS)

- Cannabinoid receptors. MUHS 2014
- Cannabinoid receptors / Long term potentiation / Nucleus accumbens. MUHS 2014, 2015
- Describe anatomy of monoamine neurotransmitter system. MUHS 2011
- Difference between neuropeptides and other neurotransmitters - discuss BDNF. MUHS 2017
- Dopamine / Temporal lobe. MUHS 2014
- Dopamine and dopaminergic pathways. MUHS 2013, 2014
- Dopamine receptors. MUHS 2011
- Dopamine receptors / Neurotransmitters. MUHS 2011
- Glutamate. MUHS 2014
- Glutamate / Glutamate Neurotransmission. MUHS 2014, 2016
- Glutamate as neurotransmission. MUHS 2016
- Management of Hyperprolactinemia in Psychiatry. MUHS 2011
- Melatonin. MUHS 2013
- MRI in schizophrenia. MUHS 2015
- Neuropeptide Y. MUHS 2012
- Neuropeptides with special reference to cholecystokinin. MUHS 2013
- Neurotrophic factors. MUHS 2013
- Neurotrophic factors / Implicit Memory / Melatonin. MUHS 2013
- Normal waves in EEG / Functional Magnetic Resonance Imaging / Dopaminergic Pathways. MUHS 2011, 2012, 2013
- Parietal lobe / Acetylcholine. MUHS 2014
- Psychiatric Manifestations of Hypothyroidism / Psychiatric Manifestations of Vitamin B12 deficiency. MUHS 2012
- Quantitative EEG / PET Scan. MUHS 2013
- Serotonin. MUHS 2017
- Serotonin dopamine antagonist. MUHS 2012
- Serotonin syndrome. MUHS 2018
- SPECT. MUHS 2021

Quick review

The whole picture in one table	
CLASSIFYING NEUROTRANSMITTERS	Five axes on one list: chemical class (small-molecule = monoamines / amino-acids / ACh, vs neuropeptide vs gasotransmitter vs lipid); function (glutamate excites, GABA inhibits, monoamines modulate); ionotropic (fast channel) vs metabotropic (slow GPCR); vesicular vs made-on-demand and retrograde (gases, endocannabinoids); Dale's principle and co-transmission.
DOPAMINE	Tyrosine to L-DOPA (TH rate-limiting) to DA; D1-like Gs, D2-like Gi. Four pathways: mesolimbic (positive symptoms), mesocortical (negative and cognitive), nigrostriatal (EPS), tuberoinfundibular (prolactin). Aberrant salience; raised presynaptic synthesis on FDOPA-PET.
SEROTONIN	Tryptophan to 5-HTP (TPH2) to 5-HT to 5-HIAA (MAO-A). 5-HT1A auto and heteroreceptor, 5-HT2A (hallucinogen and atypical-antipsychotic target), 5-HT3 ionotropic (emesis). SSRI lag = autoreceptor desensitisation. Serotonin syndrome.
NORADRENALINE AND ADRENALINE	DA to NA via DBH, then MHPG; adrenaline made by PNMT in C1 to C3 neurons. Locus coeruleus origin. alpha-1, alpha-2 autoreceptor, beta. Arousal, attention, stress; SNRIs, alpha-2 agonists, atomoxetine.
GLUTAMATE	Glutamate-glutamine cycle; NMDA (GluN1/2, Mg block, glycine/D-serine co-agonist), AMPA, kainate, mGluR. NMDA hypofunction (ketamine, PCP) is the disinhibition model of psychosis. Ketamine to BDNF to mTOR = rapid antidepressant. Excitotoxicity; anti-NMDA-receptor encephalitis.
GABA	GAD synthesis. GABA-A (pentameric Cl- channel; benzodiazepine increases frequency, barbiturate duration, plus neurosteroid, alcohol, picrotoxin block, flumazenil antagonist); GABA-B (Gi, baclofen). Neurosteroids brexanolone and zuranolone.
ACETYLCHOLINE	ChAT synthesis, AChE breakdown; nicotinic (ionotropic) vs muscarinic M1 to M5 (metabotropic). Nucleus basalis of Meynert. Cholinergic hypothesis of Alzheimer disease (ChEIs); anticholinergic delirium; xanomeline-trospium (KarXT).
NEUROPEPTIDES AND NOVEL TRANSMITTERS	Co-transmission; substance P/NK1, CRH, oxytocin and vasopressin, endogenous opioids (endorphins, enkephalins, dynorphins; mu/delta/kappa), NPY, CCK, orexin (DORAs). Novel: endocannabinoids (anandamide, 2-AG, CB1, retrograde), nitric oxide (nNOS, retrograde, LTP), TAAR1 (ulotaront).
SIGNALLING, PLASTICITY, DEVELOPMENT	GPCR: Gs to adenylyl cyclase to cAMP to PKA; Gq to PLC to IP3/DAG to PKC; Gi inhibits; both converge on CREB and gene transcription (the slow layer, hence antidepressant lag). Lithium: IMPase and GSK-3. BDNF-TrkB neurotrophic hypothesis (Val66Met). Neurodevelopment: migration, synaptic

The whole picture in one table	
	pruning (adolescent peak), critical periods, two-hit model.
NEUROENDOCRINE AXES	HPA: CRH to ACTH to cortisol; DST non-suppression in melancholia. HPT: subclinical hypothyroidism and depression, T3 augmentation, lithium and thyroid. HPG: PMDD, perinatal, menopause; prolactin and antipsychotics. Circadian: SCN clock genes (CLOCK, BMAL1, PER, CRY); melatonin from the pineal; agomelatine, ramelteon.
NEUROIMAGING	Structural: CT (bone and acute blood bright, the emergency scan) vs MRI (T1 anatomy, T2 and water bright, FLAIR suppresses CSF, DWI catches acute infarct); ventricular enlargement in schizophrenia. Functional: fMRI BOLD, PET/SPECT; hypofrontality, D2 occupancy 65 to 80%, subgenual ACC in depression, cortico-striato-thalamic loop in OCD, FDG and amyloid PET in dementia.
PHARMACOLOGY	PK (ADME): bioavailability, volume of distribution, half-life, steady state, therapeutic drug monitoring (lithium, valproate, clozapine). PD: agonist / partial / antagonist / inverse agonist; EC50 = potency, plateau = efficacy; aripiprazole partial agonist. CYP450 (2D6, 3A4, 1A2, 2C19): fluoxetine and paroxetine inhibit 2D6, smoking induces 1A2. Tolerance (PK vs PD), dopamine supersensitivity and tardive dyskinesia, discontinuation.

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FIGURE CREDITS

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PART III

III

Psychiatric Genetics

How psychiatric risk is inherited, how it is located in the genome, and what the clinic does with it.

01 Foundations

02 Methods: locating the risk

03 Mechanisms

04 Findings in the clinic

05 Discriminate

06 Apply and consolidate

Psychiatric Genetics

Six sections · 16 topics · one complete notes document

Psychiatric disorders are among the most heritable conditions in medicine, yet almost none of them obey Mendel. This chapter is built as a toolkit: each method answers one question about where the risk lives. **Learn the tool, not just the result.** The order runs the way the field itself moved: first establish that a disorder is familial and heritable (family, twin, adoption studies), then locate the risk (linkage, then genome-wide association, then rare variants and sequencing), then read it back as mechanism (epigenetics, endophenotypes, neurodevelopment), as clinical fact (heritability figures, the schizophrenia story, pharmacogenetics), and finally as something you can apply in a counselling room. Almost every answer here rewards the candidate who names the right study design and the key finding together, rather than reciting a list of genes.

HOW TO USE THESE NOTES

Every figure declares one axis and codes it in colour and shape, with a small legend. The colours are consistent throughout: **petrol** marks the method, the structure and the neutral relay; **coral** marks risk, pathology or a rare large-effect variant; and **marigold** highlights the key finding or the common-variant signal. Watch for the boxes marked **Good to remember**: they gather every named gene, locus, allele and hard number in one place so the reference facts sit apart from the reasoning.

Foundations

1 · Orientation and the genetics toolkit

Before the detail, the frame. Psychiatric disorders sit on a paradox you have to hold throughout: they are among the *most heritable* conditions in medicine, yet almost none of them are inherited in a clean Mendelian way. There is no single gene for schizophrenia the way there is one for Huntington disease. Instead, risk is **polygenic and complex**: thousands of common variants each add a sliver of liability, a minority of rare large-effect variants (copy-number variants and de novo mutations) shove a few individuals hard toward illness, and the whole thing plays out on a developing brain over time. The single move that runs through this material, repeated in the margin: **heritable but not Mendelian, common-variant-mostly but rare-variant-punchy, and read out through neurodevelopment**. Hold that and every method below has a job to do.

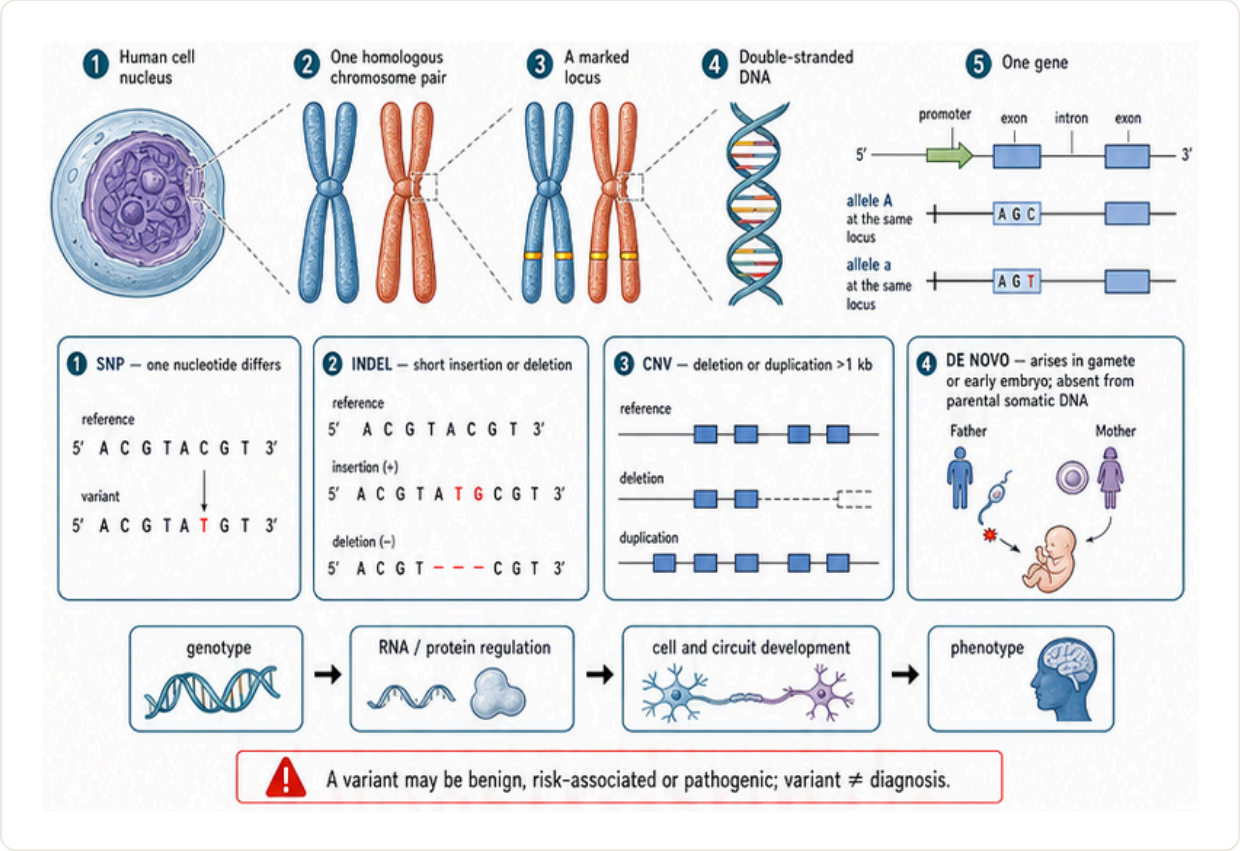


Fig 3.1 From chromosome to variant.

The reason genetics is a Paper-1 staple is that examiners test the *logic of the toolkit*, not just facts: each study design answers exactly one question, and the designs form a ladder from the crudest (does it run in families?) to the most granular (which base changed?). The classic epidemiological trio (Kaplan & Sadock 2024) establishes *that* genes matter and roughly how much; the molecular methods then ask *which* genes, and the modern aggregate methods ask *how much of one person's risk* we can now read from their genome. This topic lays out the whole map so that when a later topic drills into schizophrenia or pharmacogenomics, you already know which rung of the ladder it is standing on.

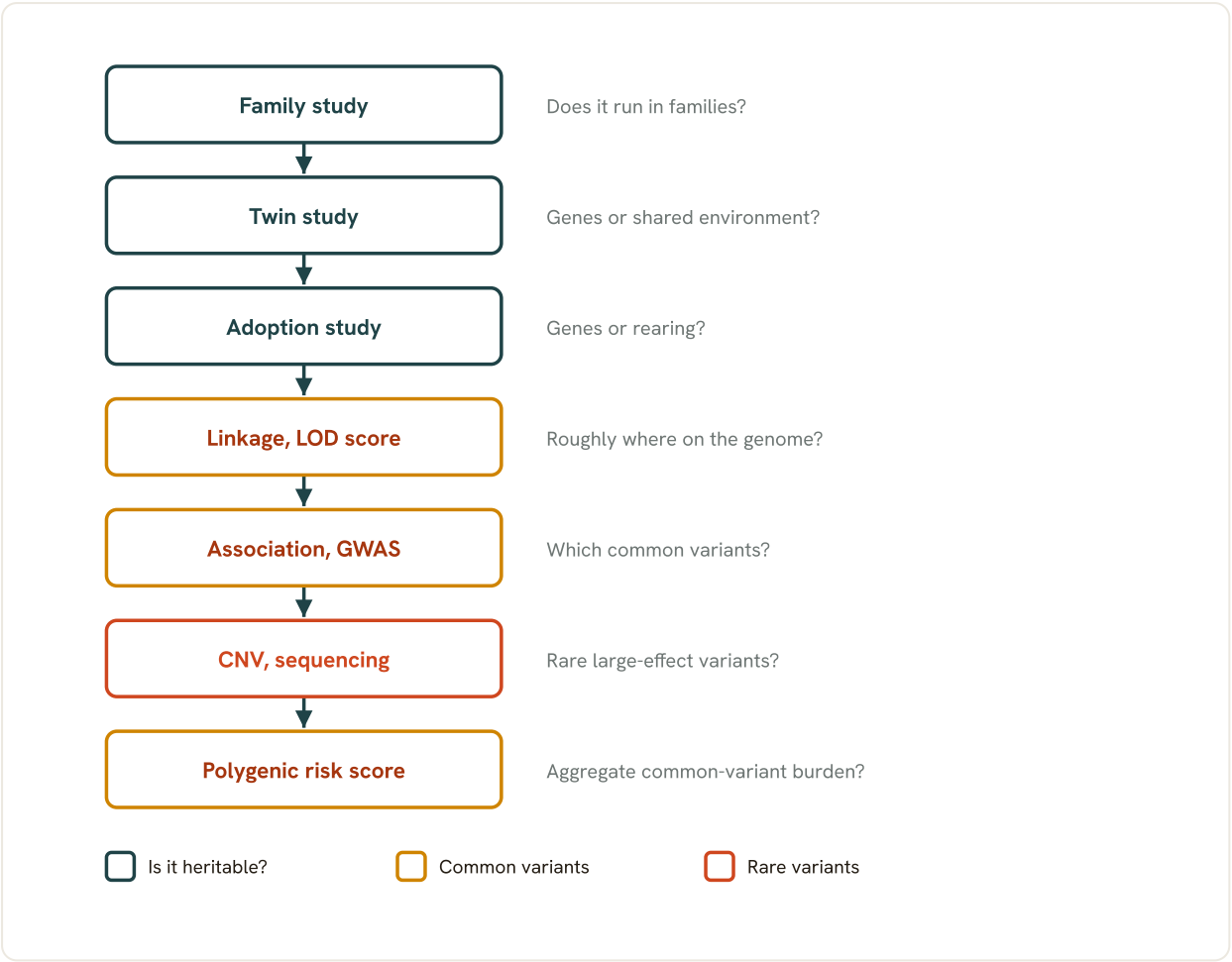


Fig 3.2 The psychiatric genetics toolkit as an evidence hierarchy. Each method answers one question, and the field moved down the ladder in this order: family, twin and adoption studies first establish that risk is heritable and separate genes from environment; linkage then genome-wide association locate the risk with rising resolution; copy-number and sequencing methods catch the rare large-effect variants; and the polygenic risk score aggregates the common-variant burden. Colour marks the job: petrol establishes heritability, marigold locates common variants, coral flags rare variants.

1.1 The central paradox: highly heritable, non-Mendelian, mostly polygenic

The frame for the whole set of notes. High **heritability** (the proportion of population variation in a trait attributable to genetic variation) tells you genes matter a great deal, but it says nothing about *how many* genes or *what kind*. Common psychiatric disorders show high heritability yet failed the classical single-gene approaches that cracked Mendelian diseases (Kaplan & Sadock 2024). The resolution is a two-tier architecture (Sullivan; Kaplan & Sadock 2024): the bulk of liability comes from a very large number of **common variants of individually tiny effect** (the polygenic component, odds ratios typically around 1.1 each), plus a smaller contribution from **rare, large-effect variants** (CNVs, de novo mutations) that individually raise risk many-fold but explain illness in only a minority. This is the liability-threshold model: many small risks summed against a threshold.

COMMON TRAP

Do not equate "high heritability" with "genetically determined" or with "inherited in families in a simple pattern." Heritability is a population statistic about variance, not a statement about an individual, and a highly heritable disorder can still be overwhelmingly polygenic with no single causative gene. Equally, a high heritability does not mean environment is irrelevant: it is a partitioning of variance in a particular population, not a fixed biological constant.

RULE **High heritability, non-Mendelian, mostly polygenic.** Common psychiatric disorders are among the most heritable in medicine yet obey no clean single-gene pattern; hold that paradox and every method below has a job.

1.2 The missing heritability, and why development is the read-out

Two loose ends these notes keep returning to. First, **missing heritability**: the variance explained by the variants we can actually measure falls well short of the heritability that twin studies imply (Manolio et al. 2009; Kaplan & Sadock 2024). For schizophrenia, SNP-based heritability captures roughly 17 to 45 percent of variance and a polygenic risk score built from GWAS explains on the order of 7 percent, against twin-study heritability estimates near 80 percent (New Oxford Textbook of Psychiatry). The gap is filled, in part, by rare variants, gene-gene and gene-environment interactions, and structural variation the arrays miss. Second, **neurodevelopment as the mechanism**: genetic risk is largely expressed by shaping how the brain is built, wired, and pruned, so the same risk allele can surface as a childhood neurodevelopmental phenotype or an adult psychosis depending on timing. Genetic risk for a childhood-onset disorder like ADHD does not differ between paediatric and adult samples, underscoring that it indexes a developmental trajectory rather than a discrete adult lesion (Kaplan & Sadock 2024).

~80%	17-45%	~7%
TWIN HERITABILITY, SCHIZOPHRENIA	SNP-BASED HERITABILITY	VARIANCE A PRS EXPLAINS

TRAP Do not read "high heritability" as "genetically determined": a highly heritable disorder can still be overwhelmingly polygenic, and heritability is a population variance ratio, silent about any individual.

1.3 The toolkit as a map: each method answers one question

This is the spine of these notes. The genetics toolkit is a ladder of study designs, and the discriminating exam answer is to bind each method to the *single question it can answer* and no more. Read the definition list as a ladder from crudest to most granular: the first three are the classical epidemiological designs (they establish *that* genes matter), the middle three are molecular localisation and discovery methods (they find *which* variants), and the last is the aggregate clinical read-out (how much of one person's risk we can now quantify).

Family studies

Ask: *does it run in families?* Compare the risk (or relative risk) of the disorder in relatives of an affected proband against the general-population rate, graded by degree of relatedness. Establishes familial

aggregation but cannot separate shared genes from shared upbringing.

Twin studies

Ask: *is the familial resemblance genetic or shared-environmental?* Compare concordance in monozygotic twins (who share effectively 100 percent of their genome) with dizygotic twins (who share on average 50 percent). A higher MZ than DZ concordance points to genetic influence, and the design yields a heritability estimate plus estimates of shared and unique environment (New Oxford Textbook of Psychiatry).

Adoption studies

Ask: *can we physically separate genes from rearing?* Adopted-away children share genes with their biological relatives but environment with their adoptive family, so higher rates in biological than adoptive relatives isolate a genetic contribution. The most rigorous separation of the two, but increasingly infeasible as adoptions decline (New Oxford Textbook of Psychiatry).

Linkage analysis

Ask: *roughly where on the genome does a risk gene sit?* Track co-inheritance of a disease with genetic markers through pedigrees; a marker that segregates with illness flags a nearby chromosomal region. Quantified by the LOD score. Powerful for rare large-effect Mendelian genes, largely unproductive for polygenic psychiatric disorders (Kaplan & Sadock 2024).

Association and GWAS

Ask: *which common variants are over-represented in cases?* Compare allele frequencies at SNP markers between cases and controls. The genome-wide association study (GWAS) does this at millions of SNPs simultaneously using microarrays, detecting common variants of small effect once samples reach tens to hundreds of thousands (Kaplan & Sadock 2024).

CNV and sequencing methods

Ask: *which rare, large-effect variants are present?* Copy-number variant mapping (via array comparative genomic hybridisation or GWAS-chip intensity) finds sub-microscopic deletions and duplications; whole-exome and whole-genome sequencing find rare point mutations and de novo variants. These uncover the punchy, individually rare risk variants (Kaplan & Sadock 2024).

Polygenic risk scores

Ask: *how much common-variant burden does this one person carry?* Sum the risk alleles across the genome, each weighted by its GWAS effect size, into a single score of genetic liability. The aggregate read-out that turns GWAS summary statistics into an individual-level index (Kaplan & Sadock 2024).

The high-yield structure: the top three designs answer *whether and how much* without touching DNA directly; linkage and association/GWAS answer *where and which*; CNV/sequencing answers *which rare variant*; and the polygenic risk score is the only tool that reports back on a single individual. Modern genome-wide approaches (GWAS, CNV mapping, polygenic analysis, sequencing) have supplanted the older linkage and candidate-gene strategies for complex psychiatric disorders (Kaplan & Sadock 2024).

1.4 The two-architecture picture: common-small versus rare-large

The reason the toolkit splits into GWAS on one side and CNV/sequencing on the other is that the two variant classes have opposite profiles, and examiners test the contrast directly. GWAS is built to catch variants that are *common but weak*; CNV and sequencing are built to catch variants that are *rare but strong*. The full genetic risk for a disorder is the sum of both.

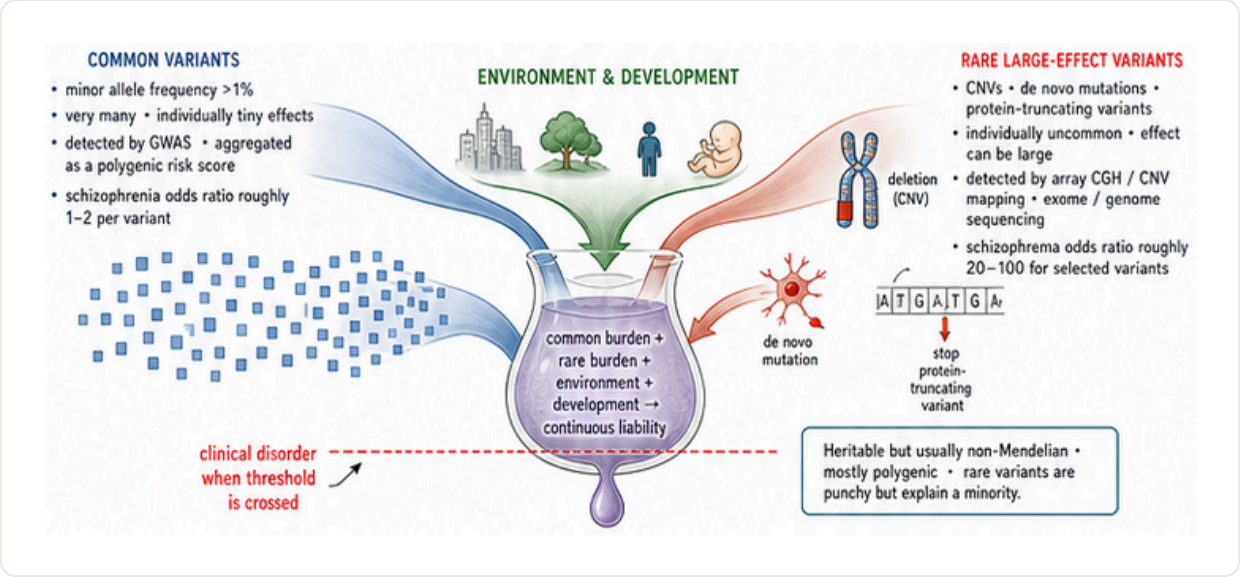


Fig 3.3 The architecture of psychiatric risk.

FEATURE	COMMON VARIANTS (GWAS)	RARE LARGE-EFFECT VARIANTS (CNV / SEQUENCING)
Population frequency	Common (minor allele frequency >1%)	**Rare, often de novo (new, non-inherited)**
Effect size per variant	Tiny: odds ratio roughly 1 to 2 for schizophrenia	**Large: odds ratio roughly 20 to 100 for schizophrenia**
Detecting tool	Genome-wide association study (SNP microarray)	**Array CGH / CNV mapping; whole-exome or whole-genome sequencing**
Sample size needed	Very large (tens to hundreds of thousands) to reach significance	**Large too, but signal is per-variant strong; low signal-to-noise for proving causality**
Aggregated as	**Polygenic risk score**	Total CNV burden; individual pathogenic variant

The classic figure (Singh, Neale & Daly, adapted in Kaplan & Sadock 2024): common variants like complement C4 raise schizophrenia odds one- to two-fold, whereas the 22q11.2 deletion and rare protein-truncating variants raise odds by 20- to 100-fold. Both tails matter, and only summing them captures full genetic risk.

1.5 The toolkit in one ladder, and the master mnemonic seeded

Before the material fans out, bind the whole ladder into one image to redraw from memory. This pearl is the spine of these notes; each later topic pays it back in detail.

THE TOOLKIT IN ONE LADDER

Climb from crude to granular, each rung a sharper question. **Family**: does it run in families? **Twin**: genes or shared environment? (MZ vs DZ concordance gives heritability.) **Adoption**: separate genes from rearing physically. **Linkage**: roughly *where* on the genome? (LOD score; good for rare Mendelian, poor for polygenic.) **Association / GWAS**: *which* common variants? (millions of SNPs, tiny effects, huge samples). **CNV / sequencing**: which rare large-effect variants? (deletions, duplications, de novo mutations, 20- to 100-fold effects). **Polygenic risk score**: how much aggregate common-variant burden does this one person carry? The first three say *whether*, the middle say *where and which*, the last says *how much, for whom*.

MNEMONIC

Families Try Adopting Little Genetic Clues Personally

Walks the ladder in order: **F**amily, **T**win, **A**doption (the classical epidemiological trio) → **L**inkage, **G**WAS/association (localisation and common-variant discovery) → **C**NV and sequencing (rare large-effect) → **P**olygenic risk score (individual aggregate). Seed it now; the consolidation block at the end pays it back as a whole-subject synthesis map.

HOLD THIS

Each method answers exactly one question. The toolkit is a ladder from crudest to most granular: family (does it run in families?), twin (genes or shared environment?), adoption (genes or rearing?), linkage (roughly where?), GWAS (which common variants?), CNV/sequencing (which rare large-effect variants?), polygenic risk score (how much aggregate burden, for whom?).

1.6 Cross-references: what is owned elsewhere

This material is the substantive genetics of psychiatric illness, not the generic machinery of study design or drug metabolism, both of which live in other notes and are only pointed to here.

Study design and biostatistics taxonomy

The general anatomy of study designs (cohort, case-control, cross-sectional), measures of association (odds ratio, relative risk), and the statistics of significance and multiple testing are owned by the Schizophrenia: aetiology, phenomenology, classification & course notes. These notes borrow those tools as applied to genetics (for example why the GWAS significance threshold is set stringently at 5×10^{-8} to correct for a million simultaneous tests) but do not re-teach the biostatistics from scratch. When a genetics topic invokes an odds ratio or a correction for multiple comparisons, point back to the Schizophrenia: aetiology, phenomenology, classification & course notes.

CYP450 and pharmacokinetic metabolism

The cytochrome P450 enzyme system, its isoenzymes and inhibitor/inducer interactions, was established on the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes. The pharmacogenetics and pharmacogenomics topic here builds the *genetic variation* in those enzymes (poor, intermediate, extensive and ultra-rapid metaboliser phenotypes, and the CPIC/DPWG prescribing guidance) on top of that pharmacokinetic foundation rather than re-deriving CYP450 itself.

GOOD TO REMEMBER

- **Schizophrenia twin-study heritability:** approximately 80 percent (New Oxford Textbook of Psychiatry), among the highest in psychiatry.
- **Schizophrenia SNP-based heritability:** roughly 17 to 45 percent of variance captured by common SNPs, illustrating the missing-heritability gap (New Oxford Textbook of Psychiatry).
- **Schizophrenia polygenic risk score:** explains on the order of 7 percent of variance in current data (New Oxford Textbook of Psychiatry).
- **ADHD heritability:** approximately 70 to 80 percent from twin meta-analyses, on a par with autism, bipolar disorder and schizophrenia (New Oxford Textbook of Psychiatry).
- **GWAS genome-wide significance threshold:** $p < 5 \times 10^{-8}$, correcting for roughly a million independent tests (Kaplan & Sadock 2024).
- **Common-variant effect size (schizophrenia):** odds ratio approximately 1 to 2 per risk allele (Kaplan & Sadock 2024).
- **Rare / CNV effect size (schizophrenia):** odds ratio approximately 20 to 100 per variant (Kaplan & Sadock 2024).
- **22q11.2 deletion (velocardiofacial / DiGeorge) syndrome:** raises schizophrenia odds by about 50-fold versus the general population (Kaplan & Sadock 2024).
- **Copy-number variant definition:** structural deletion or duplication typically larger than 1 kilobase; CNVs span about 12 percent of the genome in aggregate (Kaplan & Sadock 2024).
- **Common variant (SNP) definition:** polymorphism with minor allele frequency greater than 1 percent (Kaplan & Sadock 2024).
- **Manolio et al. 2009:** the landmark "Finding the missing heritability of complex diseases" (Nature), the reference for the missing-heritability problem.
- **LOD score:** the logarithm-of-odds statistic quantifying linkage; the metric of the pre-GWAS linkage era.

2 · Modes of inheritance and transmission models

Psychiatric disorders are the paradigm case of **complex inheritance**: they cluster in families but almost never segregate in the tidy ratios that Mendel described for the garden pea. The examinable skill is therefore to hold two frameworks in mind at once, the classical **Mendelian** single-gene patterns that underlie a handful of psychiatrically important syndromes, and the **non-Mendelian** and quantitative models that account for the common disorders. **Why it matters.** Examiners test whether you can say, with confidence, that schizophrenia, bipolar disorder, autism, ADHD and depression are **multifactorial** and **polygenic** rather than Mendelian, and whether you can then deploy the **threshold model** to explain the observations that flow from that: rising recurrence risk with severity, with number of affected relatives, and the sex-specific pattern of the Carter effect.

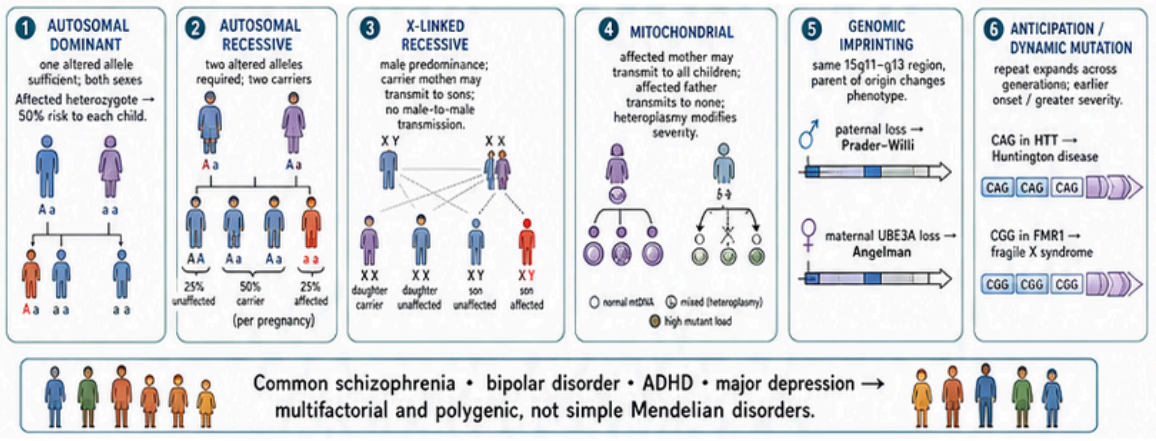


Fig 3.4 Transmission: Mendel and the exceptions.

This topic sets out the full menu of **modes of inheritance**, contrasts single-gene with oligogenic, polygenic and multifactorial architectures, and then develops the **multifactorial-threshold (liability) model** in detail because it is the single most exam-relevant transmission model in psychiatry (Kaplan & Sadock 2024; New Oxford 2020). Pedigree reading is introduced here only briefly, as an orientation; the systematic pedigree-interpretation drill is the discrimination topic.

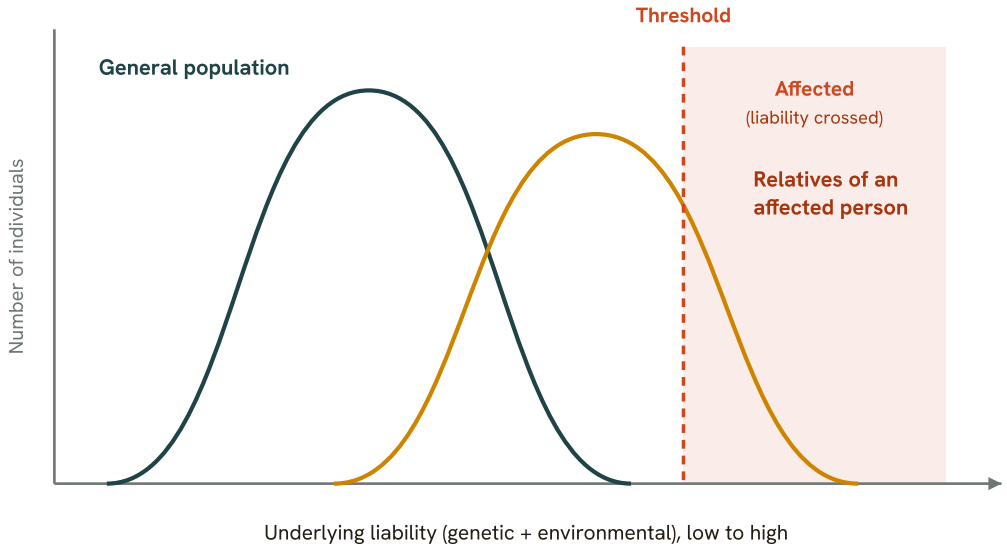


Fig 3.5 The multifactorial-threshold (liability) model. Liability, the summed effect of many genes and the environment, is normally distributed; a person is affected only once their liability crosses a threshold. Relatives of an affected person carry more of the risk alleles, so their whole distribution is shifted right (marigold) and a larger share falls beyond the threshold, which is why recurrence risk is higher in close relatives and rises with the number of affected family members. When one sex is affected less often, its threshold is higher, so its relatives carry higher risk (the basis of the Carter effect).

2.1 Mendel's three laws as the baseline

The rules a complex disorder breaks. Mendel's laws are the reference against which non-Mendelian behaviour is defined. The **Law of Dominance and Uniformity** holds that a dominant

allele masks a recessive one in the heterozygote; the **Law of Segregation** holds that the two alleles at a locus separate during gametogenesis so each parent transmits only one; and the **Law of Independent Assortment** holds that alleles at different loci are transmitted independently (an idealisation that breaks down for linked loci on the same chromosome). A disorder that obeys these laws is **monogenic** or single-gene, shows characteristic pedigree signatures, and gives fixed, high recurrence risks. The point for psychiatry is that the common disorders do exactly the opposite: their familial distributions are, in the words of the standard text, "inconsistent with simple Mendelian modes of inheritance" (Kaplan & Sadock 2024).

2.2 The three Mendelian patterns and their pedigree signatures

Autosomal dominant. One dominant allele on an autosome is sufficient to express the phenotype, so the condition affects both sexes equally, is transmitted vertically through every generation (rarely skips a generation), and confers a 50% risk to each child of an affected heterozygote. Complications examiners exploit are **reduced penetrance** (a carrier who does not express, so the pedigree appears to skip), **variable expressivity**, late age of onset (as in Huntington disease, where the family history may look negative in still-young relatives), and *de novo* mutation, which explains sporadic cases with unaffected parents. **Autosomal recessive.** Two copies are needed, so the phenotype typically appears horizontally in a single sibship of otherwise unaffected, often consanguineous, parents; the recurrence risk to a further child of two carriers is 25%. **X-linked recessive.** The mutant allele lies on the X chromosome, so affected individuals are predominantly male, there is no male-to-male transmission, and transmission runs through unaffected carrier mothers to sons (with knight's-move inheritance across the pedigree).

Penetrance

The proportion of individuals carrying a disease genotype who actually express the phenotype; reduced penetrance makes a dominant pedigree appear to skip generations.

Expressivity

The degree or severity of phenotype among those who do express it; variable expressivity means the same genotype produces different clinical pictures.

de novo mutation

A mutation arising for the first time in the affected individual (or parental germline), producing an isolated case; germline mosaicism can raise sibling recurrence risk above the near-zero expectation.

2.3 Reading a pedigree: an orientation

What the shapes encode. A pedigree is the fastest bedside route to a mode of inheritance. Squares are males, circles females, a filled symbol is affected, a horizontal line joins a mating pair, a vertical line drops to offspring, and a diagonal strike denotes a deceased individual; a double horizontal line marks consanguinity. Reading it, you ask three questions in sequence: are both sexes affected equally (autosomal) or is there a male excess (consider X-linked); is transmission vertical across generations (dominant) or clustered in one sibship (recessive); and is there male-to-male transmission (which excludes X-linkage). The systematic drill, including the

discriminators that separate mitochondrial from X-linked and dominant-with-reduced-penetrance from recessive, is developed in the pedigree-interpretation topic.

2.4 Non-Mendelian mechanism: mitochondrial (maternal) inheritance

Matrilineal, never paternal. Mitochondrial DNA is inherited almost exclusively through the ovum, so a pathogenic mtDNA variant passes from an affected mother to all of her children but is transmitted by none of her affected sons. The pedigree signature is therefore transmission through the maternal line only, with both sexes affected but only females passing the trait on. **Heteroplasmy** (a mixture of mutant and wild-type mitochondria whose ratio must exceed a tissue-specific threshold to cause disease) explains the variable severity within a matriline. Mitochondrial disorders are relevant to psychiatry as a cause of syndromic presentations with neuropsychiatric features and as one of the classic non-Mendelian patterns examiners contrast against X-linkage (New Oxford 2020).

2.5 Non-Mendelian mechanism: genomic imprinting and parent-of-origin effects

Which parent the allele came from matters. **Imprinting** is the parent-of-origin-specific silencing of an allele by DNA methylation established in the germline, so that the phenotype depends on whether the transmitting parent was the mother or the father (Companion to Psychiatric Studies 2010). The teaching pair is the 15q11-q13 region: loss of the paternally expressed genes produces **Prader-Willi syndrome** (hyperphagia, obesity, intellectual disability, and features overlapping OCD and psychosis), whereas loss of the maternally expressed *UBE3A* gives **Angelman syndrome** (severe intellectual disability, ataxia, and a characteristic happy affect). The same deletion thus yields two entirely different disorders according to parent of origin, which is the defining violation of Mendelian expectation that imprinting demonstrates.

RULE **Same 15q11-q13 deletion, opposite parent: two different syndromes.** Paternal loss gives Prader-Willi; maternal loss (of *UBE3A*) gives Angelman. Parent-of-origin dependence means imprinting.

2.6 Non-Mendelian mechanism: anticipation and dynamic mutation

Earlier and worse each generation. **Anticipation** describes a disorder that appears at a progressively earlier age and with increasing severity in successive generations. Its molecular basis is **dynamic mutation**, the unstable expansion of a trinucleotide (triplet) repeat during gametogenesis (Companion to Psychiatric Studies 2010). The two archetypes are **Huntington disease** (an expanding CAG repeat in *HTT*, where larger repeats give earlier onset, most markedly with paternal transmission) and **fragile-X syndrome** (a CGG repeat in the 5-prime untranslated region of *FMR1* on the X chromosome; once the repeat expands past the full-mutation range it silences the gene by methylation, the commonest inherited cause of intellectual disability and a recognised association with autism). It is worth noting for the exam that although repeat expansions cause these syndromic and learning-disability phenotypes, no convincing evidence links repeat expansions to the common psychiatric illnesses such as schizophrenia or bipolar disorder (Companion to Psychiatric Studies 2010).

RULE **Earlier and worse each generation means an expanding trinucleotide repeat.** Anticipation flags dynamic mutation: CAG in *HTT* (Huntington), CGG in *FMR1* (fragile-X).

2.7 From single-gene to polygenic: the spectrum of genetic architecture

A continuum, not a dichotomy. Genetic architecture is best pictured as a spectrum of the number of contributing loci and their individual effect sizes. A **single-gene (monogenic)** disorder is driven by one locus of large effect. An **oligogenic** disorder involves a small number of loci of moderate effect. A **polygenic** trait is influenced by very many loci, each of individually tiny effect, whose effects sum; this is **polygenicity**, and it is the genetic architecture now firmly established for schizophrenia, bipolar disorder, ADHD and major depression (Kaplan & Sadock 2024). A **multifactorial** trait is one in which many genes of small effect combine with environmental factors to produce risk; in psychiatry "polygenic" and "multifactorial" are used almost interchangeably because both genetic and environmental contributions are continuously distributed. The empirical signature of polygenicity is the marked inverse relationship between allele effect size and frequency: common variants each carry odds ratios below about 1.3 but, as a group, account for roughly a third of the genetic liability, while rare variants (including copy number variants) can carry large individual effects (Kaplan & Sadock 2024).

ARCHITECTURE	LOCI AND EFFECT	PSYCHIATRIC EXAMPLE	DISTINGUISHING FEATURE
Single-gene (Mendelian)	One locus, large effect	Huntington disease, fragile-X	**Mendelian pedigree; fixed high recurrence risk**
Oligogenic	Few loci, moderate effect	Some syndromic forms	**Non-Mendelian ratios but tractable locus count**
Polygenic	Very many loci, each tiny effect, additive	Schizophrenia, bipolar, ADHD, MDD	**Effect size falls as allele frequency rises**
Multifactorial	Many genes of small effect plus environment	Common psychiatric disorders	**Continuous liability crossing a threshold**

The genetic-architecture spectrum, from the single large-effect locus of Mendelian disease to the many-small-effect-genes-plus-environment model of the common psychiatric disorders.

2.8 The multifactorial-threshold (liability) model in full

A continuous liability with a categorical outcome. The **threshold model**, also called the **liability threshold** or multifactorial-threshold model, reconciles a discontinuous (present or absent) diagnosis with a continuous underlying cause. Its postulate is that every individual carries an underlying **liability**, the summed burden of all genetic and environmental risk and protective factors, which is approximately normally (Gaussian) distributed across the population. The disorder manifests only in those whose liability exceeds a critical **threshold**; below the threshold the person is unaffected, above it they are affected (New Oxford 2020). Because liability is the additive sum of many small contributions, the central-limit theorem makes its population distribution normal, which is precisely what justifies the bell-curve depiction. This model is the workhorse for conceptualising complex disorders such as ADHD, which is described as

"manifestations of an underlying continuously distributed liability, with the diagnosis lying above a certain threshold on this liability curve" (New Oxford 2020).

Why relatives sit further to the right. The crucial move is what the model predicts for relatives of an affected proband. Because relatives share genes (and often environment) with the proband, their liability distribution is shifted rightward, closer to the threshold, than that of the general population. A larger fraction of that shifted distribution therefore lies beyond the threshold, so the recurrence risk in relatives exceeds the population prevalence, and it does so more for closer relatives who share more of the proband's liability. This is exactly the pattern seen for congenital malformations and complex traits, where the first-degree-relative recurrence risk is of the order of 1 to 5% against a population incidence often of 0.1% or less (Kaplan & Sadock 2024).

2.9 Predictions the threshold model makes (and the exam loves)

Recurrence risk rises with severity. A more severe case implies a proband whose liability lies further beyond the threshold, which implies a family carrying a greater liability burden overall, which shifts the relatives' distribution further right and raises their recurrence risk. Hence more severe index cases predict higher risk to relatives. **Recurrence risk rises with the number of affected relatives.** Each additional affected relative is further evidence of a high-liability family, again shifting the relevant distribution rightward and increasing risk for the remaining members; risk is therefore not fixed as in Mendelian disease but conditional on the loading already visible in the pedigree. **Concordance and the heritability gap.** Twin studies quantify the genetic share of liability: schizophrenia has an estimated twin heritability of about 80% (Kaplan & Sadock 2024), yet current schizophrenia polygenic risk scores explain only about 7 to 7.7% of the variance on the liability scale (around 24% on the observed 0-to-1 scale), leaving a substantial "heritability gap" attributed to environmental effects, rare variants, gene-environment interplay and assortative mating (Kaplan & Sadock 2024).

2.10 Sex-specific thresholds and the Carter effect

The less-often-affected sex needs more liability. When a disorder has an unequal sex ratio, the multifactorial model accommodates it by positing **sex-specific thresholds**: the less commonly affected sex has a higher threshold, meaning a member of that sex must carry a greater liability burden to cross into the affected state. The consequence, known as the **Carter effect**, is that affected individuals of the less-often-affected (higher-threshold) sex carry, on average, a heavier liability load, and therefore transmit a higher recurrence risk to their relatives than affected individuals of the more commonly affected sex. The classic non-psychiatric illustration is pyloric stenosis (commoner in males), where the relatives of affected females carry the higher risk. In psychiatry the same logic is invoked for sex-biased conditions such as ADHD and autism, where an affected female, being of the higher-threshold sex, implies greater familial loading. Recognising that the higher-risk-transmitting relatives are those of the rarely affected sex is a frequently tested application of the model (New Oxford 2020).

HOLD THIS

Liability is normally distributed; disease appears above a threshold. Relatives sit shifted rightward, so recurrence risk exceeds prevalence, rises with closeness of relationship, severity of the index case and number affected, and (Carter effect) is higher in relatives of the rarely affected, higher-threshold sex.

COMMON TRAP

Do not call schizophrenia or bipolar disorder "Mendelian" or attribute them to a single gene. Their familial distributions are explicitly incompatible with single-major-locus inheritance and fit a polygenic, multifactorial-threshold model. Equally, do not confuse the shifted-relatives logic: the raised recurrence risk in relatives comes from their liability distribution sitting closer to the threshold, not from any single high-penetrance allele.

PEARL

Anticipation (earlier onset, greater severity each generation) should immediately make you think of an expanding trinucleotide repeat, and parent-of-origin dependence (same deletion, two different syndromes) should immediately make you think of imprinting. These two non-Mendelian mechanisms are the pair most reliably tested against the "why does this not follow Mendel" stem.

MNEMONIC

MITochondria: Mother's line, Inherited by all, Transmitted by none of the affected males.

Use this to lock the maternal-inheritance signature that separates mitochondrial from X-linked recessive: in mitochondrial disease an affected father transmits to no one, whereas in X-linked recessive an affected father transmits carrier status to all daughters.

INDIA

High rates of consanguineous marriage in parts of India raise the population load of autosomal recessive conditions, so a horizontal sibship pattern with related parents should prompt an explicit pedigree enquiry into consanguinity. For the common multifactorial psychiatric disorders, family risk counselling in Indian practice is best framed in threshold-model terms (risk raised above population baseline but not Mendelian) rather than as a fixed inherited certainty, which also keeps the message non-stigmatising.

GOOD TO REMEMBER

- **Schizophrenia twin heritability:** approximately 80% (Kaplan & Sadock 2024).
- **Schizophrenia PRS variance explained:** about 7 to 7.7% on the liability scale, around 24% on the observed 0-to-1 scale (Kaplan & Sadock 2024).
- **Common small-effect alleles in schizophrenia:** account for at least about 25% of total liability and roughly a third of genetic liability; individual odds ratios below about 1.3 (Kaplan & Sadock 2024).
- **ADHD twin heritability:** approximately 70 to 80% (New Oxford 2020).
- **Multifactorial first-degree-relative recurrence risk:** of the order of 1 to 5%, against a population incidence often 0.1% or less (Kaplan & Sadock 2024).
- **HTT (Huntington disease):** expanding CAG trinucleotide repeat; anticipation, earlier onset with larger repeats and paternal transmission.
- **FMR1 (fragile-X syndrome):** CGG repeat in the 5-prime untranslated region on the X chromosome; full-mutation methylation silencing; commonest inherited intellectual disability, autism association.
- **15q11-q13 imprinting pair:** paternal loss gives Prader-Willi syndrome, maternal loss (of *UBE3A*) gives Angelman syndrome.
- **Carter effect:** relatives of an affected individual of the less-often-affected (higher-threshold) sex carry the higher recurrence risk.

3 · Quantitative genetics: family, twin and adoption studies

Before a single risk gene had been identified, the classical epidemiological triad of family, twin and adoption studies had already established that virtually every major psychiatric disorder is substantially heritable. These designs are the historical and conceptual foundation of psychiatric genetics: they partition the observed clustering of a disorder in relatives into genetic and environmental sources, and they generate the heritability estimates that every downstream molecular study (linkage, GWAS, polygenic scores) sets out to explain. **Why it matters.** The examiner expects a candidate to move fluently from the raw observation that a disorder runs in families, through the twin comparison that says *whether* the familial aggregation is genetic, to the adoption design that *separates* genes from the rearing environment, and finally to the biometric machinery (the **ACE model**, path analysis, variance-components modelling) that turns concordance figures into numbers. Knowing the landmark studies, the core assumptions, and the standard critiques is high-yield across MCQs and vivas.

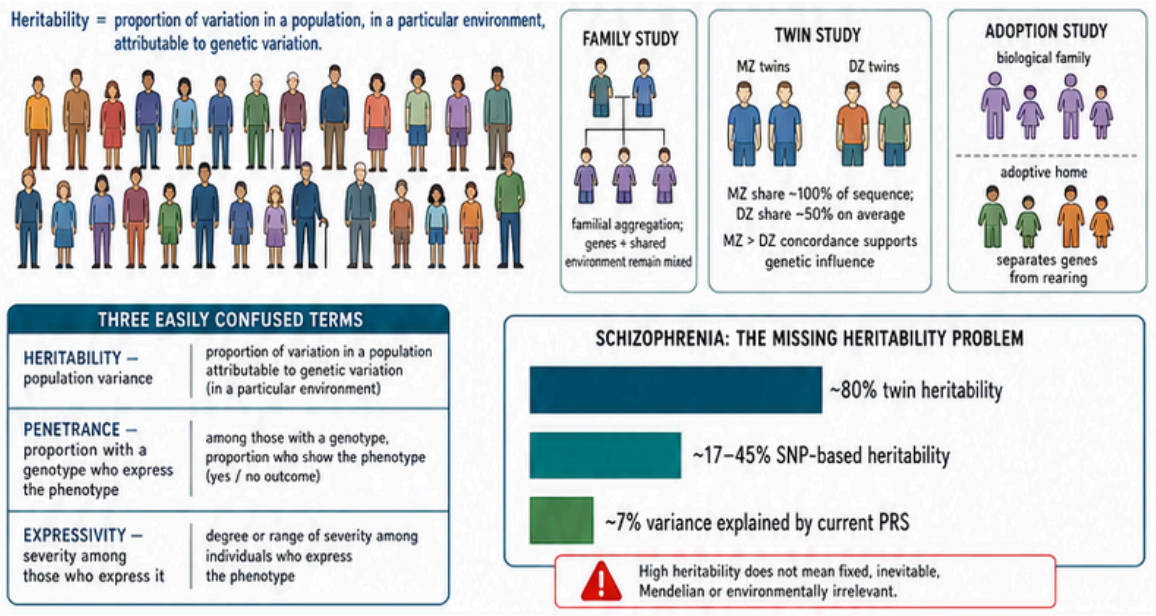


Fig 3.6 Heritability is not destiny.

The logic is sequential and each design answers a question the previous one leaves open. A **family study** establishes that a disorder aggregates in relatives but cannot separate shared genes from shared environment. A **twin study** exploits the difference in genetic sharing between monozygotic and dizygotic pairs to ask whether that aggregation is genetic. An **adoption study** physically separates the genetic parent from the rearing environment and so provides the strongest single test of a genetic contribution in humans (Tasman 2015). Read together, they yielded an unequivocal answer for schizophrenia, mood disorders and most of psychiatry: genes matter, and they matter a great deal.

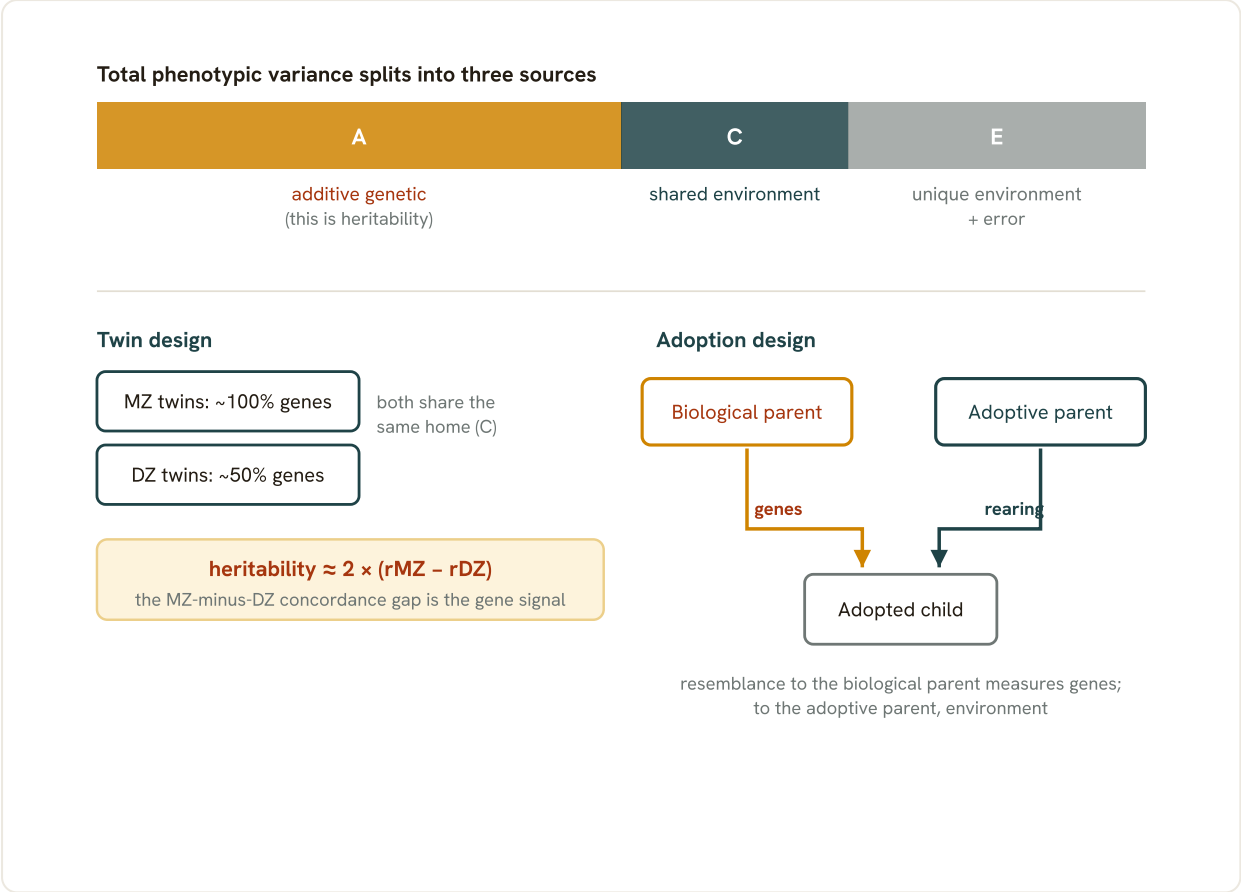


Fig 3.7 The two designs that separate genes from environment. The classical twin study exploits the fact that monozygotic twins share nearly all their genes and dizygotic twins about half, while both share the same home: the extra concordance in MZ over DZ pairs estimates heritability (Falconer's approximation, twice the MZ minus DZ correlation). The adoption study pulls genes and rearing apart in a different way: an adopted child's resemblance to the biological parent indexes genes, and resemblance to the adoptive parent indexes environment. Both feed the ACE model that partitions total variance into additive genetic (A), shared environment (C) and unique environment plus error (E).

3.1 Family studies: recurrence risk and the relative risk ratio

The starting design. A **family study** ascertains probands with the disorder and systematically assesses their relatives, comparing the frequency of the disorder among first-degree relatives (parents, siblings, offspring, who share on average 50% of their genes) with the population base rate. The output is a **recurrence risk** (the morbid risk in relatives) and, more usefully for comparison across disorders, the **relative risk ratio**, conventionally written lambda (the risk in relatives of a proband divided by the population risk). For first-degree relatives this is lambda-one; for siblings, lambda-s. Schizophrenia carries a first-degree-relative recurrence risk of roughly 6 to 10%, about a tenfold increase over the general-population risk of near 1%, so lambda-s for schizophrenia is of the order of 8 to 10 (Kaplan & Sadock 2024). **The interpretive limit.** Aggregation in a family is necessary but not sufficient evidence of genetic causation, because families share their environment as well as their genes. A family study can never, on its own, distinguish nature from nurture; it defines the phenotype's familiality and sets up the twin and adoption designs that follow.

3.2 The classical twin design: MZ versus DZ concordance

The natural experiment. The **twin study** rests on a simple genetic contrast: monozygotic (MZ) twins share essentially 100% of their DNA, whereas dizygotic (DZ) twins share on average 50%, the same as ordinary siblings, yet both twin types are assumed to share their rearing environment to a comparable degree. If a disorder is genetic, MZ pairs should show markedly higher **concordance** (the probability that the co-twin is affected given one twin is affected) than DZ pairs. If MZ and DZ concordance are equal, the familial aggregation is environmental. The greater the excess of MZ over DZ concordance, the greater the inferred heritability (New Oxford 2020).

Probandwise versus pairwise concordance. Two estimators are used and they are not interchangeable. The **pairwise** method divides concordant pairs by all pairs with at least one affected twin. The **probandwise** method counts each independently ascertained affected twin as a proband, so a doubly-ascertained concordant pair is counted twice; it yields a higher figure and is the estimator comparable to a population morbid risk. Probandwise concordance is the modern standard (Torrey 1994). Being aware of which figure a study quotes explains much of the apparent variation in published concordance rates.

3.3 Falconer's formula and heritability

From concordance to a number. **Heritability** (h-squared) is the proportion of the total phenotypic variance in a population attributable to genetic variance; it is a population parameter, not a statement about any individual, and it is specific to the population and environment studied. The classic first approximation from twin correlations is **Falconer's formula**, h-squared is approximately twice the difference between the MZ and DZ correlations, that is 2(rMZ minus rDZ) (Falconer, cited in New Oxford 2020). The doubling reflects the halving of shared genes from MZ to DZ pairs. **A worked intuition.** If rMZ is 0.5 and rDZ is 0.2, the naive estimate is 2(0.5 minus 0.2) equals 0.6, so about 60% of the variance is genetic. The formula is only a rough guide because it assumes purely additive genes and can exceed unity or misbehave when non-additive (dominance) effects or shared environment are present; formal variance-components modelling supersedes it (see 3.6).

RULE **Heritability is roughly twice the MZ-minus-DZ correlation gap.** Falconer: h-squared is about 2(rMZ - rDZ); the doubling reflects the halving of shared genes from MZ to DZ pairs.

COMMON TRAP

Heritability is not a fixed biological constant and does not describe how "genetic" a given person's illness is. A high heritability means that, in the population and environment studied, most of the variation between people is genetic; it says nothing about the modifiability of the trait, nor about the cause in any single patient. A highly heritable disorder can still be entirely prevented or treated environmentally (phenylketonuria is the standard cautionary example). Do not read h-squared of 0.8 as "80% genetic in this patient."

3.4 The ACE model and variance decomposition

Partitioning the phenotypic variance. The workhorse of modern twin analysis is the **ACE model**, which decomposes total phenotypic variance into three latent components: **A**, additive genetic variance; **C**, common (shared) environment, the environmental influences that make co-twins alike regardless of zygosity; and **E**, unique (non-shared) environment, the influences that make co-twins differ, which also absorbs measurement error. Under the model, MZ pairs correlate as A plus C and DZ pairs as one-half A plus C; the divergence between them identifies A, the residual within-MZ difference identifies E, and any residual similarity common to both twin types identifies C (New Oxford 2020). Where non-additive genetic effects are suspected the model is extended to ADE (A, dominance D, and E). Notably the **variance component** E always includes the discordance of MZ pairs, which is why any pair of identical twins discordant for a disorder is direct evidence for non-shared environmental (including stochastic and epigenetic) causation.

3.5 The equal-environments assumption and its critique

The load-bearing assumption. The entire inference from the twin design depends on the **equal-environments assumption** (EEA): that MZ and DZ twins are exposed to trait-relevant environments to an equal degree, so that any excess MZ similarity is genetic rather than environmental. **The critique.** Critics (notably Joseph) argue MZ twins are in fact treated more alike, dress alike, are confused for one another, spend more time together and evoke more similar responses, so that greater MZ concordance could partly reflect a more shared environment, inflating heritability estimates. **The defence.** The mainstream position is that the EEA holds for trait-relevant exposures: studies of twins mistaken about their own zygosity show resemblance tracks true (biological) zygosity rather than perceived zygosity, and greater MZ environmental similarity appears to be largely a consequence of their genetic identity (evoked or selected), not an independent cause of phenotypic similarity (New Oxford 2020). The EEA is the single most examinable methodological criticism of twin studies.

CLASSIC TRAP If asked for the load-bearing weakness of the twin design, name the **equal-environments assumption**: if MZ twins share more trait-relevant environment than DZ twins, heritability is inflated.

3.6 MZ twins reared apart, path analysis and segregation analysis

The strongest twin variant. The **MZ-twins-reared-apart** design studies genetically identical individuals separated early and raised in different families; their phenotypic correlation is a near-direct estimate of heritability because their shared environment (C) is minimised, so rMZ-apart approximates A. The best-known example is the Minnesota Study of Twins Reared Apart, whose reared-apart MZ correlations for many traits were only modestly below reared-together values, supporting substantial heritability (Kaplan & Sadock 2024). The design's weaknesses are selective (non-random) placement, late separation, and small, hard-to-ascertain samples.

The quantitative-methods toolkit. Three named analytic methods recur in the syllabus. **Path analysis** is a structural-equation technique that represents the causal paths from latent A, C and

E factors to the observed phenotype as a diagram, letting the A, C and E variance components be estimated (and their fit compared) simultaneously across MZ and DZ correlations (Tasman 2015). **Variance-components** (biometric) modelling is the general maximum-likelihood framework that fits the ACE or ADE models to raw twin (and family) data and formally tests whether dropping C or D worsens fit, superseding Falconer's arithmetic. **Segregation analysis** works on family (pedigree) data and asks whether the observed pattern of transmission fits a single major gene of Mendelian effect, a polygenic (many-small-genes) model, or a mixed model; for the major psychiatric disorders segregation analyses consistently rejected a single major gene and favoured polygenic or oligogenic inheritance, anticipating the highly polygenic architecture later confirmed by GWAS (New Oxford 2020).

3.7 Adoption designs: separating genes from rearing

Three configurations. The **adoption study** is the most powerful human design for disentangling genetic transmission from the family environment, because the adoptee's genetic parents and rearing parents are different people. Three canonical variants exist. In the *adoptee (adoptees') study* design, the adopted-away offspring of affected biological parents are compared with adopted-away offspring of unaffected biological parents; excess disorder in the former indexes genetic transmission (this is the Heston design). In the *adoptee's-family (parent-as-proband)* design, one starts from affected adoptees and examines rates of the disorder in their biological versus adoptive relatives; a genetic effect predicts higher rates among biological relatives. In the *cross-fostering* design, one compares adoptees with affected biological but healthy adoptive parents against adoptees with healthy biological but affected adoptive parents, directly pitting the genetic against the rearing contribution (Kaplan & Sadock 2024).

3.8 The landmark adoption studies

Heston (1966), the first. Leonard Heston's Oregon study followed 47 offspring born to hospitalised mothers with schizophrenia and adopted away in infancy, against 50 matched control adoptees; roughly 11% (5 of 47) of the index adoptees developed schizophrenia versus none of the controls, with excess sociopathy and neurosis besides. This was the first adoption evidence that the familial risk for schizophrenia is genetically transmitted, since the affected offspring never lived with their ill mothers (Companion 2010; Tasman 2015). **The Danish adoption studies.** Heston's finding was confirmed and greatly extended by the collaborative Danish-American programme of Rosenthal, Wender, Kety and Schulsinger, exploiting Denmark's national adoption and psychiatric registers. Using both the adoptee and the adoptee's-family strategies, they showed a marked excess of schizophrenia and schizophrenia-spectrum disorders among the biological relatives of schizophrenic adoptees, but not among their adoptive relatives, and the cross-fostering arm found that being reared by an ill adoptive parent did not raise risk in genetically low-risk adoptees (Tasman 2015). These studies established the schizophrenia spectrum concept and remain the paradigmatic adoption evidence in psychiatry. **The Finnish Adoptive Family Study.** Tienari's ongoing Finnish study of adopted-away offspring of mothers with schizophrenia added the crucial modern twist: risk in high-genetic-risk adoptees was concentrated in those raised in dysfunctional adoptive families, whereas a healthy adoptive

family environment appeared protective, demonstrating gene-environment interaction rather than genetic determinism (New Oxford 2020). Adoption designs were also decisive for mood disorder (Mendlewicz & Rainer 1977, showing genetic transmission of manic-depressive illness) and for antisocial personality and substance use (Crowe 1974; the Swedish Stockholm adoption studies of Cloninger, Bohman and Sigvardsson).

HOLD THIS

Three nested designs, each removing a confound the last could not. Family study proves aggregation; twin study separates genes from shared environment; adoption study severs genes from rearing. Heston (1966) was the first schizophrenia adoption study; the Danish studies (Kety, Rosenthal, Wender) established the schizophrenia spectrum.

DESIGN	GENETIC SHARING EXPLOITED	WHAT IT CONTROLS FOR	PRINCIPAL LIMITATION
Family study	Graded by relatedness (50% in first-degree)	**Nothing separates genes from shared environment**	Cannot distinguish nature from nurture
Twin study (MZ vs DZ)	MZ 100% vs DZ 50%, environment assumed equal	**Holds shared environment roughly constant across zygosity**	Rests on the equal-environments assumption
MZ reared apart	MZ 100%, shared rearing environment removed	**Removes the common environment (C) directly**	Selective placement, late separation, tiny samples
Adoption study	Biological vs adoptive relatedness dissociated	**Physically separates genes from the rearing family**	Selective placement, prenatal and perinatal confounds, register limits

The three classical designs answer successively harder questions: family studies establish familiality, twin studies test whether it is genetic, and adoption studies (especially the reared-apart and cross-fostering variants) sever genes from rearing altogether. The discriminator for each is what it holds constant or removes.

3.9 Gene-environment interaction and gene-environment correlation

Two distinct phenomena, often confused. **Gene-environment interaction** (GxE) means the effect of an environmental exposure on the phenotype differs according to genotype (or equivalently, genetic risk is expressed only, or more strongly, under a given exposure); the Finnish adoption finding above is a textbook example, and the classic molecular illustration is the moderation of the effect of childhood maltreatment on antisocial outcome by MAOA activity (Caspi 2002, contested in later meta-analyses). **Gene-environment correlation** (rGE) is different: it means exposure to an environment is itself partly under genetic control, so genes and environment are non-randomly associated (Plomin, DeFries & Loehlin 1977).

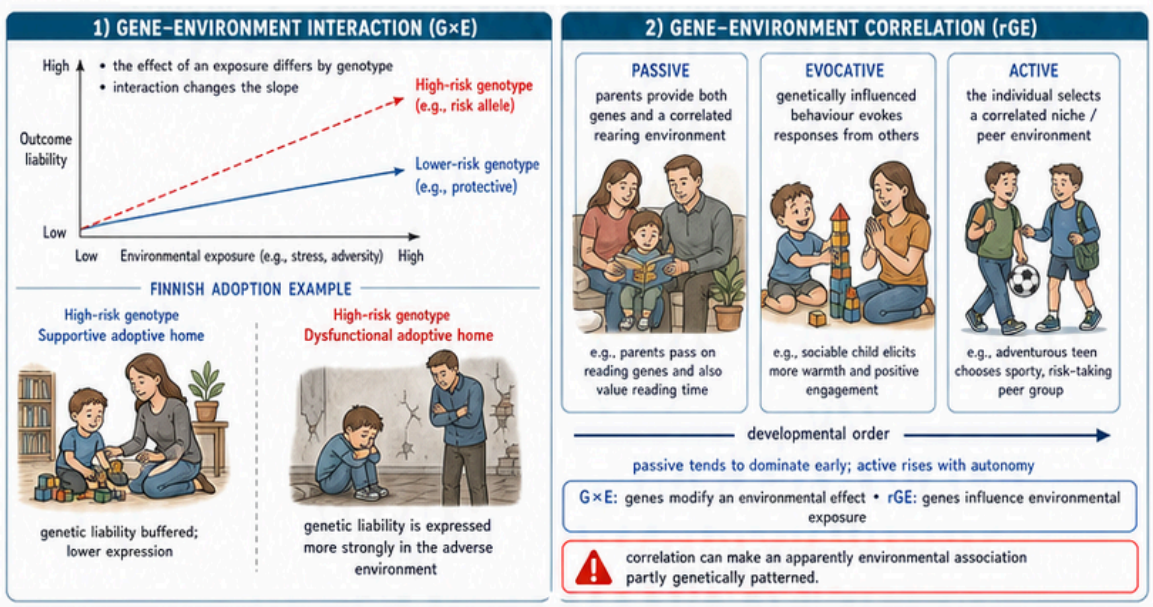


Fig 3.8 Gene and environment: interaction is not correlation.

Three forms of gene-environment correlation. Following Plomin and later Scarr and McCartney (1983), rGE takes three forms. **Passive rGE**: the child passively inherits both risk genes and a correlated rearing environment from the same biological parents (an anxious parent transmits both anxiety-related genes and an anxious home). **Evocative (reactive) rGE**: the child's genetically influenced behaviour evokes correlated responses from others (an irritable, genetically-influenced temperament elicits harsh parenting). **Active (niche-picking) rGE**: the individual actively seeks out environments correlated with their genotype (a sensation-seeking adolescent selects a deviant peer group). The developmental prediction is that passive rGE dominates in early childhood and gives way to active rGE with increasing autonomy (New Oxford 2020). Recognising rGE is essential because it means an apparently "environmental" risk factor identified in a family study may be a marker of genetic risk, one reason adoption and twin designs remain indispensable.

PEARL

A clean one-line discriminator: gene-environment *interaction* is about the environment having a different *effect* depending on the genes (multiplicative moderation); gene-environment *correlation* is about the genes influencing which *environment* a person encounters (non-random exposure). Interaction changes the slope; correlation changes the exposure.

MNEMONIC

ACE decomposes; PEA are the three correlations

The twin variance components are **A**dditive genetic, **C**ommon environment, **E**nvironment (unique). The three gene-environment correlations, in developmental order, are **P**assive (inherited genes plus inherited environment), **E**vocative (behaviour evokes responses), **A**ctive (niche-picking). ACE for the model, PEA for the correlations.

INDIA

Formal twin and adoption registries comparable to the Danish, Swedish and Finnish national registers do not exist at scale in India, so most Indian genetic-epidemiology data derive from family (morbid-risk) studies rather than twin or adoption designs. When counselling Indian families about recurrence risk, the practical figures used are the first-degree-relative risks from these family studies (of the order of 6 to 10% for schizophrenia in a first-degree relative), while remembering that consanguinity, common in parts of India, can inflate familial aggregation for recessive contributions and complicate the interpretation of a family history.

GOOD TO REMEMBER

- **Falconer's formula:** h-squared is approximately 2(rMZ minus rDZ); the doubling reflects the halving of shared genes from MZ to DZ.
- **ACE model:** variance equals A (additive genetic) plus C (common/shared environment) plus E (unique environment plus error); MZ correlate as A+C, DZ as one-half A + C.
- **Schizophrenia twin concordance (probandwise):** Farmer 1987 reported MZ 47.6% vs DZ 9.5%; Onstad 1991 reported MZ 48% vs DZ 4%.
- **Schizophrenia heritability (modern):** Hilker 2018 (Danish twin/psychiatric registers, over 30,000 pairs) found MZ 33% vs DZ 7% probandwise concordance and heritability of 79% (73% for the spectrum).
- **Autism twin data:** Folstein & Rutter reported MZ 36% vs DZ 0% pairwise (higher with broader phenotype); Sandin 2017 (over 37,000 twin pairs) estimated ASD heritability at about 83%.
- **First-degree-relative recurrence risk, schizophrenia:** roughly 6 to 10%, about a tenfold increase over the general-population risk of near 1% (lambda-s of the order of 8 to 10).
- **Heston (1966):** first schizophrenia adoption study (Oregon); about 11%, 5 of 47, of adopted-away offspring of schizophrenic mothers developed schizophrenia vs 0 of 50 controls.
- **Danish adoption studies:** Rosenthal, Wender, Kety & Schulsinger; excess schizophrenia-spectrum disorder in biological (not adoptive) relatives of schizophrenic adoptees; established the schizophrenia spectrum concept.
- **Finnish Adoptive Family Study (Tienari):** genetic risk expressed mainly in dysfunctional adoptive families, demonstrating gene-environment interaction.
- **Mood disorder adoption evidence:** Mendlewicz & Rainer 1977, genetic transmission of manic-depressive illness.
- **Equal-environments assumption:** the critical, load-bearing assumption of the twin design; challenged by Joseph, defended by misassigned-zygosity data.
- **Gene-environment correlation (Plomin 1977; Scarr & McCartney 1983):** passive, evocative, active, shifting from passive to active across development.

Methods: locating the risk

4 · Linkage analysis, LOD score and gene mapping

Before the genome-wide association era, the dominant strategy for finding disease genes was to follow a marker and a putative disease locus *through families* and ask whether they travel together more often than chance allows. This is **linkage analysis**, and its scoring statistic, the **LOD score**, is a recurring viva favourite: examiners want the value of 3, its meaning as 1000:1 odds, and why a method that cracked Huntington disease and cystic fibrosis **largely failed** in schizophrenia and

bipolar disorder. That failure is the whole reason the field pivoted to genome-wide association, so this topic is the conceptual hinge of these notes.

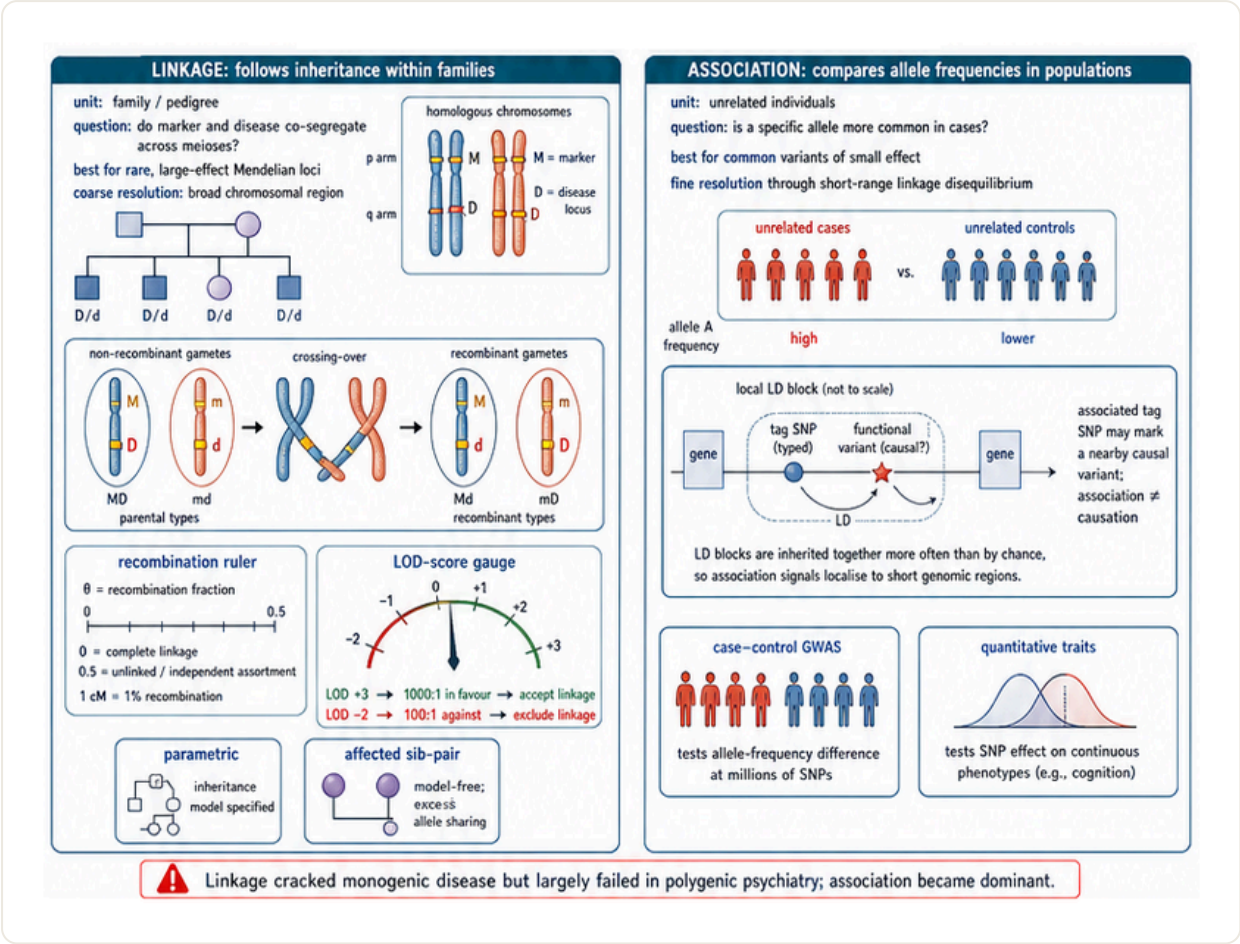


Fig 3.9 Linkage versus association.

The examinable core is a chain of ideas: recombination gives a measurable **genetic distance**; genetic **markers** (RFLP to microsatellite to SNP) let you track chromosomal segments; the recombination fraction feeds a likelihood ratio that becomes the LOD score; parametric linkage needs a specified model, non-parametric (affected sib-pair) does not; and the endpoint is **gene mapping** by positional cloning. Grasp that chain and you can answer any permutation the paper throws at you (Companion to Psychiatric Studies 2010; New Oxford Textbook of Psychiatry 2020).

4.1 Linkage versus association: the fundamental split

Two different questions, two different units. **Linkage** asks whether a marker and a disease locus *co-segregate within families*, tracked across meioses in pedigrees; the unit of analysis is the family. **Association** asks whether a marker allele *co-occurs with disease at the population level*, i.e. is more common in cases than controls; the unit is the unrelated individual. Linkage tolerates any allele at the linked marker (it cares only about recombinant versus non-recombinant transmission), whereas association implicates a specific allele. Linkage detects loci at coarse resolution over tens of centimorgans; association, exploiting the short range of linkage disequilibrium, localises to well under 1 cM (Companion to Psychiatric Studies 2010).

4.2 Recombination fraction theta and genetic distance

Recombination is the ruler. During meiosis, crossing-over between homologous chromosomes reshuffles alleles. The **recombination fraction** (theta) is the probability that a crossover falls between two loci, so it ranges from 0 (the marker is physically inside the gene and never separates) to 0.5 (independent assortment, i.e. unlinked). The nearer two loci sit, the smaller theta and the more often they are inherited together. The Companion likens it to cutting a pack of cards: adjacent cards are least likely to be separated by repeated cuts, distant cards as likely as not. The unit of genetic distance is the **centimorgan (cM)**, defined so that 1 cM corresponds to a 1% recombination frequency; across the human genome 1 cM averages roughly 1 megabase, but the two maps are not interchangeable (see 4.8).

4.3 Genetic markers through history: RFLP to STR to SNP

You cannot track a segment you cannot see. Linkage needs polymorphic markers of known Mendelian inheritance densely spaced along the genome. The marker technology evolved in three generations, and knowing the sequence is a clean exam point (New Oxford Textbook of Psychiatry 2020; genetic-mapping primer, Ott lab).

RFLP (restriction fragment length polymorphism)

First-generation DNA marker (1980s). Sequence variants create or abolish restriction-enzyme cut sites, giving differently sized fragments. Sparse, mostly biallelic, low information content. RFLPs revived family linkage as a genome-wide method.

Microsatellite / STR (short tandem repeat)

Second generation (1990s). Di-, tri- or tetra-nucleotide repeats varying in copy number; highly polymorphic and multi-allelic, so far more informative per locus. Panels of a few hundred microsatellites powered the classic genome-wide linkage scans.

SNP (single-nucleotide polymorphism)

Current standard. Single base-pair variants, usually biallelic but present in millions across the genome and amenable to chip-based genotyping. Individually less informative than an STR but hugely denser; SNPs made genome-wide association feasible.

4.4 Parametric linkage and the LOD score

The scoring statistic examiners want by name. **Parametric** (model-based) linkage specifies the mode of inheritance in advance: penetrance, disease-allele frequency and the recombination fraction. The recombination fraction is estimated by maximum likelihood, and the evidence for linkage is expressed as the **LOD score** (logarithm of the odds; log10 of a likelihood ratio). The numerator is the likelihood of the observed pedigree data assuming linkage at a given theta; the denominator is the likelihood assuming no linkage (theta = 0.5). By convention a **LOD score of +3** is accepted as proof of linkage, corresponding to odds of **1000:1** in favour (10 to the power 3), and a **LOD score of -2** excludes linkage, corresponding to odds of **100:1 against** (Companion to Psychiatric Studies 2010). If good model parameters are known, parametric linkage is very powerful; when the model is uncertain, mis-specification erodes that power.

PEARL

A LOD score is a base-10 logarithm, so it converts multiplicatively: LOD 3 means 10^3 = 1000:1 odds for linkage, LOD -2 means 10^2 = 100:1 odds against. The asymmetric thresholds (+3 to accept, -2 to exclude) reflect the low prior probability that any two random loci are linked, which is why more evidence is demanded to declare linkage than to reject it.

4.5 Non-parametric linkage: the affected sib-pair method

Model-free linkage for complex traits. When the mode of inheritance is unknown (true of every psychiatric disorder), parametric linkage is unsafe because a wrong model destroys power. **Non-parametric** (model-free) linkage sidesteps this by asking only about *allele sharing*. The prototype is the **affected sib-pair** method: two affected siblings share, by chance, 0, 1 or 2 alleles identical-by-descent at any locus, with expected proportions 25%, 50%, 25%. If a locus contributes to the disease, affected sibs share marker alleles at that locus *more often than chance*. The method makes no assumption about penetrance or dominance, relying only on the known Mendelian transmission of the markers. A particular form of affected-sib-pair analysis has a 1:1 correspondence with LOD-score analysis for a fully penetrant recessive disease, and many allele-sharing results are still reported as LOD scores (Ott lab genetic-mapping primer; Companion to Psychiatric Studies 2010).

TRAP Parametric (model-based) linkage needs the mode of inheritance specified in advance, so it is unsafe for psychiatric disorders where the model is unknown; use the model-free affected-sib-pair method instead.

4.6 From linkage to gene: positional cloning

Linkage gives a region, not a gene. **Positional cloning** is the strategy of moving from a mapped chromosomal interval to the actual causal gene using position alone, without prior knowledge of the gene's function (contrast the functional-candidate approach, which starts from a gene of known biology). The pipeline: a genome-wide linkage scan localises the disease to a broad interval; the interval is progressively narrowed by additional markers and by linkage disequilibrium; candidate genes within the region are then sequenced for causal variants. Positional cloning delivered the great single-gene successes (Huntington disease, cystic fibrosis) and, in psychiatry, identified *DISC1* by cloning the breakpoint of a balanced t(1;11) translocation that co-segregated with major psychiatric illness in a large Scottish family (Millar et al 2000; Blackwood et al 2001).

4.7 Fine-mapping with linkage disequilibrium

Sharpening a coarse hit. Once linkage flags an approximate location, **fine-mapping** narrows it using **linkage disequilibrium** (LD), the non-random co-occurrence of alleles at nearby loci in a population. Because a founder mutation stays coupled with neighbouring marker alleles for many generations, disease-associated alleles cluster in a small window around the true gene. In large outbred populations LD decays over very short distances (of the order of 0.3 cM, i.e. a few hundred kilobases), giving far higher mapping resolution than family linkage. Isolated founder populations (the classic example being the Afrikaans-speaking population of South Africa) retain

LD over several centimorgans, which can help or hinder depending on the design (Ott lab genetic-mapping primer 2001). Family-based LD designs use the case-parent *trio* and compare transmitted versus non-transmitted parental alleles, which controls for population stratification.

4.8 Genetic maps versus physical maps

Two rulers for one genome. A **genetic (linkage) map** orders loci by recombination frequency, with distance in centimorgans; it reflects how often crossovers separate loci. A **physical map** orders loci by actual DNA base pairs, with distance in kilobases or megabases, and the ultimate physical map is the reference genome sequence itself. The two do not scale uniformly: recombination is not evenly distributed, so recombination hotspots stretch the genetic map relative to the physical map, while cold regions (for example near centromeres) compress it. Roughly 1 cM averages 1 Mb genome-wide, but this ratio varies severalfold by location, which is why a linkage peak defines a region that must then be resolved on the physical map.

4.9 Why linkage largely failed in psychiatry, and the shift to association

The exam's punchline. Linkage is powerful for rare, highly penetrant, single-gene (Mendelian) disorders where one locus of large effect segregates cleanly in pedigrees. Psychiatric disorders are the opposite: *polygenic*, built from many common variants each of tiny effect, with incomplete penetrance, phenocopies, genetic heterogeneity (different loci in different families) and no clear mode of inheritance. Under these conditions family linkage is badly underpowered, its handful of variants of large effect simply are not there to be found, and the early psychiatric linkage literature became notorious for non-replication (New Oxford Textbook of Psychiatry 2020). Because association (case-control) designs detect common variants of small effect far more efficiently, and dense SNP chips made this genome-wide, the field abandoned linkage for the **genome-wide association study** (GWAS), which is hypothesis-neutral, needs no candidate pre-selection, and permits rigorous ancestry matching. This shift is why modern psychiatric genetics reports polygenic loci and polygenic risk scores rather than single linked genes.

HOLD THIS

Linkage cracks rare Mendelian genes but largely failed in psychiatry. Polygenic architecture, incomplete penetrance, phenocopies and locus heterogeneity leave family linkage underpowered, which is exactly why the field pivoted to genome-wide association.

COMMON TRAP

Do not equate a linkage peak with a gene. Linkage localises a disease to a chromosomal *region* spanning many megabases and dozens of genes; identifying the causal gene requires the further steps of fine-mapping and positional cloning. Similarly, do not confuse the two failure modes of linkage in psychiatry: the problem is not measurement but biology, namely many small-effect variants that no family-based linkage design is powered to catch.

CLINICAL ANCHOR

The clearest psychiatric payoff of positional cloning is *DISC1* (Disrupted-in-Schizophrenia-1), named after the t(1;11) breakpoint it disrupts. The translocation co-segregated with schizophrenia and affective psychosis in a Scottish pedigree at a LOD score of 7.1, far above the threshold of 3, illustrating that when a single large-effect variant genuinely exists in a family, linkage remains decisive. Such variants are the exception, not the rule, in common psychiatric illness.

FEATURE	LINKAGE ANALYSIS	ASSOCIATION STUDY
Unit of analysis	Families / pedigrees (co-segregation across meioses)	**Unrelated individuals (case-control population co-occurrence)**
Effect size detectable	**Rare variants of large effect (Mendelian loci)**	Common variants of small effect (polygenic)
Allele specificity	Allele-agnostic (recombinant vs non-recombinant)	**Implicates a specific allele**
Statistic / threshold	LOD score; +3 proof, -2 exclusion	P value; genome-wide significance $p < 5 \times 10^{-8}$
Mapping resolution	Coarse (tens of cM, many megabases)	**Fine (sub-cM, exploits short-range LD)**
Success in psychiatry	**Largely failed for common disorders; non-replication**	Now dominant; hundreds of polygenic loci, PRS

Linkage versus association across the four axes examiners test: unit of analysis, detectable effect size, resolution, and track record in psychiatric disorders.

MNEMONIC

"LOD 3, odds 1000; minus 2, out the door"

LOD +3 accepts linkage at 1000:1 odds in favour; LOD -2 excludes it at 100:1 against. Pair this with the direction check: positive LOD supports linkage, negative LOD argues against it.

GOOD TO REMEMBER

- **LOD score +3:** conventional threshold for proof of linkage, equals odds of 1000:1 (10^3) in favour (parametric linkage).
- **LOD score -2:** conventional threshold to exclude linkage, equals odds of 100:1 (10^2) against.
- **Recombination fraction (theta):** ranges 0 (never separated, i.e. inside the gene) to 0.5 (unlinked, independent assortment).
- **Centimorgan (cM):** unit of genetic distance, 1 cM = 1% recombination, averaging roughly 1 megabase genome-wide (varies by location).
- **Affected sib-pair sharing:** expected identity-by-descent proportions 25% / 50% / 25% for 0 / 1 / 2 shared alleles under no linkage; excess sharing indicates a disease locus.
- **RFLP, microsatellite/STR, SNP:** three successive marker generations underpinning gene mapping.
- **DISC1 (t(1;11)):** schizophrenia/affective-psychosis candidate cloned from a balanced translocation breakpoint in a Scottish family; linkage LOD 7.1 (Millar et al 2000; Blackwood et al 2001).
- **GWAS genome-wide significance:** conventional threshold p < 5 x 10 to the -8, correcting for roughly one million independent common variants.

5 · Association, GWAS, candidate genes, CNVs and polygenic risk scores

Why this matters. Psychiatric genetics moved in one generation from a graveyard of irreproducible **candidate gene** claims to a robust, sample-size-driven **genome-wide association study** (GWAS) enterprise. The examiner wants you to narrate that arc: why underpowered candidate studies failed, how the **common-disease-common-variant** hypothesis and consortium-scale GWAS finally delivered replicable hits, where rare **copy number variants** sit on the risk spectrum, and why a **polygenic risk score** that captures real biology still cannot predict any individual's diagnosis. The unifying idea is the genetic architecture of complex disorders: many common alleles of tiny effect plus a few rare variants of large effect, with a persistent **missing heritability** gap between them.

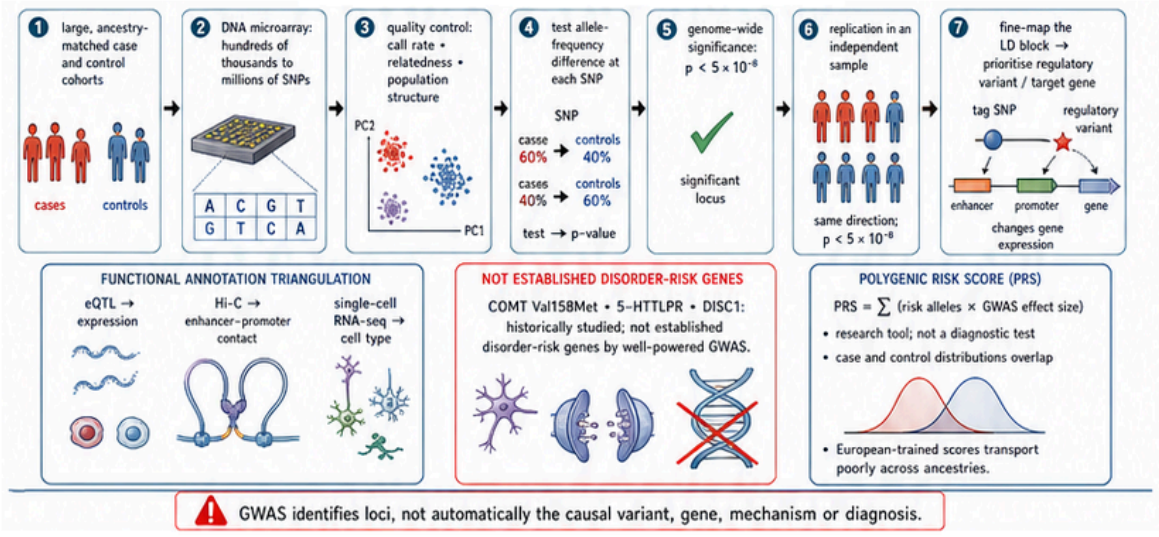


Fig 3.10 How a GWAS finds a locus.

Ground your answer in named findings rather than generalities: the 22q11.2 deletion as the single largest known genetic risk for schizophrenia, the MHC/complement-C4 signal, and the shared loci (e.g. CACNA1C) that blur the schizophrenia to bipolar boundary. These are the load-bearing facts, drawn from Kaplan and Sadock (2024), the New Oxford Textbook, and the Companion to Psychiatric Studies.

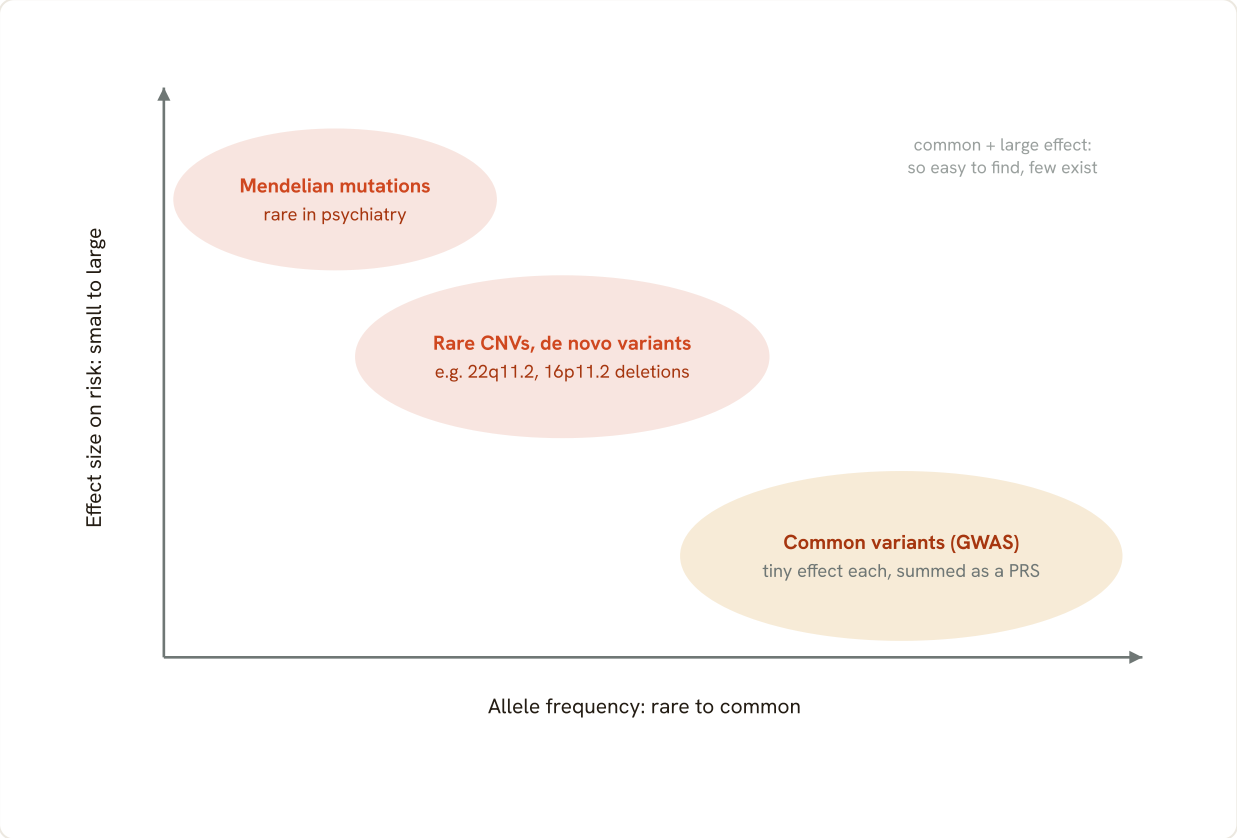
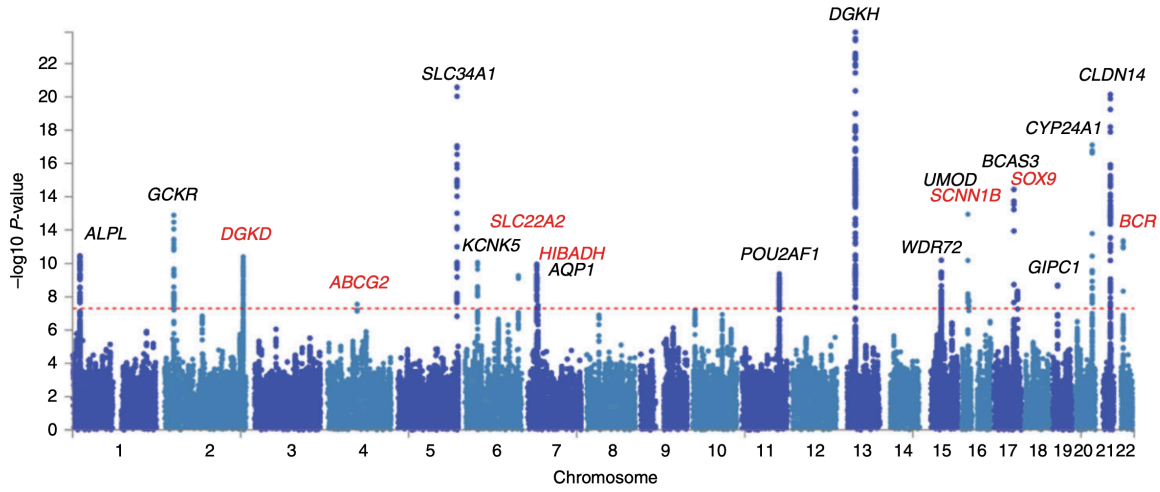


Fig 3.11 The genetic architecture of psychiatric disorders on the allele-frequency by effect-size plane. Risk variants trade off frequency against effect: a very few rare mutations carry large effects (top left, uncommon in psychiatry), rare copy-number and de novo variants sit in the upper band with moderate-to-large effects (the 22q11.2 deletion is the clearest example in schizophrenia), and the bulk of common inherited risk lies bottom right as thousands of common variants each of tiny effect, which genome-wide association detects and a polygenic risk score sums. The empty top-right corner (common and large effect) explains why such variants would already have been found, and the gap between what these methods capture and twin heritability is the missing heritability problem.



Representative GWAS Manhattan plot: S. A. Howles, A. Wiberg, M. Goldsworthy et al., CC BY 4.0, via Wikimedia Commons

Fig 3.12 What a genome-wide association study produces: a Manhattan plot. Each dot is one single-nucleotide polymorphism, placed left to right by its position along the chromosomes, and its height is the strength of association (the negative log base ten of the p-value). The dashed horizontal line marks genome-wide significance (5 x 10 to the minus 8); the peaks rising above it are the associated loci. A psychiatric GWAS looks exactly like this: each significant peak adds only a sliver of risk, which a polygenic risk score later sums across the genome. The plot shown is a representative GWAS used to illustrate the method.

5.1 Association studies: the basic logic and its currencies

The design. An **association study** compares allele frequencies at a genetic marker between unrelated cases and controls: if an allele is over-represented in cases, it (or a variant near it) may raise risk. This is more powerful than linkage for common variants of small effect, which is exactly the architecture complex psychiatric disorders turned out to have (Companion to Psychiatric Studies).

Direct vs indirect association. Because alleles are inherited in blocks, a typed marker need not be causal: **linkage disequilibrium** (LD, the non-random co-inheritance of nearby alleles) means a neutral tag SNP can flag a nearby functional risk allele. GWAS exploits this, so most GWAS hits are markers pointing to a region rather than the causal variant itself (Kaplan and Sadock 2024).

SNP (single-nucleotide polymorphism)

A single base-pair change (e.g. adenine to guanine); occurs roughly once per 1,200 bases; the workhorse marker of GWAS.

Common variant

Minor allele frequency above 1% in the population.

Linkage disequilibrium (LD)

Non-random association of alleles at nearby loci, decaying with recombination distance; lets a tag SNP stand in for an untyped causal allele.

Pleiotropy

One gene affecting multiple traits or disorders; many of the same loci raise risk for schizophrenia, bipolar disorder and ASD.

5.2 The candidate-gene era and its replication failure

The approach. Before genome-wide genotyping, researchers were forced to pre-select a handful of **candidate genes**, chosen either positionally (under a linkage peak) or functionally (a biologically plausible neurotransmitter gene). For schizophrenia alone, more than 1,500 studies examined nearly 800 candidate genes (Tasman 2015).

The cautionary tale. Almost none survived. Farrell and colleagues (2015), reviewing the most-discussed schizophrenia candidates (COMT, DTNBP1/dysbindin, DISC1, DAOA, RGS4, HTR2A, DRD3) against genome-wide data, found the classic candidate literature did not yield clear insight into the genetic basis of schizophrenia: these historical candidates were not supported at genome-wide significance, and the original serotonin-transporter and DISC1 psychiatric associations largely did not replicate (Companion to Psychiatric Studies).

Why they failed. Underpowered samples chasing tiny true effects, publication bias toward positive results, weak priors on which genes to test, and flexible analytic choices produced a literature dominated by false positives (Ioannidis and colleagues). Even where a real effect existed, replication studies were themselves too small to confirm it. The lesson embedded in every modern GWAS is the need for enormous samples and built-in replication.

> **COMMON TRAP**
>
> Do not quote COMT val158met or 5-HTTLPR (the serotonin-transporter length polymorphism, SLC6A4) as established risk genes for a psychiatric disorder. In the exam these are the canonical examples of candidate-gene claims that did not replicate at genome-wide significance. The safe framing: "historically studied candidate, not supported by well-powered GWAS." DISC1 (Disrupted-in-Schizophrenia-1) belongs in the same cautionary basket.

5.3 The common-disease-common-variant hypothesis

The pivot from linkage. Linkage studies, so successful for Mendelian disease, failed to deliver reproducible schizophrenia loci; no Mendelian form of schizophrenia was ever found. This failure was read as evidence against a few genes of major effect, and reframed as the **common-disease-common-variant** (CD/CV) hypothesis: risk is conferred by many common variants, each of small effect, that are old enough to be widespread in the population (Tasman 2015).

Why it justified GWAS. If risk alleles are common, they can be tagged by common SNPs on an array and detected in case-control samples, provided the sample is large enough to see effects with odds ratios near 1.1 to 1.4. CD/CV is the theoretical warrant for genome-wide genotyping; it does not exclude a complementary role for rare, high-penetrance variants (the two-tier architecture in 5.7).

5.4 GWAS methodology: arrays, the Manhattan plot and the 5e-8 threshold

The platform. A GWAS uses a DNA microarray ("gene chip") to assay hundreds of thousands to millions of SNPs across the whole **genome-wide** span simultaneously in tens to hundreds of thousands of people, then tests each SNP for a frequency difference between cases and controls (Kaplan and Sadock 2024).

The Manhattan plot. Results are displayed with chromosomal position on the x-axis and the negative log10 of each SNP's p-value on the y-axis, so the strongest associations rise as skyscraper-like peaks (hence "Manhattan"). A horizontal line marks the significance threshold; peaks crossing it are the reported loci.

Genome-wide significance = 5e-8. Because roughly a million independent tests are performed, the conventional threshold is set at p less than 5 x 10 to the power minus 8 (5e-8), a Bonferroni-style correction for the predicted false positives when a million tests are run (Kaplan and Sadock 2024). Meeting this bar is what separates a credible locus from noise, and is why so many early, small psychiatric GWAS reported nothing.

The QQ plot. A quantile-quantile plot graphs observed against expected p-values under the null. Points hugging the diagonal until an upward tail at the extreme suggest true polygenic signal; an early, uniform lift of the whole line signals confounding (typically population stratification or cryptic relatedness), quantified by the genomic inflation factor lambda. The QQ plot is the standard quality-control read-out for a GWAS.

RULE **Genome-wide significance is $p < 5 \times 10^{-8}$.** It is a Bonferroni-style correction for roughly a million independent common-variant tests, and is the bar that separates a credible locus from noise.

5.5 The Psychiatric Genomics Consortium and sample-size scaling

Size was the missing ingredient. The decisive move was collaborative pooling. The **Psychiatric Genomics Consortium** (PGC) aggregated samples across more than 30 countries, and the schizophrenia signal scaled almost linearly with case number: an early GWAS reporting a handful of loci grew, once tens of thousands of cases were assembled, into the landmark 2014 analysis of about 36,989 cases and 113,075 controls that identified 128 independent associations across 108 distinct genomic loci (Companion to Psychiatric Studies; Kaplan and Sadock 2024).

What the hits mean biologically. At least three-quarters of these loci contained protein-coding genes, enriched for dopamine (DRD2), glutamate (GRIN2A, GRM3) and voltage-gated calcium-channel (CACNA1C) signalling. Most associated variants do not change protein sequence; they most likely alter gene expression, which makes functional interpretation hard (Companion to Psychiatric Studies).

CLINICAL ANCHOR

Named schizophrenia findings worth carrying into a viva. The **MHC/complement-C4 signal** on chromosome 6 is the single most robustly associated locus, though its effect is modest (odds ratio about 1.2); Sekar and colleagues (2016) showed the association is driven by structural variation raising expression of complement component C4A, plausibly linked to excessive synaptic pruning. **DRD2** (the target of every antipsychotic) emerging as a GWAS hit closed a satisfying loop between genetics and pharmacology. **CACNA1C** is a canonical cross-disorder locus shared with bipolar disorder, underlining that genetic boundaries between the two are permeable.

5.6 Copy number variants and named recurrent syndromes

Definition. A **copy number variant** (CNV) is a structural change, a deletion or duplication of a DNA segment larger than 1 kilobase, altering gene dosage. CNVs are common in aggregate (about 12% of the genome is copy-number variable) and mostly benign, but a subset of large, recurrent, gene-rich CNVs carry substantial psychiatric risk (Kaplan and Sadock 2024).

22q11.2 deletion: the flagship. The recurrent hemizygous microdeletion at 22q11.2 was the first de novo CNV described in schizophrenia (Karayiorgou 1995) and, before the GWAS era, the only DNA variant indisputably pathogenic for the disorder (Companion to Psychiatric Studies). It causes velocardiofacial syndrome (DiGeorge syndrome), with cardiac outflow defects, palatal anomalies, hypocalcaemia and learning difficulty, and raises the odds of schizophrenia roughly 50-fold, the single largest known genetic risk (Kaplan and Sadock 2024). Because carriers are recognisable clinically, the psychosis link was demonstrable early.

Other recurrent risk CNVs. A recurring set of loci shows a similar many-to-one, pleiotropic pattern (one CNV, several neurodevelopmental outcomes): 16p11.2 (deletion and duplication, strongly tied to autism and developmental delay), 1q21.1, the 15q11-13 region, 3q29, and deletions disrupting NRXN1 (neurexin-1, a presynaptic cell-adhesion gene). Total CNV burden is elevated in schizophrenia and autism relative to controls, and disease-associated CNVs are larger and more gene-rich than benign ones. Chromosomal microarray is now standard first-line testing in autism and intellectual disability, yielding a molecular diagnosis in over 20% of children tested (Kaplan and Sadock 2024).

~50-fold	~12%	>20%
22Q11.2 RAISES SCHIZOPHRENIA ODDS	OF GENOME IS COPY-NUMBER VARIABLE	CMA MOLECULAR-DIAGNOSIS YIELD IN ASD/ID

LOCUS	CHANGE	SYNDROME / EPONYM	PRINCIPAL PSYCHIATRIC ASSOCIATION
22q11.2	Deletion	**Velocardiofacial / DiGeorge**	**Schizophrenia (about 50-fold; largest known single risk); ADHD, anxiety**
16p11.2	Deletion / duplication	16p11.2 microdeletion/duplication	Autism, developmental delay, intellectual disability
1q21.1	Deletion / duplication	1q21.1 recurrent CNV	Schizophrenia, autism, developmental delay
15q11-13	Duplication	15q duplication (maternal)	Autism; (paternal deletion gives Prader-Willi)
15q11.2	Deletion	15q11.2 (BP1-BP2)	Schizophrenia, epilepsy, developmental delay
NRXN1 (2p16.3)	Deletion	NRXN1 deletion	Schizophrenia, autism, intellectual disability

Recurrent, high-risk copy number variants and their named cytogenetic syndromes; 22q11.2 deletion is the flagship, carrying the single largest known genetic risk for schizophrenia (Kaplan and Sadock 2024; Companion to Psychiatric Studies).

5.7 The genetic architecture plane: allele frequency vs effect size

The core inverse relationship. Plot allele frequency against effect size and a clear gradient appears. Common GWAS SNPs are frequent but tiny in effect (odds ratios about 1.1 to 1.4). Rare CNVs and protein-truncating variants are the opposite: uncommon in the population but with large effect (odds ratios of roughly 20 to 100 for the strongest, e.g. 22q11.2). Mendelian, single-gene disorders sit in the far corner: very rare, near-deterministic effect (Kaplan and Sadock 2024).

Why the corners are empty. There are essentially no common variants of large effect for schizophrenia (a variant that common and that harmful would be culled by natural selection, because affected individuals have markedly reduced fecundity). This is why the disorder is polygenic on the common-variant side and driven by rare, often de novo, variants on the large-effect side. Both tiers must be summed to understand an individual's total genetic liability.

5.8 Polygenic risk scores: construction and limits

Construction. A **polygenic risk score** (PRS, also risk-profile scoring) is built from GWAS summary statistics. In a discovery sample, each SNP is assigned a weight (its estimated effect size); in an independent target individual, you count the risk alleles carried and sum them, weighted, to a single number, an estimate of that person's common-variant genetic liability (Kaplan and Sadock 2024). The method traces to the International Schizophrenia Consortium (ISC), which set a deliberately loose p-value threshold, reasoning that although most such alleles are false, a highly polygenic disorder would still carry a detectable aggregate burden. The ISC confirmed this and estimated the common-variant component is spread across at least 1,000 alleles, contributing roughly one-third of the genetic risk (Companion to Psychiatric Studies).

Variance explained. Even from the largest studies, a schizophrenia **PRS** accounts for only about 7% of the variance in liability; the PGC common-variant signal explains only about 3 to 4% (New Oxford Textbook; Companion to Psychiatric Studies). Across disorders the figures are modest, and for ADHD current PRS explains on the order of 0.1 to 2% of phenotypic variance (New Oxford Textbook).

Why PRS is not yet clinically predictive. Three reasons dominate. First, low variance explained: high PRS shifts population-average risk but the distributions of cases and controls overlap heavily, so an individual score has poor discrimination. Second, portability: GWAS samples are overwhelmingly of European ancestry, and PRS performs worse when applied across ancestries (an equity problem for use in Indian and other non-European populations). Third, PRS captures only the common-variant tier, ignoring the large-effect CNVs and rare variants that matter most for the highest-risk individuals. PRS is a powerful research instrument for genetic architecture, but not a diagnostic test.

HOLD THIS

A PRS sums common-variant burden but cannot diagnose an individual. It explains only about 7% of schizophrenia liability, case and control distributions overlap heavily, and European-derived scores transport poorly to other ancestries.

TRAP Do not quote COMT val158met, 5-HTTLPR (SLC6A4) or DISC1 as established risk genes: they are the canonical candidate-gene claims that did not replicate at genome-wide significance.

INDIA

The Eurocentric ancestry bias of GWAS discovery samples is not an abstraction for Indian practice. A PRS derived in European cohorts loses accuracy in South Asian genomes because LD structure and allele frequencies differ, so any near-term "genetic risk report" marketed for Indian patients should be read with strong caution. Broadening reference panels to non-European ancestries is the stated route to more equitable PRS.

5.9 Missing heritability: where the rest may hide

The gap. Twin studies put schizophrenia heritability high (broadly in the 60 to 80% range for the most heritable psychiatric disorders), yet SNP-heritability (the variance captured by common GWAS variants) and PRS explain only a single-digit-to-modest fraction. The difference is **missing heritability** (Manolio and colleagues 2009).

Candidate hiding places. Several, and probably several at once: (1) rare variants of larger effect, including CNVs and protein-truncating single-nucleotide variants, poorly tagged by common-SNP arrays; (2) many more common variants of effect too small to reach 5e-8 at current sample sizes (still-larger GWAS keep finding them); (3) gene-gene and gene-environment interactions and structural variation not well captured; (4) overestimation of twin heritability itself (shared-environment and equal-environment assumptions). The field's working answer is that no single mechanism accounts for the gap; ever-larger biobank-scale GWAS plus whole-genome and exome sequencing for rare variants are chipping at it from both ends (Companion to Psychiatric Studies; New Oxford Textbook).

MNEMONIC

Common is Small, Rare is Tall

The genetic architecture plane in one line: common variants (GWAS SNPs) are frequent but Small in effect; rare variants (CNVs, protein-truncating variants) are uncommon but Tall in effect. The empty corner (common and tall) is emptied by natural selection.

PEARL

The whole story is a parable about statistical power. Candidate-gene studies failed not because the biology was wrong but because they were underpowered and multiplicity-uncorrected; GWAS succeeded not because it was cleverer but because consortia made it big enough. The genome-wide significance threshold of 5e-8 is the institutional memory of that lesson.

GOOD TO REMEMBER

- **Genome-wide significance threshold:** p less than 5 x 10 to the power minus 8 (5e-8), correcting for about a million tests.
- **22q11.2 deletion:** velocardiofacial / DiGeorge syndrome; single largest known genetic risk for schizophrenia, about 50-fold increased odds; first de novo CNV described in schizophrenia (Karayiorgou 1995).
- **16p11.2 (deletion/duplication):** recurrent CNV, autism and developmental delay.
- **1q21.1:** recurrent deletion/duplication; schizophrenia, autism, developmental delay.
- **15q11-13 (maternal duplication):** autism (paternal deletion of the region gives Prader-Willi).
- **NRXN1 (neurexin-1, 2p16.3) deletion:** schizophrenia, autism, intellectual disability.
- **MHC / complement C4A:** most robustly associated schizophrenia locus (chromosome 6), effect modest (odds ratio about 1.2); C4A implicated in synaptic pruning (Sekar 2016).
- **DRD2:** GWAS-significant schizophrenia locus; antipsychotic target, closing the genetics-pharmacology loop.
- **CACNA1C:** voltage-gated calcium channel; cross-disorder locus shared by schizophrenia and bipolar disorder.
- **COMT (val158met), 5-HTTLPR (SLC6A4), DISC1:** classic candidate genes that largely failed to replicate at genome-wide significance (Farrell 2015); the cautionary examples.
- **PGC schizophrenia GWAS (2014):** about 36,989 cases, 113,075 controls; 128 independent associations at 108 distinct loci.
- **ISC (2009):** common-variant risk spread across at least 1,000 alleles, contributing roughly one-third of genetic risk; origin of polygenic risk scoring.
- **Schizophrenia PRS variance explained:** about 7% of liability (PGC common-variant signal about 3 to 4%); not clinically predictive at the individual level.
- **ADHD PRS variance explained:** about 0.1 to 2% of phenotypic variance.
- **Twin heritability (most heritable psychiatric disorders):** broadly 60 to 80%; the gap to SNP-heritability is the missing heritability (Manolio 2009).

6 · Novel genetic approaches and gene therapy

Array-based **GWAS** gave psychiatric genetics its first robust, replicable common-variant hits, but it is deliberately blind to two things: the rare, large-effect variation that a genotyping chip does not carry, and the biological **mechanism** that turns a statistical association at a locus into a disease. This topic is the Paper-1 delta on everything that has moved beyond the chip: high-throughput **sequencing** to find rare and *de novo* variation, **functional genomics** and stem-cell models to translate a locus into a mechanism, **causal-inference** methods such as Mendelian randomization, **biobank**-scale cohorts, polygenic scores as a research and emerging stratification tool, and finally **gene therapy**, where the honest examination answer is that monogenic neurology has moved but polygenic psychiatry has not (Kaplan & Sadock 2024; New Oxford 2020).

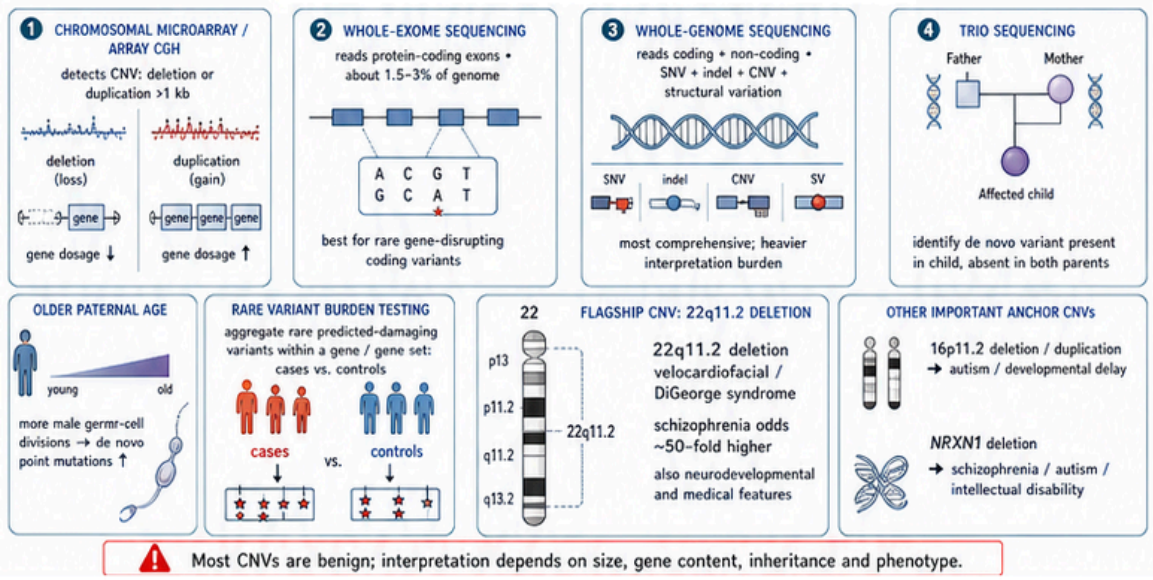


Fig 3.13 Rare variants: which tool finds what?.

Why it matters. Examiners increasingly ask you to place a method against a question: which technology finds rare variants, which infers causality from observational genetic data, why a polygenic disorder is a poor candidate for gene editing. **Framing.** Hold one organising idea throughout: *the architecture dictates the tool*. Rare large-effect variants (autism, intellectual disability, some schizophrenia) are found by sequencing and are conceptually near a targeted therapy; common small-effect variants (the bulk of adult psychiatric liability) are found by GWAS, summarised by polygenic scores, and are nowhere near a molecular cure.

6.1 Sequencing: whole-exome and whole-genome sequencing

What each reads, and why the choice matters. **Whole-exome sequencing** (WES) captures and sequences only the protein-coding portion of the genome, about 1.5 to 3% of the total, which lowers cost and greatly improves interpretability because a coding variant has a readable consequence on protein (Kaplan & Sadock 2024; Wang et al. 2019). It is described in the standard reference as "good for finding gene-disrupting rare variants" (Kaplan & Sadock 2024). **Whole-genome sequencing** (WGS) resequences the entire genome and can in principle detect every class of variation at once, single-nucleotide variants, small insertions and deletions, and structural and copy-number variants, including the regulatory, non-coding variation that WES misses; it is the more comprehensive but more expensive choice. Both have supplanted the older linkage and candidate-gene strategies for gene discovery (Kaplan & Sadock 2024).

RULE **The architecture dictates the tool.** Rare large-effect variants are found by sequencing and sit near a targeted therapy; common small-effect variants are found by GWAS, summed as a PRS, and are nowhere near a molecular cure.

6.2 Rare-variant burden testing

Counting damaging variants against chance. Because any single rare variant is, by definition, seen in too few people to reach significance on its own, the analytic trick is the **rare-variant**

burden test: aggregate all rare (minor allele frequency below 1%), predicted-damaging variants within a gene or gene-set and ask whether cases collectively carry a heavier burden than controls. This requires very large samples but has been productive, most famously the finding of an increased burden of ultra-rare protein-altering variants among people with schizophrenia (Genovese et al. 2016, in Wang et al. 2019). A key statistical companion is the **mutation-intolerance** metric: genes can be scored for how strongly they resist loss-of-function variation (the pLI score, probability of loss-of-function intolerance), so that a damaging variant landing in a highly intolerant gene is prioritised as likely pathogenic (Kaplan & Sadock 2024; Wang et al. 2019).

6.3 De novo mutations, autism, and the paternal-age effect

New mutations in the child, absent in the parents. A **de novo mutation** is one present in the affected proband but in neither biological parent, so it is discovered by sequencing parent-child **trios** (two parents plus affected child) or quads (adding an unaffected sibling) and filtering the child's variants against both parents (Wang et al. 2019). De novo variants are individually rare but tend to be more disruptive than inherited variants, which makes them a powerful route into sporadic disease. Their contribution is greatest in the early-onset neurodevelopmental disorders: penetrant de novo mutations are estimated to contribute to autism risk in roughly 11% of trio families, and of de novo loss-of-function variants in autism about 43% are estimated to be pathogenic (against about 13% of de novo missense variants) (Iossifov et al. 2014; Sanders et al. 2015, in Wang et al. 2019). Autism (ICD-11 6A02, DSM-5-TR autism spectrum disorder) and intellectual developmental disorders together dominate the de novo literature. **The paternal-age effect.** Because the male germline keeps dividing across the lifespan, the number of de novo point mutations transmitted rises steadily with paternal age; this is the molecular basis for the epidemiological association of advancing paternal age with schizophrenia and autism in offspring (Malaspina et al. 2001, in Wang et al. 2019). It is the mechanistic pearl that links a demographic risk factor to a class of variant.

6.4 Functional genomics: from a locus to a mechanism

Bridging the association gap. Most GWAS hits sit in non-coding regulatory DNA, so knowing the associated variant does not tell you which gene it acts on or how. Functional genomics is the toolkit that closes that gap. **eQTL** mapping (expression quantitative trait loci) identifies variants that predict the expression level of a gene, so a risk variant that is also an eQTL points to the gene whose dosage it alters (Kaplan & Sadock 2024). **TWAS** (transcriptome-wide association study) formalises this: it imputes genetically-predicted gene expression from eQTL reference data and tests that predicted expression against disease, moving the unit of association from an anonymous SNP to a named gene. **Chromatin conformation** methods, notably **Hi-C** (a chromosome-conformation-capture assay), reveal which physically distant regulatory regions loop into contact with a promoter, so a non-coding variant can be assigned to the gene it actually regulates in three dimensions (Kaplan & Sadock 2024). **Single-cell** RNA sequencing resolves which specific cell type expresses a risk gene, and **MPRA** (massively parallel reporter assay) tests

thousands of candidate regulatory variants at once for their effect on expression. Together these define the mechanistic chain: variant, regulatory element, target gene, cell type, pathway.

6.5 Cellular models: iPSC-derived neurons and brain organoids

Patient biology in a dish. The Nobel-winning discovery that adult somatic cells (skin fibroblasts, hair-follicle cells) can be reprogrammed into **induced pluripotent stem cells** (iPSCs) lets us build neurons that carry an individual patient's exact genetic background, then differentiate them into the neuronal and glial types relevant to the disorder (Yamanaka; New Oxford 2020). iPSC-derived neurons from lithium-responsive bipolar patients show hyperexcitability and dysregulated calcium signalling that lithium itself corrects, tying a clinical phenotype to a cellular one (New Oxford 2020). **Brain organoids** are self-organising three-dimensional cultures that histologically resemble developing human brain and model architecture and connectivity that flat cultures cannot (Kaplan & Sadock 2024; New Oxford 2020). These models are where a genetic finding is functionally validated, and, combined with **CRISPR**/Cas9 editing to introduce or reverse a candidate variant, they let one ask whether a specific mutation is causal for a cellular phenotype (New Oxford 2020).

6.6 Causal inference: Mendelian randomization

Genes as nature's randomised trial. Observational associations cannot distinguish cause from confounding or reverse causation. **Mendelian randomization** (MR) exploits the fact that alleles are randomly allocated at conception, so a genetic variant that raises an exposure (a putative risk factor) acts as an **instrumental variable** that is largely free of the confounding and reverse causation that plague conventional epidemiology (Kaplan & Sadock 2024). If the variant that raises the exposure also raises disease risk, that supports a causal path. The examinable psychiatric applications are instructive precisely because they cut both ways: two-sample MR has supported a causal influence of cannabis use liability on schizophrenia risk, whereas MR has failed to find that genetically-predicted thyroid function causally influences major depression, and has not found that smoking heaviness causally influences anxiety or depression (Kaplan & Sadock 2024; New Oxford 2020). MR is now a standard way to interrogate whether an epidemiological correlate of psychiatric illness is cause or bystander.

6.7 Biobank-scale genetics

Scale as the enabling technology. The recurring lesson of psychiatric genetics is that discovery is sample-size limited, and the modern answer is the population **biobank**: cohorts of hundreds of thousands with linked genotype, deep phenotype, imaging, and health-record data. The **UK Biobank** (about 500,000 participants) has enabled analyses ranging from the medical consequences of pathogenic CNVs in adults to multimodal population brain imaging, and the US **All of Us** programme is explicitly building a more ancestrally diverse resource (Kaplan & Sadock 2024). Biobanks power the large GWAS, provide the replication samples for polygenic scores, and supply the instruments and outcomes for Mendelian randomization; they are the substrate on which the other methods run.

6.8 Polygenic scores as research tool and emerging stratifier

Summing thousands of tiny effects into one number. A **polygenic risk score** (PRS) sums an individual's risk alleles across the genome, each weighted by its GWAS effect size, into a single estimate of genetic liability (Kaplan & Sadock 2024). As a research tool it is well established: PRS quantifies SNP-based heritability, tests genetic overlap between disorders (a schizophrenia PRS also predicts bipolar liability), and positions categorical diagnosis at the tail of a continuous population liability. As a **clinical stratification** tool it remains emerging rather than deployed: current scores explain only a modest fraction of liability, so they shift population-level probabilities rather than diagnose individuals, and, critically, they are derived overwhelmingly from European-ancestry samples and therefore transport poorly to other ancestries, an equity limitation the standard text flags explicitly (Kaplan & Sadock 2024). The honest exam line: a research workhorse and a plausible future stratifier, not yet a clinical test.

6.9 Gene therapy: the monogenic-neurology precedent

Where molecular correction already works. Gene therapy has become real in single-gene neurological disease, which is the precedent examiners want you to cite. In **spinal muscular atrophy** (SMA), an autosomal-recessive motor-neuron disease caused by loss of *SMN1*, two mechanistically distinct approaches are licensed: **nusinersen**, an **antisense oligonucleotide** directed at the *SMN2* gene that modifies its splicing to raise functional SMN protein, given as a repeated intrathecal infusion; and a one-time gene-replacement therapy that uses an **AAV** (adeno-associated virus) vector to deliver a working copy of *SMN1* to motor neurons, raising SMN protein and improving survival (Kaplan & Sadock 2024). In **Huntington disease**, an autosomal-dominant expanded-CAG-repeat disorder, huntingtin-lowering antisense oligonucleotides reached human trials, the proof-of-concept that a defined, single-gene neuropsychiatric disorder is a tractable target even though efficacy results have been mixed. The general toolkit, then, is three-fold: **antisense oligonucleotides** that alter splicing or knock down a transcript, **AAV**-vector gene replacement, and **CRISPR**/Cas9 editing that introduces or reverses a mutation at the DNA level (New Oxford 2020; Kaplan & Sadock 2024).

6.10 Why polygenic psychiatry is not near gene therapy

Architecture forbids a single target. Every gene-therapy success above shares a feature the common psychiatric disorders lack: a single, known, large-effect causal gene. Schizophrenia, bipolar disorder, and major depression are polygenic, driven by thousands of common variants each of tiny effect (individual odds ratios typically below 1.3) plus a scatter of rare variants and heavy environmental contribution, so there is no one locus to edit or replace, and correcting any single variant would move risk negligibly (Kaplan & Sadock 2024). The realistic near-term yield of psychiatric genetics is therefore not a cure but mechanism, drug-target nomination (a GWAS gene as a pharmacological lead), risk stratification, and pharmacogenomics, not germline or somatic editing of a polygenic phenotype.

HOLD THIS

Gene therapy works for single-gene neurology, not polygenic psychiatry. Every precedent (spinal muscular atrophy, Huntington disease) has one large-effect causal gene; schizophrenia, bipolar disorder and depression have no single locus to edit or replace.

6.11 Sequencing versus array-GWAS: choosing the tool

A one-glance comparison. The following table is the examinable summary of which technology answers which question, the point being that no single platform does everything.

METHOD	VARIATION CAPTURED	BEST USE CASE	KEY LIMITATION
Array-GWAS	Common SNPs (chip content)	Common small-effect risk loci, PRS, heritability	**Blind to rare and novel variants; misses de novo**
Whole-exome sequencing	Coding variants (about 1.5 to 3% of genome)	Rare gene-disrupting and de novo coding variants	**Misses non-coding regulatory and most structural variation**
Whole-genome sequencing	All classes (SNV, indel, CNV, structural)	Comprehensive rare and regulatory variant discovery	**Highest cost; heavy interpretation burden for non-coding hits**
Trio de novo design	De novo variants absent in parents	Sporadic autism, intellectual disability, severe cases	**Needs parent samples; small yield outside neurodevelopmental disorders**

Discovery technologies mapped to the variant class each is built to find; the take-home is that architecture, common versus rare versus de novo, dictates the tool.

COMMON TRAP

Do not describe gene therapy as an emerging treatment for schizophrenia, bipolar disorder, or depression. The gene-therapy precedents (SMA, Huntington disease) are all single-gene disorders with a defined causal target; the common psychiatric disorders are polygenic with no such target, which is exactly why they are not near gene therapy. Equally, do not conflate WES and WGS: WES reads only the coding exome and misses non-coding and most structural variation, whereas WGS reads the whole genome.

COMMON TRAP

An eQTL, TWAS, or Mendelian-randomization result is not proof of a mechanism by itself; it is a prioritisation or a causal-inference signal that still needs functional validation (typically iPSC or organoid models plus CRISPR editing). Mendelian randomization in particular is only as good as its instrument: a variant with pleiotropic effects violates the core assumption and can produce a false causal claim.

PEARL

The paternal-age effect is the cleanest link between epidemiology and molecular genetics: the male germline keeps dividing, so older fathers transmit more de novo point mutations, which is the mechanistic explanation for advancing paternal age as a risk factor for schizophrenia and autism. If a stem asks why paternal (not maternal) age matters and why de novo variants are the currency, this is the answer.

MNEMONIC

SEQ-FM-CB-P: SEQuence it, work out the Function and Model it, infer Causality in a Biobank, then score the Polygene.

Walks the modern pipeline in order: sequencing (WES/WGS, de novo, burden) to find variants; functional genomics and cellular models (eQTL, TWAS, Hi-C, iPSC, organoids) to reach mechanism; causal inference (Mendelian randomization) and biobank scale to test and power it; polygenic scores as the summary output. Gene therapy sits outside this loop, reserved for the monogenic disorders.

INDIA

Two practical points for Indian practice. First, the ancestry bias of GWAS and polygenic scores is not abstract: scores trained on European-ancestry biobanks transport poorly to South Asian populations, so a PRS quoted in the literature should not be applied clinically to Indian patients without ancestry-matched validation. Second, the gene-therapies discussed are extremely high-cost, single-gene neurology interventions; when counselling families about the common polygenic psychiatric disorders, the message is that management is pharmacological and psychosocial, framed in liability terms, with no genetic cure on the horizon, which also keeps counselling non-stigmatising.

GOOD TO REMEMBER

- **WES (whole-exome sequencing):** captures protein-coding genome, about 1.5 to 3%; good for rare gene-disrupting variants (Kaplan & Sadock 2024).
- **WGS (whole-genome sequencing):** reads all variant classes (SNV, indel, CNV, structural); more comprehensive, more expensive.
- **De novo mutation yield in autism:** penetrant de novo mutations contribute to about 11% of trio families; about 43% of de novo loss-of-function variants estimated pathogenic (about 13% of missense) (Iossifov et al. 2014; Sanders et al. 2015).
- **Detected DNM rate (predominantly whole-exome):** roughly 1.3 de novo mutations per individual across neuropsychiatric sequencing cohorts in denovo-db, a sequenced-exome yield and not the genome-wide new-mutation rate (Wang et al. 2019).
- **SETD1A:** loss-of-function variants implicated as a schizophrenia susceptibility gene (Takata et al. 2014).
- **Schizophrenia ultra-rare variant burden:** increased burden of ultra-rare protein-altering variants in schizophrenia (Genovese et al. 2016).
- **GWAS genome-wide significance threshold:** P = 5 x 10 to the minus 8 (Kaplan & Sadock 2024).
- **Common psychiatric risk alleles:** individual odds ratios typically below 1.3 (Kaplan & Sadock 2024).
- **UK Biobank:** about 500,000 participants with linked genotype, phenotype, imaging, and records; All of Us builds a more diverse US resource.
- **Nusinersen:** SMN2-directed antisense oligonucleotide (splice modifier) for spinal muscular atrophy, intrathecal (Kaplan & Sadock 2024).
- **SMA AAV gene replacement:** one-time AAV-vector delivery of a working SMN1 copy (Kaplan & Sadock 2024).
- **Huntingtin-lowering ASO:** antisense oligonucleotide against HTT reached human Huntington disease trials; efficacy mixed.
- **CRISPR/Cas9:** genome-editing tool to introduce or reverse disease-associated mutations, used experimentally with iPSC and organoid models (New Oxford 2020).
- **Cannabis and schizophrenia:** two-sample Mendelian randomization supports a causal influence of cannabis use liability on schizophrenia risk (Kaplan & Sadock 2024).

Mechanisms

7 · Epigenetics in psychiatry

The missing half of nature and nurture. Twin studies fix the heritability of schizophrenia near 81 percent and of bipolar disorder near 85 percent (Kaplan & Sadock 2024), yet common variants explain only a fraction of that liability, and monozygotic concordance for schizophrenia sits slightly below 50 percent. **Epigenetics** occupies exactly this gap: it is the molecular layer through which environment writes onto a fixed genome, and it is the single most examinable route by which stress, adversity, and development translate into altered gene expression without touching the DNA sequence.

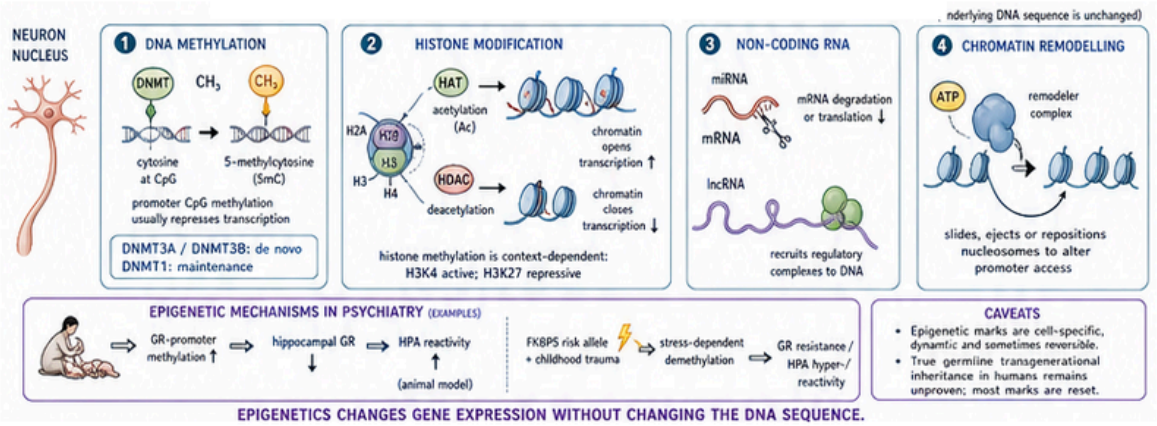
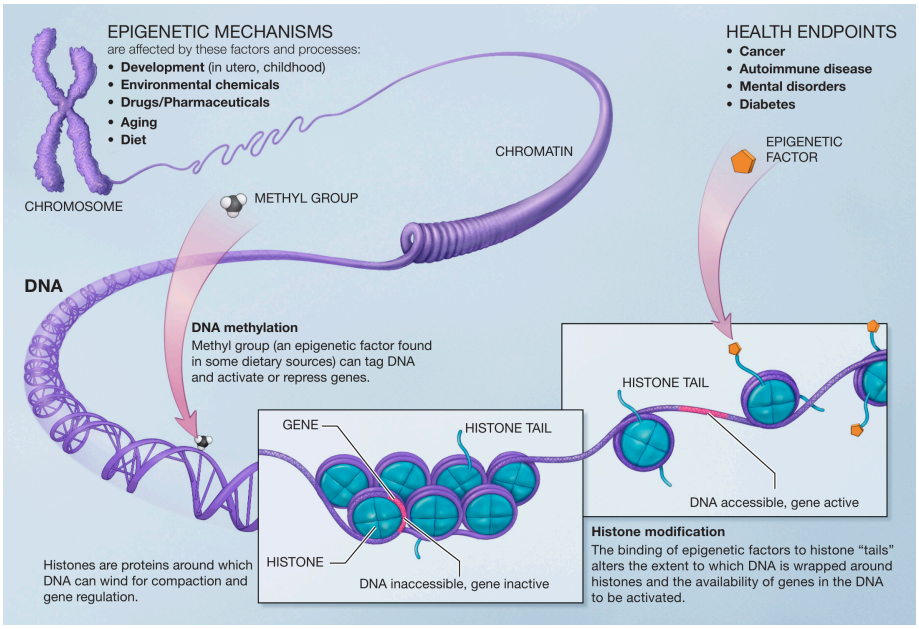


Fig 3.14 Epigenetics: same sequence, different expression.

For the exam, hold three anchors: a clean **definition**, the four **mechanisms** (DNA methylation, histone modification, non-coding RNA, chromatin remodelling), and the flagship human stories (genomic imprinting in Prader-Willi versus Angelman; maternal-care and glucocorticoid-receptor methylation; the FKBP5 gene-by-environment interaction in PTSD). Epigenetics is the substrate that makes gene-environment interaction mechanistic rather than statistical.



Epigenetic mechanisms: National Institutes of Health, public domain, via Wikimedia Commons

Fig 3.15 The two main epigenetic mechanisms, shown from chromosome to DNA. DNA methylation adds a methyl group that tags the sequence and tends to silence transcription without changing the letters of the code. Histone modification alters how tightly DNA is wound around the nucleosome: loosely wound DNA is accessible and its genes active, tightly wound DNA is inaccessible and silent. These marks are laid down by development, early-life environment, drugs, ageing and diet, which is how experience becomes a stable, sometimes heritable, change in gene expression.

7.1 Definition and why it matters

Waddington's term, sharpened. Conrad Waddington fused "genetics" and "epigenesis" in 1942; the working definition today is a stable, potentially heritable change in gene expression that

arises from a modification of the chromosome without any alteration of the underlying DNA sequence (Kaplan & Sadock 2024). The genetic code is one-dimensional, identical in every cell, and unmoved by environment. The epigenetic code is a dynamic three-dimensional layer of proteins and non-coding RNAs, unique to each cell type, and it changes rapidly in response to environmental cues. This is how one genome builds a neuron and a hepatocyte, and how a postmitotic neuron rewrites synaptic-plasticity genes after experience.

~81%	~85%	<50%
SCHIZOPHRENIA HERITABILITY	BIPOLAR DISORDER HERITABILITY	MZ CONCORDANCE, SCHIZOPHRENIA

7.2 DNA methylation and CpG islands

The most examined mechanism. DNA methyltransferases (DNMTs) transfer a methyl group to the 5 position of the cytosine ring at a CpG dinucleotide, generating 5-methylcytosine (Kaplan & Sadock 2024). CpG dinucleotides cluster at high density in **CpG islands** that mark the promoters of active housekeeping genes and are normally unmethylated; aberrant methylation of an island produces a highly repressive, often heritable, chromatin state (X-inactivation and imprinted genes are the classic examples). Methylation silences transcription two ways: it blocks a transcription factor from binding, or it recruits a methyl-binding protein (for example MeCP2) that pulls in HDAC-containing repressive complexes such as NuRD. Three DNMTs matter: DNMT3a and DNMT3b establish methylation de novo, while DNMT1 is the maintenance enzyme that copies the pattern onto the daughter strand at the replication fork, which is why methylation is heritable across mitosis.

7.3 Histone modification: the histone code

Acetylation opens, methylation reads either way. DNA is wound around a histone octamer (H2A, H2B, H3, H4) to form the nucleosome; the protruding N-terminal tails carry reversible marks that set chromatin accessibility (Kaplan & Sadock 2024). **Acetylation** neutralises positively charged lysines, loosens the histone-DNA grip, and activates transcription; histone acetyltransferases (HATs, for example CBP/p300) write it and histone deacetylases (HDACs) erase it. **Histone methylation** is context-dependent: H3K4, H3K36, and H3K79 methylation activate, whereas H3K9, H3K27, and H4K20 methylation repress. This combinatorial logic is the histone code, and it is the direct target of the therapeutic HDAC inhibitors discussed below.

RULE **Methylation silences, acetylation opens.** DNA methylation tends to repress transcription; histone acetylation loosens the histone-DNA grip and activates it, all without changing the base sequence.

7.4 Non-coding RNA and chromatin remodelling

The other two mechanisms. Small and long non-coding RNAs, including microRNAs (miRNAs), silence transcripts and guide chromatin-modifying complexes to specific loci; altered miRNA expression is reported across depression and psychosis, and, critically, miRNA in sperm has been implicated in transmitting the effects of early trauma to offspring (see 7.8). **ATP-dependent chromatin remodellers** (SWI/SNF and related families) hydrolyse ATP to slide, evict, or reposition nucleosomes, maintaining nucleosome-free regions at active promoters. These four

mechanisms do not act in isolation: methylation recruits histone modifiers, which recruit remodellers, forming the self-reinforcing cascades that make epigenetic states stable.

7.5 Genomic imprinting: Prader-Willi versus Angelman

The single best imprinting question in psychiatry. Genomic imprinting is parent-of-origin-specific gene expression established by methylation marks laid down in the germline. Prader-Willi and Angelman syndromes both arise from the same 15q11-q13 locus, and which syndrome results depends entirely on which parental copy is lost (Kaplan & Sadock 2024). Prader-Willi (ICD-11 LD90.3) follows loss of the paternally expressed genes (paternal deletion, or maternal uniparental disomy) and presents with neonatal hypotonia and failure to thrive giving way to hyperphagia, childhood obesity, hypogonadism, and mild intellectual disability. Angelman syndrome follows loss of maternal UBE3A function (maternal deletion, paternal disomy, or a maternal UBE3A mutation) and presents with severe intellectual disability, ataxia, seizures, and a characteristic happy, excitable demeanour.

FEATURE	PRADER-WILLI SYNDROME	ANGELMAN SYNDROME
Locus	15q11-q13	**15q11-q13 (same region)**
Parent-of-origin lesion	**Loss of paternal contribution**	**Loss of maternal UBE3A**
Usual mechanism	Paternal deletion or maternal uniparental disomy	Maternal deletion, paternal disomy, or maternal UBE3A mutation
Key genes	SNRPN, NDN, SNORD116 (paternally expressed)	**UBE3A (maternally expressed)**
Core phenotype	Hypotonia then hyperphagia, obesity, hypogonadism, mild ID	Severe ID, ataxia, seizures, inappropriate laughter
Feeding history	**Failure to thrive, then insatiable appetite**	Not the defining feature

Same 15q11-q13 locus, opposite parental origin: the archetypal demonstration that methylation, not sequence, decides the phenotype.

7.6 Early-life programming: maternal care and the glucocorticoid receptor

The Meaney model. In rodents, high maternal licking-and-grooming during the first postnatal week produces adult offspring with reduced methylation at the hippocampal glucocorticoid-receptor promoter, higher GR expression, and a better-regulated, less reactive stress axis; low-care offspring show the opposite pattern (Meaney and Szyf, summarised in Kaplan & Sadock 2024). The mark is developmentally programmed yet pharmacologically reversible: HDAC inhibitors demethylate and raise GR, while intracerebral methionine (a methyl donor) re-methylates the promoter and increases stress reactivity in adults. This is the paradigm case of behaviour writing a stable epigenetic mark on a stress-axis gene.

7.7 Childhood adversity, FKBP5, and the human translation

From rat brain to human suicide brain. Postmortem hippocampus from suicide decedents with documented childhood abuse shows increased methylation at the GR promoter and reduced GR

expression, mirroring the low-care rat (McGowan and colleagues, in Kaplan & Sadock 2024). The mechanistically richest human example is **FKBP5**, a co-chaperone that restrains the glucocorticoid receptor. The rs1360780 risk allele permits stronger stress-induced FKBP5 induction; in carriers, childhood trauma drives demethylation of a functional glucocorticoid-response element, locking in a GR-resistant, hyper-reactive HPA phenotype and raising PTSD and depression risk in a dose-dependent way (Klengel et al. 2013). This is gene-by-environment interaction made molecular: the genotype sets susceptibility, early trauma supplies the epigenetic hit, and only the combination produces disorder.

HOLD THIS

Methylation is the molecular bridge from environment to gene expression. FKBP5 is the flagship: the rs1360780 risk allele plus childhood trauma demethylates a glucocorticoid-response element, locking in a GR-resistant, hyper-reactive HPA phenotype and raising PTSD and depression risk (Klengel 2013).

7.8 Transgenerational epigenetic inheritance (state the caveat)

Real signals, contested mechanism. Human observational data are suggestive: prenatal exposure during the Dutch Hunger Winter of 1944 to 1945 was associated, six decades later, with reduced methylation of the imprinted IGF2 gene, specific to periconceptional timing (Heijmans et al. 2008); offspring of Holocaust survivors show altered FKBP5 methylation and cortisol (Yehuda et al. 2016). Animal work is stronger: odour fear-conditioning before conception transmits behavioural and sperm-methylation changes across two generations, and injecting sperm RNA from stressed males into naive oocytes reproduces the offspring phenotype (Gapp et al. 2014). The caveat to state explicitly in any answer: true germline transgenerational inheritance in humans remains unproven, because most marks are erased at two global demethylation waves (gametogenesis and post-fertilisation), and confounding by shared environment, in-utero exposure, and maternal effects is very hard to exclude.

TRAP Do not overclaim epigenetic heredity: true germline transgenerational inheritance in humans remains unproven, because marks are largely reset at two demethylation waves.

7.9 Epigenetic clocks and accelerated biological ageing

A quantifiable biomarker. **Epigenetic clocks** estimate chronological age from DNA-methylation levels at a defined panel of CpG sites with high accuracy (Horvath 2013). When methylation age runs ahead of calendar age the excess is termed epigenetic age acceleration, and it is reported in severe mental illness, in trauma exposure, and with adverse environmental exposures such as tobacco smoke. The appeal for psychiatry is practical: methylation is a stable analyte measurable from a very small number of cells, which is exactly the property a field with no validated diagnostic biomarker needs; SKA2 methylation as a candidate predictor of suicidal behaviour is discussed in this same K&S chapter as an example of the biomarker promise.

7.10 Therapeutic angle: HDAC inhibitors and epigenetic editing

Drugs that move the marks. Several established agents act epigenetically. **Valproate** is a class I HDAC inhibitor in addition to its ion-channel and GABAergic actions, which is one proposed

contributor to its mood-stabilising and neuroprotective profile (Stahl 2021); this HDAC-inhibitory activity also underlies its recognised teratogenicity. In schizophrenia models, DNMT inhibitors raise the reduced reelin expression, and chronic clozapine downregulates the mGlu2 receptor via increased HDAC2 binding at its promoter, showing that antipsychotics themselves reshape the histone landscape (Kurita et al., in Kaplan & Sadock 2024). On the horizon, dCas9-based epigenetic editing can add or remove methylation at a chosen locus without cutting DNA, and the Prader-Willi work in which G9A histone-methyltransferase inhibitors (UNC0638, UNC0642) partially reactivated the silenced maternal locus in mice is a proof of concept for locus-specific epigenetic therapy (Kaplan & Sadock 2024).

COMMON TRAP

Do not conflate epigenetic reprogramming with mutation: DNA methylation and histone marks leave the base sequence untouched and Watson-Crick pairing intact. And do not overclaim heredity: acetylation and methylation are reversible and mostly reset in the germline, so "epigenetic inheritance" in humans is far weaker than the popular framing suggests.

PEARL

The one-line integration to give an examiner: methylation is the "molecular bridge" between the genetic code and the environment, converting a statistical gene-by-environment interaction (for example the FKBP5 risk allele plus childhood trauma) into a concrete, measurable, and in principle reversible change in gene expression.

MNEMONIC

MHNC = "My Histones Need Care"

The four epigenetic mechanisms: **M**ethylation of DNA, **H**istone modification, **N**on-coding RNA, **C**hromatin remodelling.

GOOD TO REMEMBER

- **Schizophrenia heritability:** near 81 percent (K&S 2024); MZ concordance slightly below 50 percent.
- **Bipolar disorder heritability:** near 85 percent (K&S 2024).
- **15q11-q13:** shared locus for Prader-Willi (paternal loss) and Angelman (maternal UBE3A loss).
- **Prader-Willi prevalence:** roughly 1 in 15,000 to 30,000; ICD-11 LD90.3.
- **UBE3A:** maternally expressed gene; its loss of function causes Angelman syndrome.
- **SNRPN / SNORD116 / NDN:** paternally expressed 15q11-q13 genes lost in Prader-Willi.
- **MeCP2:** methyl-CpG-binding protein; X-linked mutation causes Rett syndrome.
- **DNMT1:** maintenance methyltransferase (heritability across mitosis); DNMT3a and DNMT3b establish methylation de novo.
- **FKBP5 rs1360780:** risk allele plus childhood trauma leads to GRE demethylation, GR resistance, higher PTSD and depression risk (Klengel et al. 2013).
- **IGF2:** imprinted gene hypomethylated after periconceptional Dutch Hunger Winter exposure (Heijmans et al. 2008).
- **Glucocorticoid-receptor (NR3C1) promoter:** methylation increased by low maternal care in rats (Meaney) and by childhood abuse in human suicide brains (McGowan).
- **Horvath clock (2013):** DNA-methylation estimator of biological age; acceleration reported in severe mental illness.
- **Valproate:** class I HDAC inhibitor (Stahl 2021); links to mood stabilisation and to teratogenicity.
- **Gapp et al. 2014:** sperm-RNA-mediated transgenerational transmission of early-life trauma effects in mice.

8 · Endophenotypes and genetic markers

Why this matters. The heritability of a disorder like schizophrenia is high (60 to 80% from twin studies), yet the road from the genome to the diagnostic checklist is long and noisy. A DSM or ICD label is a **categorical**, subjectively rated, heterogeneous endpoint: two patients carrying the same diagnosis may share almost no symptoms, and unaffected relatives who carry risk alleles score as unaffected. The **endophenotype** strategy was designed to shorten that road, by mapping genes to heritable, quantitative, biologically simpler intermediate traits that sit inside the genotype-to-phenotype pathway rather than at its clinical terminus (Kaplan and Sadock 2024). The examiner wants two things: the Gottesman and Gould (2003) criteria that define a valid endophenotype, and a working list of the named neurophysiological and neurocognitive endophenotypes of schizophrenia with the criteria they satisfy.

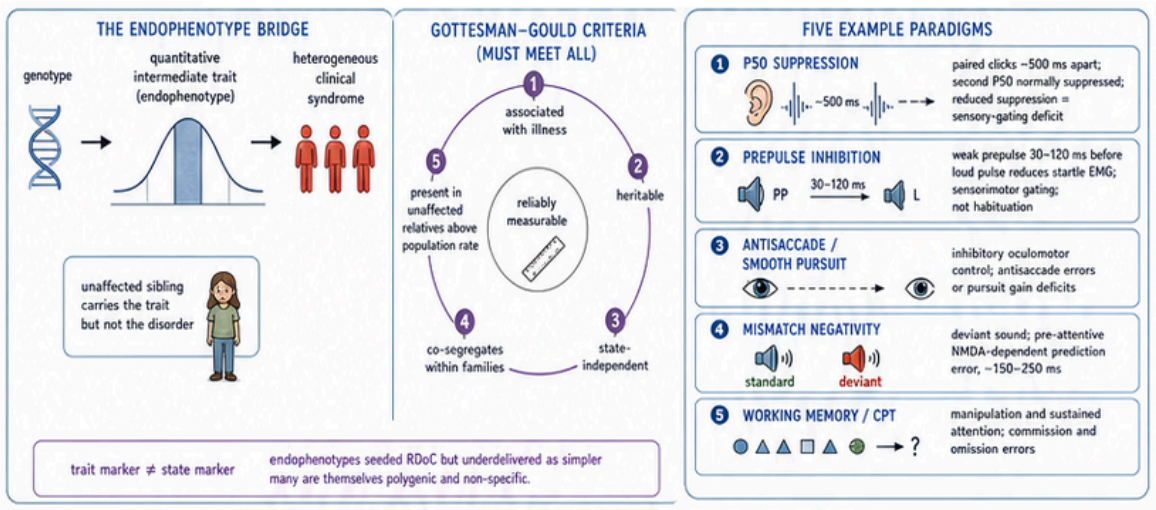


Fig 3.16 Endophenotypes: between gene and syndrome.

The concept also carries a cautionary coda you must deliver: after two decades, endophenotypes have **underdelivered**. A key meta-analysis (Flint and Munafo 2007) concluded that currently identified psychiatric endophenotypes are not superior to conventional phenotypic disease definitions for gene finding, because the endophenotype often turned out to be no simpler genetically, and no more heritable, than the disorder it was meant to decompose (New Oxford Textbook of Psychiatry). Anchor the answer in the named markers (P50, prepulse inhibition, mismatch negativity, antisaccade, working memory) and in the Research Domain Criteria (RDoC) framework that inherited the endophenotype logic.

8.1 The rationale: closing the genotype-to-phenotype gap

The problem. Psychiatric gene mapping relied for decades on categorical diagnoses, and this is argued to be one of the chief obstacles to progress: diagnosis rests on subjective clinical evaluation, and the menu-based classification means two people with the same disorder can display largely non-overlapping symptom sets, likely reflecting distinct underlying causes (Kaplan and Sadock 2024).

The proposed fix. Map **quantitative traits** hypothesised to lie between the genes and the disorder, and that may be simpler to map genetically. Gottesman and Shields imported the term "endophenotype" into schizophrenia research, and Gottesman and Gould (2003) formalised it; the application of these traits to gene finding is now called **deep phenotyping**. Because an endophenotype is "closer to genes" than a diagnostic category, it is expected to carry more power in gene-mapping studies. For a disorder with about 1% prevalence and 60 to 80% heritability, analysing a quantitative endophenotype has been estimated to be roughly 100-fold more efficient than analysing the categorical diagnosis, translating to about a 10-fold increase in statistical power (Greenwood et al. 2019).

8.2 Terminology: endophenotype, intermediate phenotype, biomarker

Endophenotype

A heritable, quantitative trait on the pathway between genotype and clinical phenotype; internal (not visible to the naked eye), measured by biochemical, neurophysiological, neuropsychological or neuroimaging methods (Gottesman and Gould 2003).

Intermediate phenotype

Used interchangeably with endophenotype in Kaplan and Sadock and the New Oxford Textbook; strictly, some authors reserve "intermediate phenotype" for any trait between gene and disease without requiring familial co-segregation.

Biomarker

Any measurable indicator of a biological state; broader than endophenotype, which additionally requires heritability and a specified relation to illness in families. A state marker tracks the active illness; a trait marker (the endophenotype ideal) persists in remission.

Trait vs state

The state-independence criterion is exactly what separates an endophenotype (trait marker, present whether or not the person is currently ill) from a state marker (present only during the episode).

8.2b The Gottesman and Gould (2003) criteria

The five criteria. A candidate must satisfy the following to qualify as a useful endophenotype (Gottesman and Gould 2003; Kaplan and Sadock 2024). These are the load-bearing list for a viva.

MNEMONIC

A HERD Co-segregates

Associated with illness in the population; **HER**itable; state-independent (the "unchanging" trait, here folded under HERD as the stable trait); **D**etectable in unaffected relatives at higher rates than the general population; and it **Co-segregates** with the illness within families. Unpacked as five: (1) associated with the illness in the population, (2) heritable, (3) state-independent (present whether or not the illness is active, with good test-retest stability), (4) co-segregates with the illness within families, (5) found in non-affected family members at a higher rate than in the general population. A practical sixth requirement for gene finding is that it be reliably and objectively measurable.

Why relatives are the crux. Criteria 4 and 5 are what make an endophenotype worth the extra effort: an unaffected relative who carries the risk alleles but has not crossed the clinical threshold still shows the trait, so the trait indexes latent genetic liability rather than the illness or its treatment. This is why endophenotype studies are typically family-based and enriched for genetic loading (Greenwood et al. 2019).

RULE **The family criteria are what make an endophenotype worth the effort.** Beyond heritable and state-independent, it must co-segregate with illness in families and appear in unaffected relatives above the population rate, so it indexes latent liability rather than the illness or its treatment.

8.3 Sensory gating: P50 suppression

The paradigm. P50 is an early positive component of the auditory event-related potential recorded at the vertex about 50 ms after a click. In the paired-click paradigm, two identical clicks are presented about 500 ms apart; in healthy subjects the P50 to the second click is markedly

attenuated relative to the first. This suppression is a measure of **sensory gating**, the brain's ability to suppress its response to repeated, irrelevant stimuli. People with schizophrenia show less P50 suppression, interpreted as a failure of inhibitory gating (Tasman 2015).

TRAP Do not call an endophenotype "just a biomarker" or "an early symptom": a state marker present only in the acute episode is disqualified by the state-independence criterion.

Genetic anchor. A linkage of the sensory-gating deficit to the alpha-7 nicotinic acetylcholine receptor gene (CHRNA7) on chromosome 15q13-14 has been reported, and nicotine transiently normalises the deficit (most antipsychotics, except possibly clozapine, do not). This makes P50 the prototypical schizophrenia endophenotype with a plausible molecular substrate (Tasman 2015). The deficit persists in medicated patients (state-independence) and occurs in unaffected relatives, but it is not specific to schizophrenia, appearing in other psychiatric and neurological conditions.

8.4 Sensorimotor gating: prepulse inhibition (PPI)

The paradigm. Prepulse inhibition is the normal reduction of the acoustic startle reflex (measured as eye-blink electromyography) when a weak prepulse precedes the startling pulse by roughly 30 to 120 ms. It indexes **sensorimotor gating** (it engages both a sensory stimulus and a motor reflex). PPI is reduced in schizophrenia relative to controls, and the deficit is relatively stable across time (Tasman 2015).

Meets the criteria. PPI deficits are present in unaffected relatives and are significantly heritable within schizophrenia families (about 45 to 50%); broad-sense heritability rises to about 47% in families with high genetic vulnerability versus about 29% when family history is not considered, so PPI behaves as a marker of risk rather than a consequence of illness (Greenwood et al. 2019). It is cross-species (measurable in rodents, where dopamine agonists like apomorphine disrupt it), which is why it is a favoured translational endophenotype for RDoC. Distinguish from P50: P50 is EEG-based habituation of an evoked potential; PPI is EMG-based reflex modulation and is not a form of habituation; the two are only weakly correlated.

8.5 Oculomotor markers: smooth pursuit and antisaccade

Smooth-pursuit eye movements. Impaired smooth-pursuit tracking of a moving target (with intrusive saccades) is one of the oldest and most replicated schizophrenia markers, present in patients and in a substantial fraction of their unaffected first-degree relatives, and a classic candidate endophenotype (New Oxford Textbook).

Antisaccade (AS). The subject must fixate a central target and, when a peripheral cue appears, look in the opposite direction; performance is the ratio of correct antisaccades to interpretable saccades. It is an electrophysiological measure of inhibitory failure. Schizophrenia patients show a large deficit (effect size about 1.0), the measure is stable, it is documented in first-degree relatives, and heritability is about 42 to 57% (Greenwood et al. 2019). A B-SNIP consortium GWAS of pursuit initiation and antisaccade error rate implicated genes in nuclear trafficking

(IPO8), axon guidance (PCDH12), nerve-signal transduction (NRSN1) and synaptic glutamate release (SH3GL2).

8.6 Auditory deviance: mismatch negativity (MMN)

The paradigm. Mismatch negativity is the ERP component elicited when an infrequent "deviant" auditory stimulus interrupts a train of "standard" stimuli; it is the difference waveform (deviant minus standard) peaking about 150 to 250 ms after the deviant, and, like PPI, it is preattentive (elicited whether or not the subject attends). Reduced MMN amplitude is one of the most robust findings in schizophrenia, with a large effect size of about 1.0 that is largely unaffected by medication and stable across symptom fluctuations (Greenwood et al. 2019).

Meets the criteria and predicts onset. MMN is about 68% heritable and is present in individuals at genetic risk; reduced MMN has shown promise for predicting transition to psychosis in clinical high-risk cohorts, giving it a prognostic edge over most other markers. It reflects NMDA-receptor-dependent auditory prediction-error, tying it to the glutamate hypothesis (Greenwood et al. 2019).

8.7 Neurocognitive endophenotypes: working memory and attention

Working memory (letter-number sequencing, LNS). A Wechsler Memory Scale subtest requiring the subject to reorder an intermixed string of letters and numbers; it taps verbal working memory with manipulation. Schizophrenia patients and their relatives show persistent deficits; the LNS is highly heritable (about 39% individually) and ranks well for stability and effect size, making working memory a core neurocognitive endophenotype (Greenwood et al. 2019). Working-memory deficits also serve as an endophenotype in ADHD.

Sustained attention (continuous performance test, CPT). Attention deficits date to Bleuler's original descriptions. CPTs (degraded-stimulus DS-CPT, identical-pairs CPT-IP) measure vigilance; patients show large deficits (mean effect size about 1.18), typically unaffected by psychotropics and stable over time. Deficits are reliably present in unaffected relatives, with heritability about 39 to 49% in healthy families and about 38 to 79% in schizophrenia families (Greenwood et al. 2019). General cognitive ability itself is genetically anticorrelated with schizophrenia (COGENT reported a genetic correlation of about minus 0.17).

8.8 Endophenotypes beyond schizophrenia and the imaging tier

Mood and other disorders. In major depression, endophenotypes include heightened processing of negative stimuli, executive and memory deficits, and abnormal prefrontal-amygdala activation on fMRI; the New Oxford Textbook notes their use to reduce the heterogeneity of depression. In bipolar disorder, candidate endophenotypes include cognitive deficits (executive function, attention), altered P300, and structural amygdala and prefrontal changes. In ADHD, response inhibition, working memory and reduced P300 are studied; in ASD, social-cognition and sensory-processing deficits; in OCD, impaired cognitive flexibility and response inhibition with orbitofrontal-striatal hyperactivity (New Oxford Textbook). An impulsivity endophenotype has been proposed as a marker of vulnerability to stimulant addiction (New Oxford Textbook).

Imaging and RDoC. Structural and functional MRI measures (hippocampal volume reduction, prefrontal activation, connectivity) are treated as imaging endophenotypes or "imaging intermediate phenotypes." The endophenotype logic was explicitly adopted by the NIMH **Research Domain Criteria** (RDoC), which takes objectively measurable, dimensional constructs across units of analysis (from genes to circuits to behaviour) as its starting point, on the assumption that specific neural systems underlie specific behavioural dimensions cutting across DSM categories (Tasman 2015).

ENDOPHENOTYPE	DOMAIN / MEASURE	SZ EFFECT (APPROX)	HERITABILITY	IN RELATIVES	STATE-INDEPENDENT
P50 suppression	Sensory gating (auditory ERP, paired click)	Reduced suppression	**Heritable; linked to CHRNA7 (15q13-14)**	**Yes**	Yes (persists on medication)
Prepulse inhibition (PPI)	Sensorimotor gating (startle EMG)	Reduced PPI	**about 45 to 50%**	**Yes**	Yes (stable over time)
Mismatch negativity (MMN)	Preattentive auditory deviance (ERP)	Reduced amplitude, d about 1.0	**about 68%**	**Yes (at-risk carriers)**	Yes (medication-independent)
Antisaccade (AS)	Oculomotor inhibition	Reduced correct ratio, d about 1.0	**about 42 to 57%**	**Yes (first-degree)**	Yes (stable)
Smooth-pursuit	Oculomotor tracking	Impaired pursuit, intrusive saccades	Heritable (classic marker)	**Yes (first-degree)**	Yes
Letter-number sequencing (LNS)	Verbal working memory	Reduced score	**about 39%**	**Yes**	Yes (persistent)
Continuous performance test (CPT)	Sustained attention	Reduced, d about 1.18	**about 39 to 79% (SZ families)**	**Yes**	Yes (psychotropic-independent)

Named schizophrenia endophenotypes mapped against the Gottesman and Gould (2003) criteria: heritable, present in unaffected relatives above population rate, and state-independent. Effect sizes and heritabilities from the PMC review of SZ endophenotypes (Greenwood et al. 2019) and Tasman 2015.

8.9 The genes behind the endophenotypes: a glutamate and neuregulin network

Convergence on a pathway. The Consortium on the Genetics of Schizophrenia (COGS) genotyped candidate genes against these endophenotypes and found 71 SNP-endophenotype associations across 28 genes, with 8 genes showing pleiotropic association across multiple endophenotypes: CTNNA2, ERBB4, GRID2, GRIK3, GRIK4, NOS1AP, NRG1 and RELN (Greenwood et al. 2019). Independent GWAS of schizophrenia diagnosis and of neurocognitive endophenotypes implicated an overlapping set (ATXN7, CSMD1, DRD2, GRIN2A, GRIN3A, GRM3), and rare-variant burden fell on GRIN1, GRIN3A and SLC1A2 (Singh et al. 2022). The

network converges on **glutamatergic neurotransmission and synaptic plasticity**, consistent with the glutamate (NMDA-hypofunction) hypothesis and with NRG1-ErbB4 signalling.

Largest single endophenotype GWAS. The largest GWAS of PPI to date (LOGOS) identified and replicated common variants in NGF and CALN1 at genome-wide significance, and higher schizophrenia polygenic risk was associated with worse PPI, tying the endophenotype back to the polygenic architecture of the disorder (Greenwood et al. 2019).

8.10 Why endophenotypes underdelivered

The core disappointment. The founding promise was that an endophenotype would be genetically simpler than the disorder, controlled by fewer genes of larger effect and therefore easier to map. This largely did not hold: most psychiatric endophenotypes turned out to be about as polygenic and often no more heritable than the disorders themselves, so the expected gain in gene-finding power failed to materialise. A meta-analysis by Flint and Munafo (2007) concluded that identified endophenotypes are not superior to conventional phenotypic disease definitions for this purpose (New Oxford Textbook). The LOGOS PPI result (many small-effect loci) exemplifies the polygenicity even at the endophenotype level (Greenwood et al. 2019).

Other limits. Endophenotypes are effortful and expensive to assess, reducing achievable sample sizes just when large samples turned out to be the decisive ingredient in psychiatric gene finding. Many candidate markers (P50, PPI, MMN) are also non-specific, appearing across schizophrenia, bipolar disorder and other conditions, so a positive marker does not cleanly index one disorder. The field's response has been to fold the endophenotype logic into dimensional frameworks (RDoC) and into biobank-scale studies rather than to expect single traits to crack the genetic architecture alone (New Oxford Textbook; Tasman 2015).

HOLD THIS

The endophenotype bet mostly lost: the intermediate trait was usually just as polygenic as the diagnosis. Flint and Munafo (2007) found identified endophenotypes are not superior to conventional disease definitions for gene finding; the enduring legacies are the five Gottesman-Gould criteria and the dimensional RDoC framework.

CLINICAL ANCHOR

None of these markers is a clinical test. There is no validated blood, ERP or eye-tracking assay that diagnoses schizophrenia or predicts it in an individual patient; they operate at the group level and index latent liability, not diagnosis. Their real clinical relevance is conceptual: they explain why an unaffected sibling of a patient with schizophrenia can carry measurable neurophysiological "soft signs" of the illness without being ill, and they underpin high-risk research (reduced MMN as a candidate psychosis-transition predictor).

COMMON TRAP

Do not describe an endophenotype as merely "a biomarker" or "an early symptom." The distinguishing features an examiner is listening for are heritability and the family criteria: present in unaffected relatives above the population rate, and co-segregating with illness in families. A marker that appears only during the acute episode (a state marker) is explicitly disqualified by the state-independence criterion. Also do not overclaim: the honest examination answer states that endophenotypes have underdelivered as gene-finding shortcuts (Flint and Munafo 2007).

INDIA

Endophenotype paradigms (P50, PPI, MMN, antisaccade, CPT) are relatively low-cost, equipment-based and culture-fair compared with lengthy neuropsychological batteries, which suits high-risk and first-episode research in Indian academic settings where large biobank-scale GWAS infrastructure is limited. The specificity and underdelivery caveats apply identically: these remain research tools, not diagnostic assays for clinical use.

PEARL

The endophenotype was a bet that the trait between gene and diagnosis would be genetically simpler than the diagnosis. The bet mostly lost: the intermediate trait was usually just as polygenic. The enduring legacies are conceptual, not methodological, the five Gottesman and Gould criteria as a rigorous definition of a heritable trait marker, and RDoC as the dimensional framework that absorbed the idea.

GOOD TO REMEMBER

- **Gottesman and Gould (2003):** five endophenotype criteria: associated with illness in the population; heritable; state-independent; co-segregates within families; found in unaffected relatives above the general-population rate (plus reliably measurable).
- **Efficiency claim:** for a disorder with about 1% prevalence and 60 to 80% heritability, a quantitative endophenotype is about 100-fold more efficient than the categorical diagnosis (about 10-fold power gain).
- **P50 suppression:** auditory ERP paired-click sensory gating; deficit linked to CHRNA7 (alpha-7 nicotinic receptor, chromosome 15q13-14); normalised transiently by nicotine, not by most antipsychotics.
- **Prepulse inhibition (PPI):** startle sensorimotor gating; heritability about 45 to 50% (about 47% in high-vulnerability families vs about 29% otherwise); cross-species; largest GWAS (LOGOS) implicated NGF and CALN1.
- **Mismatch negativity (MMN):** preattentive auditory-deviance ERP; effect size about 1.0; heritability about 68%; NMDA-dependent; candidate predictor of psychosis transition.
- **Antisaccade:** oculomotor inhibition; effect size about 1.0; heritability about 42 to 57%; B-SNIP GWAS implicated IPO8, PCDH12, NRSN1, SH3GL2.
- **Smooth-pursuit eye movements:** classic, highly replicated schizophrenia marker; deficits in first-degree relatives.
- **Letter-number sequencing (working memory):** heritability about 39%; deficits in patients and relatives.
- **Continuous performance test (sustained attention):** effect size about 1.18; heritability about 39 to 79% in schizophrenia families.
- **COGS pleiotropic gene set (8 genes across endophenotypes):** CTNNA2, ERBB4, GRID2, GRIK3, GRIK4, NOS1AP, NRG1, RELN; network converges on glutamate and NRG1-ErbB4 signalling.
- **Diagnosis-overlap GWAS genes:** DRD2, GRIN2A, GRIN3A, GRM3, ATXN7, CSMD1; rare-variant burden in GRIN1, GRIN3A, SLC1A2.
- **Underdelivery (Flint and Munafo 2007):** identified psychiatric endophenotypes are not superior to conventional phenotypic disease definitions for gene finding; most are as polygenic as the disorder.
- **RDoC:** NIMH Research Domain Criteria adopted the endophenotype logic as dimensional, cross-diagnostic constructs measurable from genes to circuits to behaviour.

9 · Neurodevelopmental genetics and cross-disorder pleiotropy

This is the topic that reframes everything else in these notes. Heritability and GWAS tell you *how much* of the risk is genetic; this topic tells you *how* that risk is enacted, and the answer is through **neurodevelopment**. Psychiatric risk genes are not scattered at random across the genome or across the lifespan: they cluster in genes that build and prune synapses, remodel chromatin, and regulate transcription, and their protein products are most active in the prenatal and early postnatal brain. Hold that single idea, that genetic liability is a developmental programme gone slightly awry, and both the **neurodevelopmental hypothesis** of schizophrenia and the modern picture of autism as a disorder of fetal cortical wiring fall out of the same logic (Owen et al., New Oxford Textbook 2020).

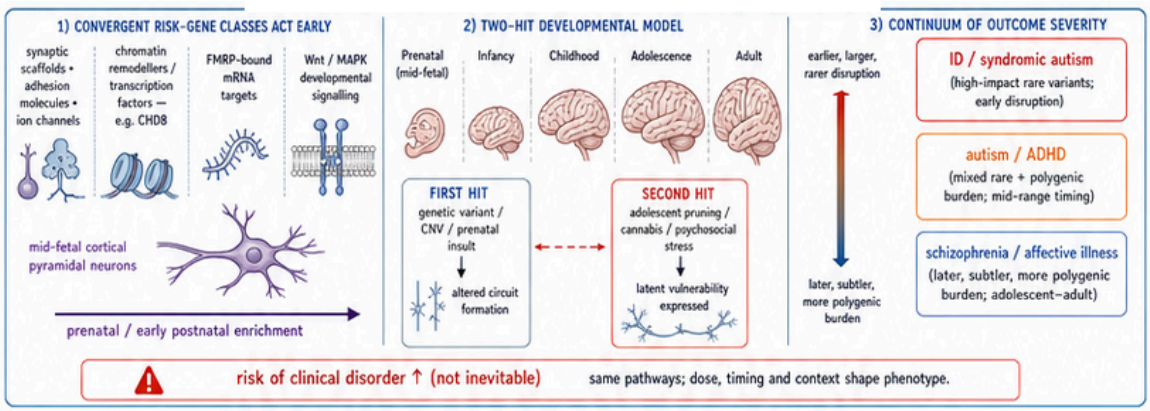


Fig 3.17 Genetic risk builds a developmental brain.

Exam framing. The second half of this topic is where the field has moved fastest and where examiners now probe: **cross-disorder pleiotropy**. Common-variant risk does not respect diagnostic borders. The same alleles push liability across schizophrenia, bipolar disorder, depression, ADHD and autism, producing high **genetic overlap** and a possible **p-factor**, a general dimension of psychopathology. This is the genetic engine behind the categorical-versus-dimensional debate, so learn the two halves, the neurodevelopmental mechanism and the cross-disorder architecture, as one argument: shared developmental genes give shared disorders. Cross-reference the novel-approaches topic for de novo mutation detection and the polygenic risk score material.

9.1 The neurodevelopmental model: genetic risk is a developmental lesion, not an adult one

The **neurodevelopmental hypothesis** holds that the genetic and early-environmental liability to major psychiatric disorders acts on the developing brain long before symptoms appear, leaving a static or slowly evolving vulnerability that is later unmasked by maturation and stress (Kaplan & Sadock 2024). Schizophrenia is the paradigm: the same children who later develop psychosis show, on average, an excess of minor neurodevelopmental abnormalities, delayed milestones, and neurological soft signs years before onset, and the risk-conferring biology is expressed in fetal and perinatal life. The corollary that examiners love is that adult-onset disorders are increasingly reconceptualised as having identifiable prodromal and subclinical childhood manifestations, so the "adult" and "developmental" categories are a continuum in time, not a dichotomy (Kaplan & Sadock 2024).

Two-hit framing. The **two-hit model** gives the mechanism a shape: a first hit (a genetic variant, or an early insult such as a copy number variant, obstetric complication or prenatal infection) primes the developing circuit, and a second hit (adolescent synaptic pruning, cannabis, psychosocial stress) is required to convert latent vulnerability into overt illness. Adolescence matters because it is the period of steep synaptic elimination in association cortex, precisely the process implicated by the risk genes below.

RULE **Genetic risk is enacted through neurodevelopment, not an adult lesion.** Risk genes cluster in synapse, chromatin and transcription and are most active in the prenatal and early postnatal brain; a first hit primes the circuit and a second (pruning, cannabis, stress) unmasks it.

9.2 What the risk genes actually do: synapse, chromatin and FMRP-target enrichment

The single most important empirical fact of modern psychiatric genetics is that risk genes are not random: gene-set enrichment analyses converge on a small number of neurodevelopmental biological processes (Owen et al., New Oxford Textbook 2020). Autism risk genes discovered by whole-exome sequencing illustrate this convergence best, because rare disruptive variants point to individual genes.

Synaptic function

Risk genes encode postsynaptic scaffolding proteins, cell-adhesion molecules and ion channels at excitatory synapses. Convergence on *synapse formation and function* is the dominant theme across autism, schizophrenia and intellectual disability.

Chromatin remodelling and transcriptional regulation

A large fraction of high-confidence autism genes are chromatin remodellers and transcription factors (the prototype is *CHD8*). These are master regulators: disrupting one perturbs the expression of hundreds of downstream neurodevelopmental genes.

FMRP targets

Autism and schizophrenia risk genes are significantly enriched for messenger RNAs bound by the **fragile X mental retardation protein (FMRP)**, the translational repressor lost in fragile X syndrome. This links idiopathic (non-syndromic) disorder back to a monogenic model of synaptic protein dysregulation.

Wnt and MAPK signalling

Additional convergent developmental pathways governing neuronal proliferation, migration and differentiation.

Spatiotemporal signature. Beyond *what* the genes do, *when and where* they act is diagnostic. Autism risk genes are preferentially expressed in **cortical pyramidal (glutamatergic projection) neurons during mid-fetal development** (Owen et al., New Oxford Textbook 2020). This prenatal, cortical, excitatory-neuron signature is the molecular fingerprint of a neurodevelopmental disorder and is exactly why the illness is framed as a wiring problem laid down before birth.

TRAP A low common-variant genetic correlation (schizophrenia-autism 0.16) can coexist with strong overlap at the rare-variant level (shared CNVs and de novo genes): the level of analysis changes the answer.

CLINICAL ANCHOR

The complement gene *C4* is the cleanest schizophrenia example of this developmental logic. C4 tags synapses for elimination by microglia; a common structural allele that raises C4 expression is associated with schizophrenia and is biologically plausible because *excessive synaptic pruning* in adolescence would thin association-cortex connectivity precisely when the disorder declares itself (Kaplan & Sadock 2024). One risk allele, one developmental process, one age of onset.

9.3 De novo mutations and the paternal-age effect

Where a disorder has high heritability yet a very large monozygotic-to-dizygotic concordance gap, **de novo mutations** (new variants present in the child but neither parent) are implicated as a constant source of rare, high-penetrance risk (Tasman 2015). They are the genetic reason a "highly heritable" disorder can appear sporadically in a family with no affected relatives.

The autism de novo story. Three groups simultaneously published exome scans of de novo variation in autism in 2012 (Kaplan & Sadock 2024). Likely-gene-disrupting de novo variants (nonsense, splice-site, frameshift) in brain-expressed genes carry large effects, and recurrent hits on the same gene across unrelated probands is what identifies high-confidence risk genes. Two exam-critical features:

- **Paternal origin, roughly 4:1.** De novo point mutations are overwhelmingly paternal in origin, in about a **4-to-1** ratio, because spermatogonia keep dividing throughout a man's life and accumulate replication errors (Kaplan & Sadock 2024).
- **Paternal-age effect.** De novo mutation load, and consequently offspring risk of autism and schizophrenia, rises with **advanced paternal age** (Tasman 2015). This is the mechanistic bridge between an epidemiological risk factor and molecular genetics, and a favourite single-best-answer link.

De novo CNVs. The recurrent 22q11.2 microdeletion was the first de novo copy number variant described in schizophrenia; genome-wide scans then showed de novo CNVs occur at higher rates in schizophrenia and autism than in controls, and that the genes they hit are enriched for neural and synaptic function (Tasman 2015). Because strong negative selection removes these variants from the population within a few generations, recurrent pathogenic CNVs must keep arising through independent de novo events.

9.4 The neurodevelopmental continuum: a severity gradient from ID to schizophrenia

The same genetic and biological machinery, dosed differently, appears to produce a graded family of conditions rather than discrete diseases. Intellectual disability, autism, ADHD and schizophrenia share risk factors and are increasingly viewed as points along a **neurodevelopmental continuum** or gradient of severity (Owen et al., New Oxford Textbook 2020).

Two lines of evidence anchor the gradient. First, *burden tracks severity*: large, damaging copy number variants and the most disruptive de novo variants are commonest in intellectual disability and syndromic autism, less common in higher-functioning autism, and rarer still in

schizophrenia and ADHD, where common-variant polygenic risk carries relatively more of the load. Second, the ADHD GWAS showed that common-variant risk for the clinical diagnosis is genetically continuous with population-wide cognitive and behavioural traits, supporting the view that a categorical diagnosis sits at the extreme tail of a continuously distributed liability in the general population (Kaplan & Sadock 2024).

PEARL

Read the gradient as a dial on two variables at once: **variant rarity/severity** and **developmental timing**. The earlier and more severe the developmental disruption, the more you see rare high-penetrance variants and the more the phenotype shifts toward intellectual disability and syndromic autism; the later and subtler the disruption, the more it is polygenic common-variant risk and the phenotype shifts toward ADHD, schizophrenia and affective illness. Same genes, different dose and timing.

9.5 Cross-disorder pleiotropy: shared common-variant risk and genetic correlations

Pleiotropy is the property of one gene, or one variant, influencing more than one trait or disorder. It is now regarded as a pervasive, not exceptional, feature of psychiatric genetics: a substantial fraction of the genetic influence on psychopathology transcends diagnostic boundaries (Smoller et al. 2019; Gandal & Geschwind 2021). Pleiotropy is measured at every level, from single loci up to genome-wide **genetic correlation** (the correlation between two disorders of the effect sizes of shared SNPs, estimated by methods such as LD score regression).

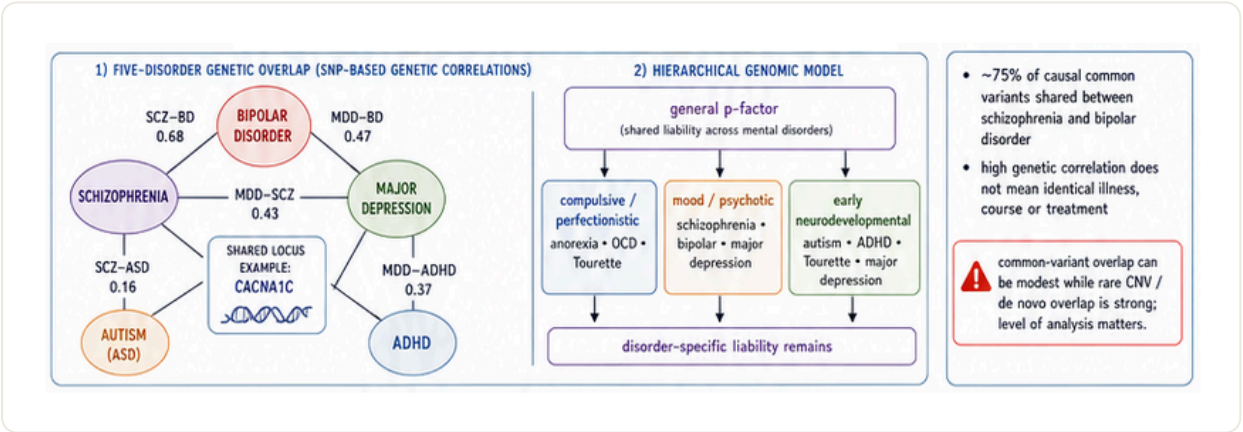


Fig 3.18 Pleiotropy: genetic risk crosses diagnostic borders.

The PGC cross-disorder analyses. The 2013 Cross-Disorder Group of the Psychiatric Genomics Consortium examined five disorders (autism, ADHD, bipolar disorder, major depression, schizophrenia) and found substantial **genetic overlap** (Cross-Disorder Group of the PGC 2013). The correlations were disorder-specific in magnitude, which is why the exact numbers are worth carrying, and they slot neatly onto the continuum from 9.4.

DISORDER PAIR	SNP-BASED GENETIC CORRELATION (RG)	READING
Schizophrenia and bipolar disorder	**0.68**	Highest pair; the two are largely a shared genetic liability
Major depression and bipolar disorder	0.47	Strong mood-axis overlap
Major depression and schizophrenia	0.43	Substantial affective-psychotic overlap
Major depression and ADHD	0.32	Moderate
Schizophrenia and autism	0.16	Modest at the common-variant level

SNP-based genetic correlations from the 2013 PGC cross-disorder analysis. The discriminator is the schizophrenia-bipolar value of 0.68, the exam anchor for the collapse of the Kraepelinian dichotomy at the genetic level.

0.68 SCZ-BD GENETIC CORRELATION (HIGHEST)	**~75%** CAUSAL COMMON VARIANTS SHARED, SCZ-BD	**0.16** SCZ-ASD (MODEST, COMMON-VARIANT)

How much is truly shared. Causal-mixture modelling of the schizophrenia-bipolar overlap estimated that about **75%** of the causal common variants influencing the two disorders are shared (Smoller et al. 2019). Independent evidence converges: post-mortem cortical transcriptomic profiles across these disorders correlate strongly with their pairwise genetic correlations (r about 0.79), and the Brainstorm Consortium, mapping 25 brain disorders, found genetic correlations clustered tightly among the psychiatric disorders (ADHD, depression, bipolar, anxiety, schizophrenia) but little overlap with neurological disorders, showing psychiatric pleiotropy is specific, not an artefact (Smoller et al. 2019). Individual loci show it too: *CACNA1C* is associated with bipolar disorder, schizophrenia and autism (Smoller et al. 2019).

COMMON TRAP

Do not equate a high genetic correlation with genes acting in the same direction, and do not read it as clinical interchangeability. Genetic correlation is a population-level average across thousands of SNPs; two disorders with rg = 0.68 still have distinct clinical courses, treatment responses and disorder-specific variants. Equally, a low rg (schizophrenia-autism at 0.16) at the *common-variant* level coexists with *strong* overlap at the *rare-variant* level (shared CNVs, shared de novo genes). The level of analysis, common versus rare variant, changes the answer, which is exactly the point examiners test.

9.6 The genetic p-factor and the structure of psychopathology

If common-variant risk is so widely shared, does a general dimension of psychopathology exist at the genetic level? Applying **genomic structural equation modelling** to eight disorders, the PGC decomposed the genetic correlation matrix into **three correlated genomic factors** that together accounted for more than half of the genetic variation across these disorders (Smoller et al. 2019):

Factor 1: compulsive/perfectionistic

Anorexia nervosa, obsessive-compulsive disorder, Tourette syndrome.

Factor 2: mood and psychotic

Schizophrenia, bipolar disorder, major depression.

Factor 3: early-onset neurodevelopmental

Autism, ADHD, Tourette syndrome, with major depression also loading here.

The p-factor. That these three factors are themselves correlated is the genetic case for a **p-factor**, a single general dimension of liability to psychopathology sitting above the specific factors, the genomic analogue of the general "p" originally derived from phenotypic covariation. The neurodevelopmental factor is the most genetically integrated, consistent with the theme of this whole topic: shared developmental genes are what generate shared liability.

Where the field is in 2025. The scale has grown. A 2019 PGC analysis of eight disorders found 136 genome-wide loci, of which 109 were pleiotropic (shared across more than one disorder); a 2024 functional follow-up (Won and Sullivan, in *Cell*) showed that pleiotropic variants are active for *longer* across brain development and hit genes more sensitive to disruption than disorder-specific variants, reinforcing the developmental basis of shared risk. A 2025 cross-disorder analysis of 14 disorders in *Nature* identified several hundred loci, a large share of them pleiotropic. The clinical promise, still on the horizon, is that pleiotropic variants may be optimal drug targets because one intervention could act across multiple disorders (Won and Sullivan 2024).

HOLD THIS

Shared developmental genes produce shared disorders. Pervasive pleiotropy and a genetic p-factor mean common-variant risk crosses diagnostic borders; the schizophrenia-bipolar rg of 0.68 is the single strongest genetic argument against the Kraepelinian dichotomy.

9.7 Implications for the categorical-versus-dimensional debate

This is where the genetics feeds directly back into nosology and gives you a ready-made discussion answer. The DSM and ICD categories are, by design, atheoretical and drawn around clinical syndromes; the genetic data are telling us those borders do not map cleanly onto biology (Smoller et al. 2019).

- **Against pure categories.** Pervasive pleiotropy, high genetic correlations, shared CNVs and a genetic p-factor all argue that liability is continuous and trans-diagnostic, not carved at discrete joints. The schizophrenia-bipolar rg of 0.68 is the single strongest genetic argument against the Kraepelinian dichotomy.
- **Not purely dimensional either.** Disorders retain *specific* genetic signal and specific loci alongside the shared component, and clinical course and treatment response still discriminate them. The honest position is *hierarchical*: a general p-factor and a few broad factors on top, with disorder-specific liability underneath.

- **Toward a bottom-up nosology.** Genomic factor structures offer an empirical, biology-first reorganisation of psychopathology, the same impulse behind dimensional frameworks such as RDoC and HiTOP. The likely future is a system that keeps clinically useful categories while formally acknowledging shared, continuously distributed neurodevelopmental liability underneath them (Smoller et al. 2019).

MNEMONIC

"SHARED DEVELOPMENT"

Synaptic, chromatin and FMRP-target enrichment; **H**igh genetic correlations (SCZ-BD 0.68); **A**utism = mid-fetal cortical pyramidal neurons; **R**are de novo variants, paternal 4:1; **E**ight-disorder three-factor structure; **D**imensional p-factor. The common thread is that shared *developmental* genes produce shared *disorders*.

GOOD TO REMEMBER

- **SCZ-BD genetic correlation rg = 0.68:** highest cross-disorder pair (2013 PGC); the genetic collapse of the Kraepelinian dichotomy.
- **MDD-BD rg = 0.47; MDD-SCZ rg = 0.43; MDD-ADHD rg = 0.32; SCZ-ASD rg = 0.16:** the other 2013 PGC five-disorder correlations.
- **~75% shared causal common variants (SCZ-BD):** causal-mixture estimate of the proportion of common causal variants shared between schizophrenia and bipolar disorder.
- **PGC eight-disorder genomic SEM: three factors:** compulsive (AN, OCD, TS); mood-psychotic (SCZ, BD, MDD); early-onset neurodevelopmental (ASD, ADHD, TS, MDD); >50% of genetic variation; genetic basis of the p-factor.
- **2019 PGC: 136 loci, 109 pleiotropic:** eight-disorder cross-disorder GWAS.
- **Won and Sullivan 2024 (Cell): 683 variants:** pleiotropic variants active longer in neurodevelopment and hit more disruption-sensitive genes than disorder-specific ones.
- **2025 Nature, 14 psychiatric disorders:** several hundred loci mapped, a large share pleiotropic; latest cross-disorder landscape.
- **CACNA1C:** classic pleiotropic locus associated with bipolar disorder, schizophrenia and autism.
- **22q11.2 deletion:** first de novo CNV described in schizophrenia; raises schizophrenia odds roughly 50-fold; the paradigm pleiotropic CNV.
- **Complement C4 allele:** higher-expression C4 allele associated with schizophrenia via excessive adolescent synaptic pruning.
- **CHD8:** prototypical high-confidence autism gene; a chromatin remodeller.
- **FMR1 / FMRP targets:** autism and schizophrenia risk genes enriched for FMRP-bound transcripts (link to fragile X syndrome).
- **65 ASD risk genes:** from combined de novo exome and CNV data across >5000 families (Autism Genome Project and Simons Simplex Collection).
- **De novo point mutations ~4:1 paternal bias:** and positively correlated with advanced paternal age, the mechanism behind the paternal-age effect in autism and schizophrenia.
- **Brainstorm Consortium:** genetic correlations cluster among psychiatric disorders with little overlap with neurological disorders (pleiotropy is specific).

Findings in the clinic

10 · Heritability across major disorders

A single comparative table of heritability and twin concordance across the major psychiatric disorders is one of the highest-yield objects in all of psychiatric genetics: it is asked directly in MCQs ("which disorder is most heritable?"), it frames vivas on any single condition, and it anchors the conceptual questions about what heritability actually means. The candidate is expected to reproduce an ordered hierarchy from the highly heritable neurodevelopmental and psychotic disorders at the top, through the moderately heritable substance-use and eating disorders, down to the internalising (depressive and anxiety) disorders at the base, and then to state precisely what a heritability figure does and does not claim. **Why it matters.** The numbers are examinable to the decade, but the deeper marks are won by knowing that heritability is a population variance ratio in a specified environment, not a property of an individual patient and not a statement about immutability (Kaplan & Sadock 2024).

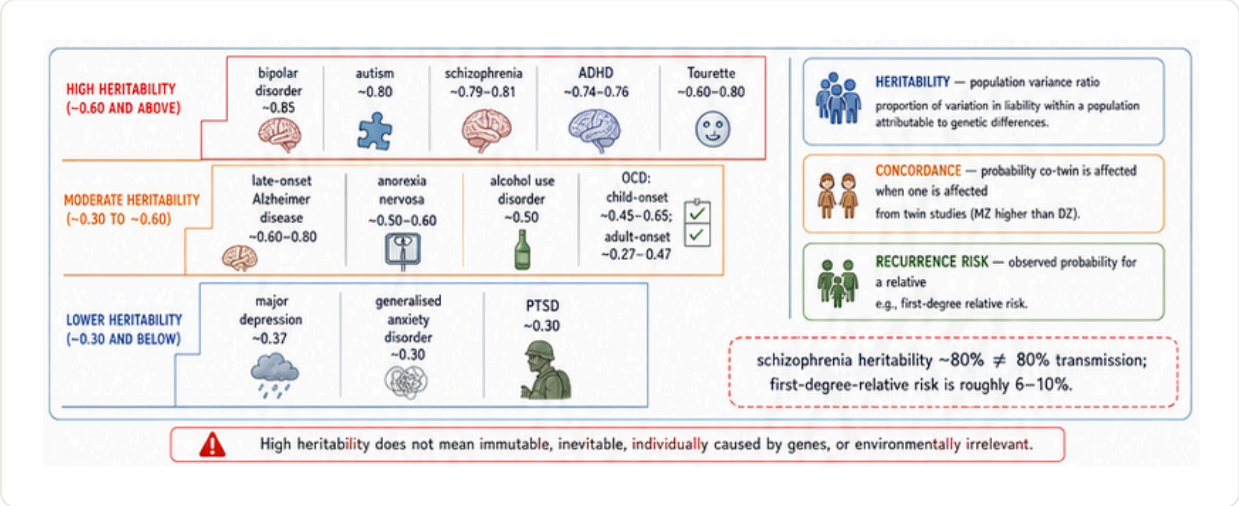


Fig 3.19 Heritability across major disorders.

The hierarchy is remarkably stable across textbooks and across the two great methodologies (classical twin studies and modern population-register sibling studies). Broadly, the neurodevelopmental disorders (autism, ADHD) and the two classic functional psychoses on the psychotic and mood axes (schizophrenia, bipolar disorder) cluster at heritabilities of roughly 0.75 to 0.85; anorexia nervosa, alcohol use disorder and obsessive-compulsive disorder sit in the 0.4 to 0.6 band; and major depression, the generalised anxiety and stress-related disorders occupy the low 0.3s (New Oxford 2020). The same ordering recurs whether one reads concordance rates or variance-decomposition heritabilities, which is itself the strongest internal validation of the twin design.

10.1 Reading the two currencies: concordance and heritability

Concordance is a probability; heritability is a variance ratio. **Concordance** is the probability that the co-twin is affected given that one twin is affected (probandwise is the modern standard, and is the figure comparable to a morbid risk). **Heritability** (narrow-sense h-squared) is the

proportion of the total phenotypic variance in a population that is attributable to additive genetic variance. The bridge between them is the excess of monozygotic (MZ) over dizygotic (DZ) concordance: a large MZ-over-DZ gap implies high heritability (Falconer's first approximation, h-squared is about 2 times the difference in twin correlations). The two currencies carry the same ordering of disorders but are not interchangeable numbers, and mixing them is a common source of error when quoting figures.

10.2 The comparative table across disorders

The core object. The table below collates the standard exam figures. The heritability column gives the twin-study or family-study estimate quoted in the reference texts; the concordance column gives representative probandwise MZ and DZ rates where a canonical figure exists. Ranges reflect genuine between-study variation, not uncertainty about which is "correct"; where a single landmark estimate is conventionally quoted, it is named in the source column.

DISORDER (ICD-11 / DSM-5-TR)	MZ VS DZ CONCORDANCE	HERITABILITY (H-SQUARED)	SOURCE / LANDMARK
Schizophrenia (6A20)	**MZ ~46 to 50% vs DZ ~9 to 14%**	~0.79 to 0.81	Sullivan meta-analysis 2003 (81%); Hilker 2018 Danish registers (79%)
Bipolar disorder (6A60)	**MZ ~40 to 70% (often quoted ~60%) vs DZ ~5 to 20%**	~0.85 (up to ~0.9)	McGuffin 2003; Kieseppa 2004 (0.93 for narrow BP-I); K&S 2024
Autism spectrum disorder (6A02)	MZ high vs DZ low (early studies MZ ~60 to 90%, DZ ~0 to 10%)	~0.80 (range ~0.5 to 0.9)	Sandin 2017 twin meta-analysis (~0.83); New Oxford 2020
ADHD (6A05)	MZ markedly > DZ	~0.74 to 0.76 (twin ~0.70 to 0.80)	Faraone; twin-study consensus (K&S 2024)
Anorexia nervosa (6B80)	MZ > DZ	~0.5 to 0.6 (twin), family ~0.4	Bulik; New Oxford range 0.28 to 0.74
Alcohol use disorder / dependence (6C40)	MZ > DZ	~0.5	K&S 2024; Prescott & Kendler
Obsessive-compulsive disorder (6B20)	MZ > DZ; higher in child-onset	Child-onset ~0.45 to 0.65; adult-onset ~0.27 to 0.47	van Grootheest twin meta-analysis 2005
Major depressive disorder (6A70)	MZ ~40% vs DZ ~20%	~0.37	Sullivan meta-analysis 2000 (0.37); family est. ~0.30 to 0.41
Generalised anxiety disorder (6B00)	MZ > DZ (modest)	~0.30	Hettema meta-analysis 2001 (~0.32); K&S 2024
Post-traumatic stress disorder (6B40)	MZ > DZ	~0.30	True 1993 (Vietnam twin registry); New Oxford 2020

DISORDER (ICD-11 / DSM-5-TR)	MZ VS DZ CONCORDANCE	HERITABILITY (H-SQUARED)	SOURCE / LANDMARK
Tourette syndrome / tic disorder (8A05.0)	**MZ 53% (TS) and 77% (any tic) vs DZ 8% and 23%**	High (~0.6 to 0.8)	Price 1985; twin-study consensus
Alzheimer disease (late-onset) (8A20)	MZ > DZ	High (~0.6 to 0.8); APOE-e4 major locus	Gatz 2006 Swedish twins (~0.58 to 0.79); APOE on chr 19

The heritability hierarchy: neurodevelopmental and psychotic/bipolar disorders at the top (~0.75 to 0.9), eating, substance-use and OCD in the middle (~0.4 to 0.6), depressive and anxiety and stress-related disorders at the base (~0.3). Concordance and heritability carry the same ordering. Several concordance and heritability entries carry genuine between-study spread and are flagged for verification in the metadata.

~0.85	~0.80	~0.37	~0.30
BIPOLAR (MOST HERITABLE)	SCHIZOPHRENIA AND AUTISM	MAJOR DEPRESSION	GAD AND PTSD (BASE)

10.3 The top of the hierarchy: schizophrenia, bipolar, autism, ADHD

The most heritable common psychiatric disorders. The landmark modern figure for schizophrenia is the Sullivan, Kendler and Neale twin meta-analysis of 2003, which gave a heritability of 81% (95% confidence interval roughly 73 to 90%), later corroborated by Hilker's 2018 analysis of the Danish twin and psychiatric registers (over 30,000 pairs) at 79% for narrow schizophrenia and 73% for the spectrum (New Oxford 2020). Bipolar disorder is quoted as the single most heritable major psychiatric disorder, around 0.85 and rising toward 0.9 for narrowly defined bipolar-I, with the MZ co-twin concordance conventionally given as about 60% against a DZ rate an order lower (Kaplan & Sadock 2024; McGuffin 2003). Autism and ADHD are the highly heritable neurodevelopmental disorders, autism around 0.8 (Sandin's 2017 twin meta-analysis gave about 0.83) and ADHD around 0.74 to 0.76, with twin studies clustering at 0.70 to 0.80. **The examinable point.** These four disorders form the "high-heritability" cluster and are the ones for which environmental variance, though real, contributes the smaller share of population variance.

10.4 The base of the hierarchy: depression, anxiety, PTSD

The internalising disorders are the least heritable of the common conditions. Major depressive disorder has a heritability of about 0.37 (Sullivan's 2000 meta-analysis), with MZ concordance around 40% against DZ around 20%; the large Swedish population sibling study gave a family-based estimate of 0.30, the lowest of the eight disorders it examined. Generalised anxiety disorder sits at about 0.30 (Hettema's 2001 meta-analysis of the anxiety disorders gave roughly 0.32), and post-traumatic stress disorder at about 0.30, first established in True's 1993 study of the Vietnam-era twin registry. **The interpretive corollary.** The lower heritabilities do not make these disorders "less biological"; they mean that in the studied populations a larger fraction of the variance between people is environmental (including, for PTSD, the necessary environmental trigger of trauma exposure, which caps the achievable heritability). Depression, anxiety and OCD were precisely the disorders the authors of the Swedish register study singled

out as the ones where environmental aetiological research is most likely to be fruitful (heritability under 0.50).

10.5 The special cases: OCD child-onset, anorexia, alcohol, Tourette, Alzheimer

OCD: an age-of-onset split. The single most examinable nuance in the middle of the table is that obsessive-compulsive disorder is more heritable when it begins in childhood. van Grootheest's twin meta-analysis (2005) reported obsessive-compulsive symptom heritability of roughly 0.45 to 0.65 in children against about 0.27 to 0.47 in adults, consistent with a more strongly genetic early-onset form (New Oxford 2020). **Anorexia nervosa** is moderately-to-highly heritable, twin estimates around 0.5 to 0.6 (the New Oxford range is wide, 0.28 to 0.74), with a family-register estimate of about 0.4. **Alcohol use disorder** is conventionally quoted at a heritability of about 0.5. **Tourette syndrome** is highly heritable with a very high MZ concordance (53% for the full syndrome and 77% for any tic, against 8% and 23% respectively in DZ pairs (Price 1985)), reflecting a strong, largely polygenic genetic contribution. **Alzheimer disease** (late-onset) has a high heritability, around 0.58 to 0.79 in Gatz's 2006 Swedish twin study, with the APOE-e4 allele on chromosome 19 the single largest common-variant risk locus (a heterozygote carries about a two- to three-fold risk, a homozygote considerably more).

HOLD THIS

Psychosis and neurodevelopment high, internalising low. Bipolar, autism, schizophrenia and ADHD cluster at ~0.75 to 0.9; anorexia, alcohol use and OCD in the middle; depression, GAD and PTSD near 0.3. The single richest nuance: OCD is more heritable when it starts in childhood.

CLINICAL ANCHOR

When a family asks "will my child get this too?", the heritability figure is not the answer they need; the recurrence risk is. A heritability of 0.8 for schizophrenia does not mean an 80% chance of transmission, it means that in the studied population most of the variation in liability between people is genetic. The first-degree-relative recurrence risk for schizophrenia is of the order of 6 to 10%, an order of magnitude smaller than the heritability figure, because the disorder is highly polygenic and each relative shares only half the risk alleles. Keeping heritability and recurrence risk separate in your counselling prevents both false reassurance and needless alarm.

10.6 What heritability is, and what it is not

A population parameter, not an individual one. **Heritability** is the ratio of genetic variance to total phenotypic variance in a defined population and environment. It is not the proportion of a given patient's illness that is "genetic", it is not a fixed biological constant, and it says nothing about whether a trait can be changed. The standard cautionary example is phenylketonuria: an essentially fully genetic (single-gene) disorder that is nonetheless completely preventable by an environmental intervention (dietary phenylalanine restriction). A high heritability and full environmental modifiability coexist without contradiction (Kaplan & Sadock 2024).

RULE **Heritability is a population variance ratio, not an individual statement and not immutability.** Phenylketonuria is essentially fully genetic yet fully preventable by diet; a high h-squared says nothing about modifiability or the cause in one patient.

Heritability changes with the environment. Because it is a ratio, heritability rises when environmental variance falls and falls when environmental variance rises. In a population where everyone is exposed to identical environments, the only remaining variance is genetic and heritability approaches unity; in a population with wildly variable environments the same trait can show lower heritability. Heritability is therefore always local to the population and era studied, and figures from Scandinavian registers need not transfer unchanged to other populations. It also tells you nothing about the mean level of a trait, only about the sources of variation around that mean.

10.7 The twin-heritability versus SNP-heritability gap

The missing heritability problem. Twin and family studies estimate **broad or narrow-sense heritability** from the resemblance of relatives; genome-wide association data estimate **SNP-heritability** (h-squared-SNP), the variance captured by common measured single-nucleotide polymorphisms. SNP-heritability is consistently and substantially lower than twin-heritability: in the large Swedish comparison, family-based estimates ran from 0.30 (major depression) to 0.80 (ADHD), whereas the SNP-based estimates from the same diagnoses ran from about 0.10 (alcohol dependence) to 0.28 (OCD). For schizophrenia the case-control SNP-heritability is on the order of 0.23 against a twin-heritability of about 0.81 (New Oxford 2020). **Why the gap.** The shortfall (the "missing heritability") reflects that common SNPs do not tag rare and structural variants (copy-number variants, rare coding variants), incomplete linkage-disequilibrium tagging, non-additive (dominance and epistatic) effects, gene-environment interaction absorbed into the twin estimate, and possible upward bias in twin estimates from violations of the equal-environments assumption. The largest twin-to-SNP gaps in that study were for the neurodevelopmental disorders (ADHD, autism) and schizophrenia, precisely the disorders for which rare and structural variants are known to contribute.

TRAP Do not quote the SNP-heritability of schizophrenia (~0.23) as "the heritability of schizophrenia": the twin-heritability is ~0.81, and the SNP figure is only a lower bound on what common variants capture.

COMMON TRAP

Do not read a heritability of 0.8 as "80% of this patient's illness is genetic" or as "80% chance of passing it on". Heritability is a population-level variance ratio, silent about any individual and silent about transmission risk. Equally, do not treat SNP-heritability and twin-heritability as the same quantity: the SNP figure is a lower bound on what common variants capture, not a correction to the twin figure. Quoting the SNP-heritability of schizophrenia (about 0.23) as "the heritability of schizophrenia" is wrong; the twin-heritability is about 0.81.

PEARL

A clean one-line ordering to carry into the viva: bipolar and autism and schizophrenia and ADHD are the "high" disorders (heritability roughly 0.75 to 0.9); anorexia, alcohol use disorder and OCD are "middle" (0.4 to 0.6); depression, generalised anxiety and PTSD are "low" (about 0.3). The mnemonic hierarchy runs "psychosis and neurodevelopment high, internalising low", and the single richest nuance is that OCD is more heritable when it starts in childhood.

MNEMONIC

Big Brains Are Adaptable, Ordinary Anxious Depressives

Descending the heritability ladder: **B**ipolar (~0.85), **B**rain-development autism (~0.8), **A**utism-and schizophrenia cluster and **A**DHD (~0.75), **O**CD and anorexia and alcohol (~0.4 to 0.6), then the **A**nxiety and **D**epression base (~0.3). The device just fixes the top-to-bottom order; the exact figures still have to be learned.

INDIA

Almost every heritability figure in this table derives from Scandinavian (Swedish, Danish, Finnish) or Anglo-American twin and register cohorts; India has no national twin or adoption register at comparable scale, so Indian genetic-epidemiology data come mainly from family morbid-risk studies. Because heritability is environment-specific, the imported figures should be quoted as the best available estimates rather than as validated Indian values, and consanguinity (common in parts of India) can inflate familial aggregation for any recessive contribution, complicating a family history.

GOOD TO REMEMBER

- **Schizophrenia heritability:** ~0.81 (Sullivan meta-analysis 2003, 95% CI ~73 to 90%); Hilker 2018 Danish registers 0.79 (narrow), 0.73 (spectrum).
- **Bipolar disorder heritability:** ~0.85, the most heritable major psychiatric disorder; MZ concordance often quoted ~60%; Kieseppa 2004 ~0.93 for narrow bipolar-I.
- **Autism heritability:** ~0.80 (Sandin 2017 twin meta-analysis ~0.83); early twin studies MZ concordance far exceeding DZ.
- **ADHD heritability:** ~0.74 to 0.76 (twin studies ~0.70 to 0.80); Faraone consensus.
- **Anorexia nervosa heritability:** ~0.5 to 0.6 twin (New Oxford range 0.28 to 0.74); family estimate ~0.4.
- **Alcohol use disorder heritability:** ~0.5.
- **OCD heritability:** child-onset ~0.45 to 0.65, adult-onset ~0.27 to 0.47 (van Grootheest twin meta-analysis 2005); higher in child-onset is the key nuance.
- **Major depressive disorder heritability:** ~0.37 (Sullivan meta-analysis 2000); family-register estimate ~0.30, the lowest of eight disorders.
- **Generalised anxiety disorder heritability:** ~0.30 (Hettema meta-analysis 2001, ~0.32).
- **PTSD heritability:** ~0.30 (True 1993, Vietnam-era twin registry).
- **Tourette syndrome:** high heritability; MZ concordance 53% for TS and 77% for any tic vs DZ 8% and 23% (Price 1985).
- **Alzheimer disease (late-onset):** heritability ~0.58 to 0.79 (Gatz 2006 Swedish twins); APOE-e4 (chromosome 19) the major common-variant risk allele, heterozygote ~2 to 3 fold risk.
- **SNP-heritability vs twin-heritability gap:** Swedish comparison, family-based 0.30 (MDD) to 0.80 (ADHD) vs SNP-based ~0.10 (alcohol dependence) to 0.28 (OCD); schizophrenia SNP-h-squared ~0.23 vs twin ~0.81.
- **Falconer's formula:** h-squared is approximately 2 times the difference between MZ and DZ twin correlations.

11 · Schizophrenia genetics: the integrative flagship

Why this matters. This is the essay the first paper is built to elicit: take one disorder and let it carry every method taught in these notes. **Schizophrenia** is the ideal vehicle because it is the most intensively genotyped psychiatric phenotype, and its story runs cleanly from classical genetic epidemiology (a heritability near 80% that no candidate gene could explain) through the modern two-tier architecture (a highly polygenic common-variant burden plus rare large-effect structural variants), to a mechanistic hook the examiner loves (the complement C4A signal and synaptic pruning), and finally to the clinical frontier of the polygenic risk score. A strong answer is not a list of genes; it is an argument that schizophrenia is a **neurodevelopmental** disorder of polygenic liability, in which many common alleles of tiny effect and a few rare variants of large effect converge on synaptic and neurodevelopmental biology, with environment tipping vulnerable brains over a threshold.

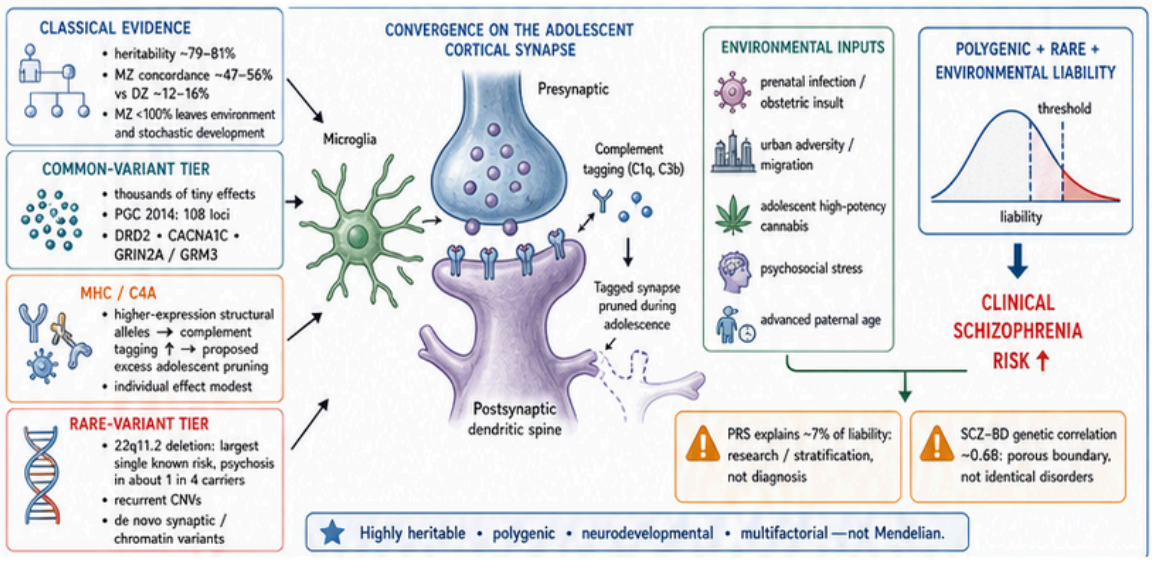


Fig 3.20 Schizophrenia: risk converges on the developing synapse.

Anchor the whole essay on a handful of load-bearing, examinable facts: heritability of the order of 80% with monozygotic concordance far above dizygotic; the 22q11.2 deletion as the single largest known genetic risk; the MHC/C4A complement signal as the most robust common-variant locus; the collapse of the candidate-gene era (COMT, DISC1, NRG1, dysbindin); and a substantial genetic overlap with bipolar disorder that makes the two-disorder boundary permeable. These are grounded in Kaplan and Sadock (2024), the New Oxford Textbook (2020) and Tasman (2015).

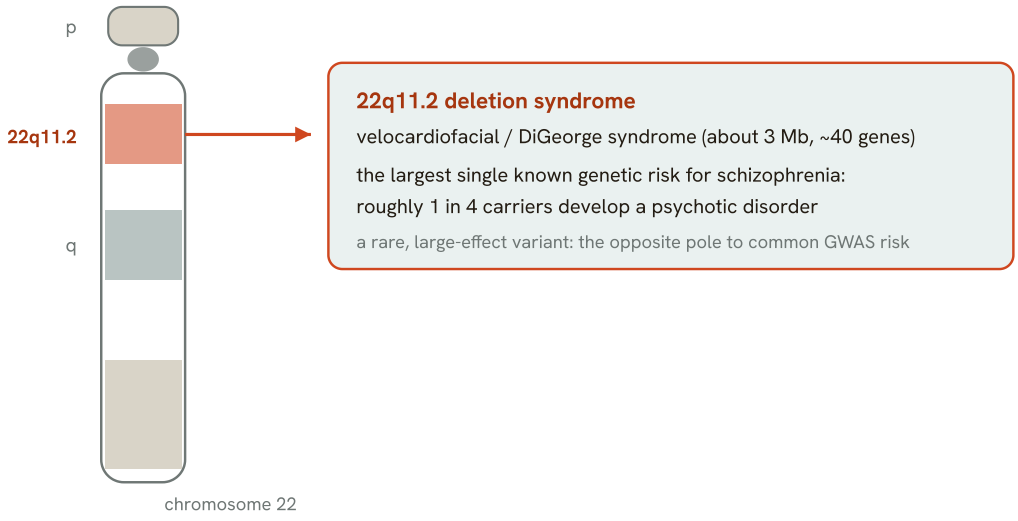


Fig 3.21 The 22q11.2 microdeletion on the long arm of chromosome 22. This roughly 3 megabase deletion of about forty genes causes velocardiofacial (DiGeorge) syndrome and is the single largest known genetic risk factor for schizophrenia: around a quarter of carriers develop a psychotic disorder. It illustrates the rare, large-effect end of the architecture spectrum from Fig 3.11, in contrast to the thousands of common small-effect variants that make up most inherited risk.

11.1 The framing move: state the architecture before the evidence

Open with the thesis. The examiner rewards a candidate who names the target before marshalling data. State it as: schizophrenia has a **complex, polygenic, multifactorial-threshold** architecture, not a Mendelian one. No single-gene form of schizophrenia has ever been found; familial distributions are, in the words of the standard text, inconsistent with simple Mendelian inheritance (Kaplan and Sadock 2024). Everything that follows, twin heritability, GWAS, CNVs, gene-environment interaction, is evidence for and refinement of that one architectural claim.

The two-tier model. Risk is carried at two ends of the frequency-effect spectrum: many **common variants** of individually tiny effect (odds ratios near 1.1, tagged by GWAS), plus rare **copy number variants** and de novo mutations of large effect (odds ratios of several-fold to fifty-fold). Between them sits the **missing heritability** gap: twin heritability near 80% but common-SNP heritability capturing only part of it. Say this once, early, and the rest of the essay slots into it.

RULE **State the architecture before the evidence.** Open the essay by naming schizophrenia as a complex, polygenic, multifactorial-threshold disorder, not a Mendelian one; every finding that follows is refinement of that claim.

11.2 Heritability and the classical evidence: twin and adoption studies

The number to know. Schizophrenia heritability is of the order of 80%, among the highest in psychiatry, with the largest twin meta-analyses placing it near 79 to 81% (Sullivan and colleagues; Hilker and colleagues 2018, the Danish twin registry). Population-register estimates run a little lower (about 64% in Lichtenstein and colleagues 2009), a discrepancy examiners like to probe: twin designs may inflate heritability by capturing gene-environment correlation and non-additive effects (New Oxford 2020).

Twin concordance. Concordance is far higher in monozygotic than dizygotic twins: Kaplan and Sadock (2024) give roughly 47 to 56% for monozygotic and 12 to 16% for dizygotic pairs, rising above 80% in monozygotic pairs with severe, typical illness. The MZ-versus-DZ gap is the core quantitative argument for a genetic contribution; the fact that MZ concordance is well below 100% is the equally important argument that genes are not the whole story (environment and stochastic development matter).

Adoption studies remove shared rearing. The Danish and Finnish adoption studies (Kety, Rosenthal, Tienari) showed that the biological relatives of adopted-away probands, not the adoptive relatives, carry the raised risk, and that offspring of affected biological parents remain at elevated risk even when reared in unaffected adoptive homes. The Finnish Adoptive Family Study (Tienari) added the gene-environment message: the biological high-risk children fared worst specifically when reared in disturbed adoptive families, an early demonstration of interaction rather than pure genetic determinism.

COMMON TRAP

Do not read heritability of 0.8 as "80% genetic in this patient." Heritability is a population variance statistic: it describes how much of the variation between people in a given population and environment is attributable to genetic differences. It says nothing about the cause in any individual, and nothing about modifiability, a highly heritable disorder can still be entirely environmentally treatable (phenylketonuria is the standard cautionary example). Misstating this is a classic viva stumble.

11.3 The candidate-gene era and the lesson it taught

What was done. Before genome-wide genotyping, researchers pre-selected a handful of biologically plausible or positionally implicated **candidate genes**. For schizophrenia, more than 1,500 studies examined nearly 800 candidates (Tasman 2015). The most-cited were COMT (catechol-O-methyltransferase, the val158met functional polymorphism, dopamine catabolism), DISC1 (Disrupted-in-Schizophrenia-1, from a Scottish family with a balanced translocation), NRG1 (neuregulin-1, synaptic and glutamatergic signalling) and DTNBP1 (dysbindin, presynaptic).

What happened. Almost none survived well-powered genome-wide scrutiny. When Farrell and colleagues (2015) tested the classic candidates against GWAS data, the historical candidate literature did not yield clear, genome-wide-significant support. Underpowered samples chasing tiny true effects, publication bias, weak priors and flexible analysis had produced a literature dominated by false positives.

The lesson, and the nuance. The examinable lesson is methodological: complex-trait genetics needs enormous samples and built-in replication, which is exactly what GWAS institutionalised. The nuance worth adding for a top answer: DISC1 illustrates why the target was wrong as much as the method. The original translocation family carried both psychosis and mood disorder, and independent studies later linked DISC1 to schizophrenia, schizoaffective disorder and bipolar disorder (Kaplan and Sadock 2024), so the gene never respected the schizophrenia construct it was named for. The candidates were not testing schizophrenia; they were testing a diagnostic category that does not map cleanly onto biology.

11.4 GWAS and the Psychiatric Genomics Consortium: the common-variant tier

Sample size was the missing ingredient. A **genome-wide association study** (GWAS) assays hundreds of thousands to millions of single-nucleotide polymorphisms across the whole genome and tests each for a case-control frequency difference, at the stringent genome-wide significance threshold of p less than 5 x 10 to the power minus 8 (correcting for about a million tests). Early psychiatric GWAS reported nothing because they were too small. The decisive move was consortium pooling: the **Psychiatric Genomics Consortium** (PGC) aggregated samples across dozens of countries, and the schizophrenia signal scaled almost linearly with case number.

The landmark result. The PGC schizophrenia GWAS (2014) analysed about 36,989 cases and 113,075 controls and identified 108 independent genome-wide-significant loci (Kaplan and Sadock 2024). At least three-quarters contained protein-coding genes, enriched for dopamine

(DRD2, the target of every antipsychotic), glutamate and synaptic plasticity (GRM3, GRIN2A, GRIA1, SRR) and voltage-gated calcium-channel signalling (CACNA1C, CACNB2). Associations were also enriched in immune-related tissue, foreshadowing the complement story. Most associated variants are non-coding, so they most likely act by altering gene expression, which makes functional interpretation the hard part.

The satisfying loop. DRD2 emerging as a GWAS hit closed the circle between unbiased genetics and 60 years of dopamine pharmacology: the receptor blocked by antipsychotics is also a genome-wide-significant risk locus. That single fact is worth a sentence in any answer.

~80%	108	~50-fold
TWIN HERITABILITY	GWAS LOCI (PGC 2014)	22Q11.2 DELETION RISK (LARGEST SINGLE)

11.5 The MHC/C4A complement signal and the synaptic-pruning hypothesis

The most robust locus. The strongest and most replicable common-variant association in schizophrenia lies in the major histocompatibility complex (MHC) on chromosome 6, a gene-dense region of extensive linkage disequilibrium. Fine-mapping this signal is the standout mechanistic success of psychiatric GWAS (Sekar and colleagues 2016).

What Sekar and colleagues showed. Human complement component 4 is encoded by two genes, C4A and C4B, which vary in structure (a HERV insertion giving long or short forms) and copy number. Sekar and colleagues genotyped these structural alleles and found that alleles raising C4A expression in brain raised schizophrenia risk in proportion to their effect on expression, with relative risks for the common structural alleles ranging from about 1.0 to 1.27. Post-mortem brain confirmed higher C4A RNA in patients than controls.

The pruning hypothesis. Complement tags synapses for elimination by microglia (C4 promotes C3 activation; C3 marks synapses for removal). In a C4-knockout mouse, C3 deposition and synaptic refinement in the visual pathway were disrupted. The inference: excess C4A drives excessive **synaptic pruning** during adolescence, plausibly the molecular basis of the long-observed grey-matter loss and reduced synaptic density in schizophrenia. This is the mechanism that links a GWAS peak to the neurodevelopmental model and to the adolescent onset of illness, the single most quotable convergence in the field.

HOLD THIS

MHC/C4A is the most robust locus, and the only one with a worked-out mechanism. Structural alleles raising C4A expression raise risk (relative risk up to about 1.27) by driving excess synaptic pruning in adolescence, tying a GWAS peak to the neurodevelopmental model and the age of onset (Sekar 2016).

CLINICAL ANCHOR

Three named common-variant findings to carry into a viva. The **MHC/C4A** signal is the most robust schizophrenia locus, effect modest (relative risk up to about 1.27), and the only one with a worked-out mechanism (excess pruning). **DRD2** as a GWAS hit unites genetics with antipsychotic pharmacology. **CACNA1C** is a canonical cross-disorder calcium-channel locus shared with bipolar disorder, the clearest single illustration that the schizophrenia-bipolar genetic boundary is porous.

11.6 The rare-variant tier: 22q11.2 deletion, recurrent CNVs and de novo mutation

22q11.2: the largest single risk. The recurrent hemizygous microdeletion at **22q11.2** was the first de novo CNV described in schizophrenia (Karayiorgou 1995) and, before the GWAS era, the only DNA variant indisputably pathogenic for the disorder. It causes velocardiofacial (DiGeorge) syndrome, cardiac outflow defects, palatal anomalies, hypocalcaemia and learning difficulty, and raises the odds of schizophrenia roughly 25 to 30-fold (often quoted as up to fiftyfold), the single largest known genetic risk (Kaplan and Sadock 2024). About one in four carriers develops a psychotic illness, so 22q11.2 deletion syndrome is a naturally occurring genetic model of schizophrenia.

A shared, pleiotropic set. A recurring group of large CNVs shows a many-to-one pattern (one CNV, several neurodevelopmental outcomes): 16p11.2 (deletion and duplication, autism and developmental delay), 1q21.1, 15q11.2, 15q13.3 (which spans CHRNA7, the alpha-7 nicotinic receptor gene tied to the P50 gating deficit) and NRXN1 (neurexin-1) deletions. Total CNV burden is elevated in schizophrenia relative to controls, and risk CNVs are larger and more gene-rich than benign ones.

De novo mutation and the paternal-age link. An excess of de novo point mutations and CNVs, disrupting synaptic and chromatin genes, is found particularly in sporadic cases. This dovetails with the epidemiological association of advanced paternal age with schizophrenia risk, since de novo mutations accumulate in the paternal germline with age, a neat gene-to-epidemiology bridge.

LOCUS / CLASS	FREQUENCY	EFFECT SIZE	DETECTION METHOD	EXAMPLE
Common SNP	Minor allele >1%	**Tiny (OR about 1.05 to 1.2)**	GWAS	MHC/C4A, DRD2, CACNA1C
Recurrent CNV	Rare	**Large (OR several-fold to about 30 to 50-fold)**	Chromosomal microarray	**22q11.2 deletion (largest single risk)**
De novo mutation	Very rare, sporadic	Large; often severe phenotype	Exome/genome sequencing	Synaptic and chromatin genes; paternal-age effect

The two-tier architecture of schizophrenia: an inverse frequency-effect relationship, common variants abundant but weak, rare structural variants scarce but powerful, with de novo mutation a sporadic third source.

11.7 Endophenotypes: neurophysiological markers of latent liability

The rationale. An **endophenotype** is a heritable, state-independent, familial trait that co-segregates with illness and is present in unaffected relatives above the population rate (the Gottesman and Gould 2003 criteria). The bet was that a trait between gene and diagnosis would be genetically simpler than the diagnosis itself, and so easier to map. Three markers recur in schizophrenia.

P50 sensory gating

Auditory evoked potential about 50 ms after a click; in the paired-click paradigm the response to the second click is normally suppressed. Reduced suppression in schizophrenia indexes failed inhibitory gating, linked to CHRNA7 (alpha-7 nicotinic receptor, 15q13-14) and transiently normalised by nicotine (Tasman 2015).

Prepulse inhibition (PPI)

Normal reduction of the acoustic startle blink when a weak prepulse precedes the pulse; indexes sensorimotor gating. Reduced in schizophrenia, heritable (about 45 to 50% within families), cross-species and dopamine-sensitive, hence a favoured translational marker.

Eye-tracking

Smooth-pursuit eye-movement dysfunction and antisaccade errors are among the oldest and best-replicated schizophrenia trait markers, present in unaffected first-degree relatives, indexing frontal-executive oculomotor control.

The verdict. Endophenotypes underdelivered as gene-finding shortcuts, the intermediate trait usually proved just as polygenic as the diagnosis (Flint and Munafo 2007). Their enduring value is conceptual: they explain how an unaffected sibling can carry measurable neurophysiological soft signs of the illness without being ill, and they seeded the dimensional RDoC framework.

11.8 Gene-environment interaction: environment tips vulnerable brains over threshold

The principle. High heritability leaves real room for environment (MZ concordance is well below 100%), and the modern model is interactional: environmental exposures raise risk chiefly in genetically vulnerable individuals, tipping latent liability over the disease threshold. The examinable exposures cluster around early neurodevelopment and adolescence.

Cannabis

Adolescent, heavy, high-potency cannabis use is associated with roughly doubled odds of later psychosis, dose-dependently; Mendelian randomisation supports a causal effect of cannabis-use liability on schizophrenia risk (Kaplan and Sadock 2024). Interaction with COMT and other risk variants has been proposed.

Urbanicity

Being born and raised in an urban environment raises schizophrenia risk in a dose-dependent way; the effect is not explained by drift and interacts with familial liability.

Migration

First- and second-generation migrant status raises risk, most markedly where the migrant group is a visible minority, implicating social defeat and chronic adversity rather than genetics of the migrating population.

Obstetric complications

Prenatal infection and maternal immune activation, hypoxia and obstetric complications, and winter-spring birth are replicated early risk factors, consistent with a prenatal neurodevelopmental insult.

Advanced paternal age

Raises risk, mechanistically tied to the accumulation of de novo mutations in the ageing paternal germline (link to 11.6).

11.9 The neurodevelopmental synthesis

The unifying model. Pull the threads together with the **neurodevelopmental** hypothesis (Weinberger, Murray): schizophrenia is the late clinical expression of an early, largely genetic disturbance of brain development, unmasked by the normal maturational events of adolescence and young adulthood. Its strongest empirical support is convergent: gene-set enrichment analyses show that schizophrenia risk genes are not random but cluster in neurodevelopmental and synaptic processes (Owen and colleagues, New Oxford 2020).

Why adolescence. The C4A pruning story gives the model a molecular clock: adolescence is the period of steep synaptic elimination in association cortex, precisely the process the complement signal implicates. Excess pruning of an already atypically wired brain plausibly explains why a disorder of neurodevelopmental origin declares itself in the late teens and twenties. Common variants set the baseline liability, rare variants and de novo mutations add large hits in a minority, and environmental exposures (cannabis, obstetric insult, urban adversity) tip the vulnerable brain over threshold, the "multiple-hit" reading of the multifactorial-threshold model.

11.10 Polygenic risk scores and the clinical horizon

Construction. A **polygenic risk score** (PRS) sums an individual's risk alleles across the genome, each weighted by its GWAS effect size, into a single number capturing common-variant liability. The schizophrenia PRS is derived directly from the PGC common-variant signal.

The honest limits. The schizophrenia PRS explains roughly 7% of liability on the liability scale (the common-variant signal itself about 3 to 4% of variance), enough to shift population risk between deciles but nowhere near enough to predict any individual's diagnosis. PRS is a research and stratification tool, not a diagnostic test; it cannot yet counsel a specific patient. Say this plainly, examiners test whether candidates over-claim.

The frontier (currency). The useful clinical horizon is cross-disorder and pharmacogenomic rather than diagnostic: PRS as one axis of transdiagnostic risk stratification, integration with rare-variant and CNV screening in early-onset or syndromic presentations, and the wider pharmacogenomic move (CPIC and DPWG CYP2D6/CYP2C19 guidance) that is already actionable for drug dosing while diagnostic PRS is not.

TRAP Do not over-claim the schizophrenia PRS: it explains only about 7% of liability, enough to shift population risk but nowhere near enough to predict any individual's diagnosis.

11.11 Genetic overlap with bipolar disorder: the permeable boundary

The evidence. Schizophrenia and bipolar disorder share substantial genetic liability. Family and twin data show cross-transmission (a schizophrenia diagnosis in one twin raises the co-twin's risk of both schizophrenia and affective psychosis), and the PGC cross-disorder analysis gives a schizophrenia-bipolar genetic correlation of about 0.6 to 0.68, the highest between any two major psychiatric disorders (Kaplan and Sadock 2024). Shared specific loci (CACNA1C, and historically DISC1, NRG1, dysbindin, G72/DAOA) sit at the interface, and 22q11.2 and other CNVs raise risk across the psychosis spectrum.

The correct reading. A genetic correlation of 0.6 does not mean the disorders are the same: two disorders with high rg still have distinct courses, treatment responses and disorder-specific variants (New Oxford 2020). The examinable conclusion is that genetic liability to psychosis is continuous and partly transdiagnostic, evidence that the Kraepelinian dichotomy is a clinical convention that genetics only partly respects, not a natural biological joint.

MNEMONIC

"HANDS on Cannabis, Urban, Migrant Paths"

Architecture in one breath: **H**eritability ~80%, **A**rchitecture two-tier (common + rare), **N**eurodevelopmental model, **D**eletion 22q11.2 (largest single risk), **S**ynaptic pruning via C4A. Then the environmental quintet: **C**annabis, **U**rbanicity, **M**igration, **P**aternal age, obstetric insult (prenatal).

PEARL

The single most integrative sentence you can write: schizophrenia is a highly heritable, polygenic neurodevelopmental disorder in which common variants of tiny effect (converging via C4A on excess synaptic pruning) set baseline liability, rare large-effect CNVs such as 22q11.2 add powerful hits in a minority, and environmental exposures tip the vulnerable adolescent brain over a multifactorial threshold, with a genetic architecture that overlaps substantially with bipolar disorder rather than respecting the diagnostic boundary between them.

INDIA

Formal twin and adoption registers on the Danish, Swedish or Finnish scale do not exist in India, so most Indian genetic-epidemiology data come from family (morbid-risk) studies rather than twin or adoption designs. When counselling an Indian family about recurrence, the practical figures are the first-degree-relative risks (of the order of 6 to 10% for schizophrenia in a first-degree relative), framed against a population risk near 1%. Two culturally specific cautions: consanguinity, common in parts of India, can inflate familial aggregation for recessive contributions and complicate a family history; and strong family expectation around marriage and childbearing means recurrence-risk counselling must be handled with care, giving population-level probabilities without implying determinism, and without naming a diagnosis to the family in a way that stigmatises the proband or unaffected relatives.

GOOD TO REMEMBER

- **Heritability:** of the order of 80% (twin meta-analyses about 79 to 81%; population registers lower, about 64% in Lichtenstein 2009).
- **Twin concordance:** monozygotic about 47 to 56% versus dizygotic about 12 to 16% (Kaplan and Sadock 2024); above 80% in severe typical illness.
- **First-degree-relative recurrence risk:** of the order of 6 to 10% against a population risk near 1%.
- **Genome-wide significance threshold:** p less than 5 x 10 to the power minus 8 (about a million tests).
- **PGC schizophrenia GWAS (2014):** about 36,989 cases and 113,075 controls; 108 genome-wide-significant loci (Kaplan and Sadock 2024).
- **MHC / complement C4A:** most robust common-variant locus (chromosome 6); structural alleles raise C4A expression and risk (relative risk up to about 1.27); excess synaptic pruning mechanism (Sekar 2016).
- **DRD2:** genome-wide-significant locus and antipsychotic target; unites genetics and pharmacology.
- **CACNA1C:** voltage-gated calcium channel; cross-disorder locus shared with bipolar disorder.
- **22q11.2 deletion:** velocardiofacial / DiGeorge syndrome; single largest known genetic risk for schizophrenia (about 25 to 30-fold, quoted up to 50-fold); roughly one in four carriers develops psychosis; first de novo CNV described (Karayiorgou 1995).
- **Other recurrent CNVs:** 16p11.2, 1q21.1, 15q11.2, 15q13.3 (spans CHRNA7), NRXN1 deletion; pleiotropic across the neurodevelopmental spectrum.
- **Candidate genes (failed to replicate at genome-wide significance):** COMT (val158met), DISC1, NRG1 (neuregulin-1), DTNBP1 (dysbindin); the cautionary examples (Farrell 2015).
- **Endophenotypes:** P50 sensory gating (CHRNA7, 15q13-14), prepulse inhibition (heritability about 45 to 50%), smooth-pursuit / antisaccade eye-tracking; Gottesman and Gould (2003) criteria.
- **Schizophrenia PRS:** explains about 7% of liability (common-variant signal about 3 to 4% of variance); not individually predictive.
- **Schizophrenia-bipolar genetic correlation:** rg about 0.6 to 0.68 (PGC cross-disorder), the highest between two major psychiatric disorders.
- **Environmental risk factors:** cannabis (about doubled odds, MR-supported causal), urbanicity, migration, obstetric complications / prenatal infection, advanced paternal age.

12 · Pharmacogenetics and pharmacogenomics

Interindividual variation in drug response is one of the oldest observations in clinical psychiatry: two patients on the same molecule at the same dose may show remission, no effect, or a serious adverse reaction. **Pharmacogenetics** is the study of how variation in *single genes* (classically drug-metabolising enzymes) shapes drug response, while **pharmacogenomics** is the broader, genome-wide study of drug response, including polygenic architecture and treatment-response polygenic risk scores (Kaplan & Sadock 2024, Licinio & Wong). Both terms are used interchangeably in much of the literature, but the distinction matters for the exam: single-gene, actionable, guideline-backed (pharmacogenetic) versus multi-gene, exploratory, precision-medicine frontier (pharmacogenomic).

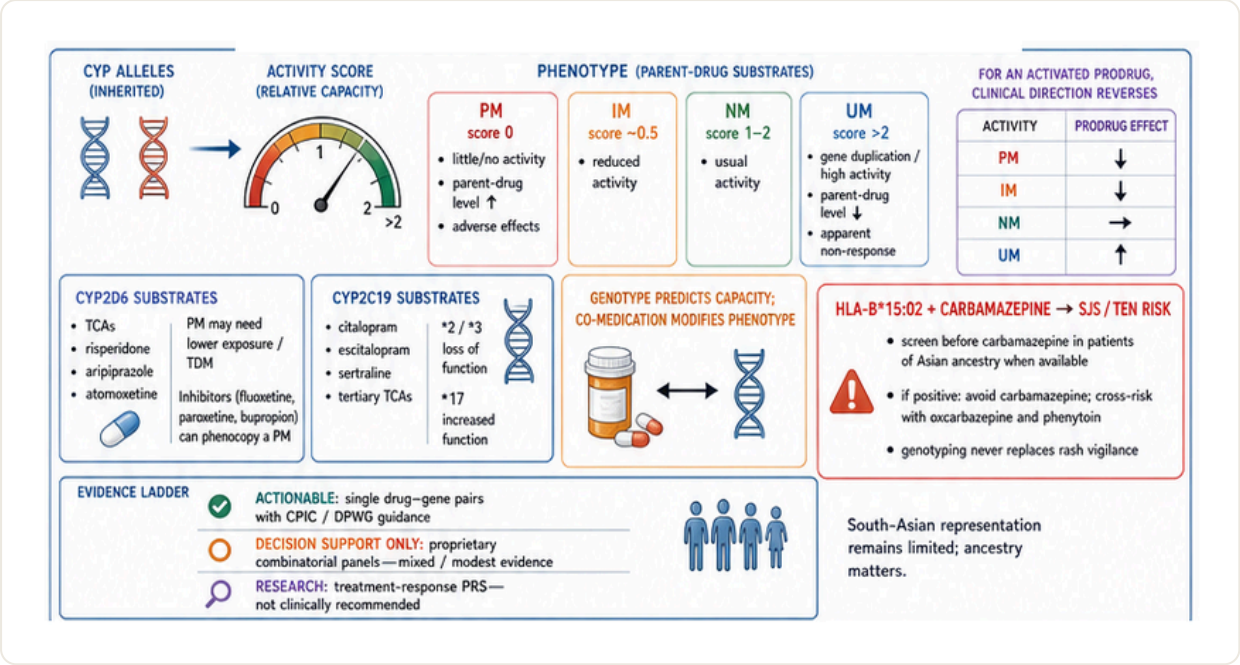


Fig 3.22 Pharmacogenetics: actionable core, hype at the edges.

Why it matters. Only a handful of drug-gene pairs are genuinely actionable, and one of them, **HLA-B*15:02** before carbamazepine, is a life-saving screen that is mandated in patients of Asian ancestry, which makes it a high-yield item for an Indian exam. The rest of the topic is a controlled deflation of hype: combinatorial commercial panels (GeneSight and similar) have weak and mixed randomised-trial support, and treatment-response polygenic scores are not yet clinical. Examiners reward candidates who can separate the evidence-based actionable core from the marketing. Cross-reference the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes for the underlying CYP450 induction and inhibition mechanics.

12.1 Two overlapping definitions

Pharmacogenetics. The study of how variation in a *single gene*, most often a drug-metabolising enzyme or an immune-response gene, alters the efficacy or toxicity of a drug (Kaplan & Sadock 2024). It is the older, narrower term, and its wins are concrete single drug-gene pairs with dosing guidance.

Pharmacogenomics

The genome-wide study of how the whole genetic profile, interacting with diet, microbiome, age and lifestyle, determines drug response. It is a multi-omic, exploratory approach that includes treatment-response polygenic risk scores and pathway analysis (psychscenehub 2023; New Oxford Textbook of Psychiatry).

Pharmacokinetic (PK) genes

Genes affecting drug absorption, distribution, metabolism and elimination, i.e. what the body does to the drug. In psychiatry, the cytochrome P450 enzymes, above all **CYP2D6** and **CYP2C19**.

Pharmacodynamic (PD) genes

Genes affecting the drug target or the tissue response, i.e. what the drug does to the body. Includes receptor and transporter variants (HTR2A, HTR2C, SLC6A4) and immune/HLA alleles that drive idiosyncratic hypersensitivity.

12.2 Metaboliser phenotypes and the activity score

Star-allele nomenclature. CYP alleles are named with the star (asterisk) system, e.g. CYP2D6*1 (reference, fully functional), *4 (null), *10 (decreased function). The combination of two inherited alleles is translated into a **metaboliser** phenotype (Kaplan & Sadock 2024).

The four phenotypes. *Poor metaboliser* (PM): two nonfunctional alleles, little or no enzyme activity, drug accumulates. *Intermediate metaboliser* (IM): reduced-function alleles, activity between poor and normal. *Normal (extensive) metaboliser* (NM/EM): standard activity, the reference phenotype. *Ultrarapid metaboliser* (UM): gene duplication or multiplication, greater than normal activity, drug cleared too fast.

The clinical trap. A UM on a standard dose looks like a non-responder (subtherapeutic levels) and a PM on a standard dose looks intolerant (accumulation and adverse effects); both are often mislabelled as treatment-refractory when the real problem is a dose mismatched to their metabolic capacity (Kaplan & Sadock 2024). For prodrugs the logic inverts: a codeine UM overproduces morphine and risks respiratory depression, while a codeine PM gets no analgesia.

Activity score (AS). Because two alleles combine and function varies continuously, CPIC assigns each allele a value (0 for null, 0.25 or 0.5 for decreased, 1 for normal) and sums them: an activity score of 0 predicts PM, 0.5 predicts IM, 1 to 2 predicts NM, and above 2 predicts UM (Gaedigk, cited in Kaplan & Sadock 2024). The score is more granular than the four discrete labels and can be substrate-dependent.

RULE **Activity score sets the phenotype: 0 is poor, 0.5 intermediate, 1 to 2 normal, above 2 ultrarapid.** A poor metaboliser on a standard dose looks intolerant; an ultrarapid one looks like a non-responder.

12.3 CYP2D6: the antipsychotic and TCA enzyme

Scope. CYP2D6 (chromosome 22) metabolises roughly **25 percent** of clinically used drugs and is arguably the single most important PK gene in psychiatry: it handles all tricyclic antidepressants, several SSRIs (fluoxetine, paroxetine, fluvoxamine), venlafaxine and duloxetine, and the antipsychotics haloperidol, risperidone, aripiprazole and perphenazine (Kaplan & Sadock 2024; Tasman). Key actionable pairs are risperidone and aripiprazole (PM: higher levels, adverse effects; UM: possible loss of effect), tricyclics (PM: reduce starting dose by roughly 50 percent and use therapeutic drug monitoring), and atomoxetine.

Atomoxetine worked example. Atomoxetine levels peak about **10-fold** higher in CYP2D6 poor metabolisers, which is why a normally rare sedation signal is over-represented in PMs and why the FDA label carries CYP2D6 dosing guidance ().

Phenocopying. A CYP2D6 inhibitor (e.g. paroxetine, bupropion, fluoxetine) can convert a genotypic normal metaboliser into a functional PM, a phenomenon called phenocopying; a drug that inhibits its own metabolism at steady state produces autophenocopying (Kaplan & Sadock 2024). Genotype therefore predicts, but co-medication modifies, the observed phenotype. See the

Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes for the CYP inhibition and induction mechanics behind this.

12.4 CYP2C19: the SSRI and clozapine enzyme

Scope. CYP2C19 (chromosome 10q24) metabolises citalopram, escitalopram and sertraline, the tertiary-amine TCAs (imipramine, amitriptyline, clomipramine), and contributes to clozapine metabolism (Kaplan & Sadock 2024; Maudsley Prescribing Guidelines). Loss-of-function alleles *2 and *3 reduce activity (PM), while the gain-of-function *17 allele increases it (UM); all three belong on a minimal PK testing panel.

Escitalopram and citalopram. CYP2C19 poor metabolisers accumulate (es)citalopram and, because these drugs are dose-dependently QT-prolonging, a maximum dose of **20 mg** citalopram is advised in PMs; CYP2C19 ultrarapid metabolisers may under-respond, and CPIC suggests choosing an alternative not primarily metabolised by CYP2C19 (CPIC). Note the *17 allele adds only about 20 percent enzyme capacity, tempering the clinical size of the UM effect.

Sertraline and clozapine. CYP2C19 PMs have higher dose-adjusted sertraline concentrations; for clozapine, genotype-informed metabolic classification (PM, IM, NM) helps interpret plasma levels, though CYP1A2 is the dominant clozapine enzyme and CYP2D6 plays almost no role (Maudsley).

12.5 HLA alleles: idiosyncratic immune reactions

HLA-B*15:02 and carbamazepine. This is the flagship pharmacodynamic (immune) pharmacogenetic association. Carriers of HLA-B*15:02 are markedly more likely to develop carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN); the allele is common in Han-Chinese and several South-East and South-Asian groups and rare in Europeans (Kaplan & Sadock 2024). CPIC and the FDA recommend genotyping before starting carbamazepine in patients of Asian ancestry; the allele also flags cross-risk with oxcarbazepine and phenytoin. Genotyping never replaces clinical vigilance.

HLA-A*31:01. A separate allele associated with carbamazepine hypersensitivity, including SJS/TEN, DRESS and maculopapular exanthema, across a broader range of ancestries than HLA-B*15:02 (Kaplan & Sadock 2024).

TPMT and azathioprine. Outside psychiatry but a classic exemplar: thiopurine S-methyltransferase (TPMT) poor-metaboliser variants cause severe, potentially fatal myelosuppression with standard-dose azathioprine, so TPMT (and NUDT15) status guides thiopurine dosing (Kaplan & Sadock 2024, PharmGKB). It is the textbook example of a PK-driven toxicity screen.

RULE **Screen HLA-B*15:02 before carbamazepine in patients of Asian ancestry.** If positive, avoid carbamazepine (and the cross-risk agents oxcarbazepine and phenytoin); it is the one mandated, life-saving pre-prescription test in psychiatry.

12.6 Pharmacodynamic response signals: HTR2A and ANK3

HTR2A. The serotonin 2A receptor gene, a candidate pharmacodynamic marker included on several commercial panels (GeneSight, Genecept), studied for antidepressant response and tolerability; its independent clinical validity remains modest (Kaplan & Sadock 2024).

ANK3. Ankyrin-3, a robust GWAS-implicated bipolar susceptibility gene, has also been examined as a pharmacogenetic signal for lithium and mood-stabiliser response; the pharmacogenomic response evidence is preliminary rather than actionable. These loci illustrate the shift from single-gene PK certainties to multi-gene PD probabilities.

12.7 Guidelines, databases and resources

CPIC

Clinical Pharmacogenetics Implementation Consortium: NIH-funded, publishes gene-drug dosing guidelines (which drug to avoid or how to adjust for a given phenotype). The dominant clinical resource.

DPWG

Dutch Pharmacogenetics Working Group: the European equivalent, issues therapeutic recommendations for actionable variants; CPIC and DPWG broadly agree but differ on some thresholds.

PharmGKB

Pharmacogenomics Knowledgebase: curated repository of variant-drug annotations, allele-frequency data and clinical-annotation levels of evidence.

PharmVar

Pharmacogene Variation Consortium: the reference catalogue of CYP star alleles (for example, more than 170 CYP2D6 alleles).

12.8 Combinatorial commercial testing and the weak evidence base

What they are. Combinatorial pharmacogenomic panels (Myriad's GeneSight, Genomind's Genecept, Invitae's panel) genotype a bundle of PK and PD genes and return a proprietary weighted, colour-coded prescribing report. GeneSight, for instance, covers eight genes (PK: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4; PD: HTR2A and SLC6A4) (Kaplan & Sadock 2024).

The evidence. Meta-analyses of randomised controlled trials comparing genetically guided to unguided prescribing (e.g. Bousman et al. 2018) suggest a modest improvement in depression remission, but the trials are heterogeneous, several are industry-sponsored and often unblinded, and large independent studies have been more equivocal, so professional bodies frame these panels as decision-support tools, not mandates (psychscenehub 2023; International Society of Psychiatric Genetics 2019). The single-drug CYP and HLA pairs, not the combinatorial algorithms, carry the real actionable weight.

12.9 The pharmacogenomic frontier: PRS for treatment response

Beyond single genes. The genuinely pharmacogenomic (as opposed to pharmacogenetic) horizon is the treatment-response polygenic risk score: aggregating thousands of common variants to

predict antidepressant, antipsychotic or lithium response. Current PRS explain little variance and are not clinically recommended (International Society of Psychiatric Genetics 2019; New Oxford Textbook of Psychiatry). Biobank-scale samples and cross-ancestry GWAS, including work on lithium response, are the active research direction; a recurring caveat for Indian practice is that South-Asian populations remain under-represented in the discovery cohorts, limiting portability of European-derived scores.

HOLD THIS

The actionable core is single drug-gene pairs, not the combinatorial panels. HLA-B*15:02 before carbamazepine and CYP-based dosing of tricyclics and citalopram carry guideline weight; GeneSight-type panels and treatment-response PRS have weak, mixed evidence and are not clinically ready.

INDIA

HLA-B*15:02 is the highest-yield actionable pharmacogenetic screen for Indian practice. The allele is common across South and South-East Asian populations, and Indian cohorts show a strong association between HLA-B*15:02 and carbamazepine-induced SJS/TEN, mirroring the Han-Chinese and Thai data (Kaplan & Sadock 2024; Lim, Kwan & Tan 2008). CPIC and FDA guidance to genotype before starting carbamazepine in patients of Asian ancestry therefore applies directly to Indian patients; where testing is unavailable, heightened clinical vigilance for early rash in the first weeks and a low threshold to stop the drug are essential. India is genetically stratified (North, South and East Indian populations are distinct), so pooling all Indians as one Asian group in dosing algorithms is a recognised limitation.

CLINICAL ANCHOR

Before starting carbamazepine in a patient of Asian ancestry, screen for HLA-B*15:02 if available; if positive, avoid carbamazepine (and oxcarbazepine and phenytoin, which share cross-risk) and select an alternative mood stabiliser. For the common antidepressants and antipsychotics, order CYP2D6 or CYP2C19 genotyping reactively, when a patient reports unusually severe adverse effects or unexplained non-response on an actionable drug (a TCA, citalopram, risperidone, aripiprazole, atomoxetine), rather than as a routine pre-prescription panel.

COMMON TRAP

Do not conflate the evidence tiers. HLA-B*15:02 to carbamazepine and CYP-based dosing of tricyclics and citalopram are actionable single-gene pairs with guideline backing. Combinatorial commercial panels and treatment-response polygenic scores are not: their randomised-trial evidence is weak, mixed and often industry-linked, and PRS for response is explicitly not recommended for clinical use. Calling GeneSight "proven" or PRS "clinically ready" is a marked-down answer.

GENE	VARIANT / PHENOTYPE	DRUG	CLINICAL ACTION
CYP2D6	Poor metaboliser (e.g. *4/*4)	Tricyclics, risperidone, aripiprazole, perphenazine	**Reduce starting dose (roughly 50 percent for TCAs), use TDM, or choose a non-CYP2D6 drug**
CYP2D6	Poor metaboliser	Atomoxetine	**Levels peak about 10-fold higher; adjust dose per FDA label, watch for sedation**
CYP2D6	Ultrarapid metaboliser	Codeine, tramadol (prodrugs)	**Avoid: overproduction of active metabolite risks respiratory depression**
CYP2C19	Poor metaboliser	Citalopram, escitalopram	**Accumulation and QT risk; cap citalopram at 20 mg or use an alternative**
CYP2C19	Ultrarapid metaboliser (*17)	Escitalopram, tertiary-amine TCAs	**Possible under-response; consider a non-CYP2C19 alternative**
CYP2C19	Poor metaboliser	Sertraline, clozapine	**Higher dose-adjusted levels; interpret plasma concentrations accordingly**
HLA-B	*15:02 positive	Carbamazepine (also oxcarbazepine, phenytoin)	**Avoid: high SJS/TEN risk; screen before starting in Asian-ancestry patients**
HLA-A	*31:01 positive	Carbamazepine	**Increased hypersensitivity (SJS/TEN, DRESS) across ancestries; caution**
TPMT	Poor metaboliser	Azathioprine (thiopurines)	**Reduce dose sharply or avoid: risk of severe myelosuppression**

Actionable psychiatric drug-gene pairs: pharmacokinetic CYP and TPMT pairs (dose adjustment) versus pharmacodynamic HLA pairs (avoidance for idiosyncratic toxicity).

MNEMONIC

"2D6 = Doses; 2C19 = Citalopram; HLA = Halt"

CYP2D6 problems are dose problems (tricyclics, risperidone, aripiprazole, atomoxetine, all metabolic, all fixed by dose adjustment or drug switch). CYP2C19 keys to Citalopram and escitalopram (the QT and 20 mg cap). HLA-B*15:02 means Halt the carbamazepine, the one immune, life-threatening, screen-before-you-start pair.

PEARL

The single most examinable distinction: pharmacogenetic PK pairs (CYP2D6, CYP2C19) tell you *how much* drug to give, whereas the pharmacodynamic HLA pairs tell you *whether* to give the drug at all. Only HLA-B*15:02 before carbamazepine in Asian-ancestry patients is a genuinely mandated, life-saving pre-prescription test in psychiatry; everything else is dose-tuning or research.

GOOD TO REMEMBER

- **CYP2D6 (chr 22):** metabolises about 25 percent of drugs; all TCAs, some SSRIs, risperidone, aripiprazole, atomoxetine; PM accumulates, UM under-responds.
- **CYP2D6*4:** commonest null allele driving the poor-metaboliser phenotype (about 75 percent of PMs are *4 homozygotes).
- **CYP2D6*10:** decreased-function allele, high frequency in East and South Asian populations.
- **CYP2C19 (chr 10q24):** citalopram, escitalopram, sertraline, tertiary-amine TCAs; *2 and *3 = loss of function (PM), *17 = gain of function (UM).
- **CYP2C19 PM + citalopram:** accumulation and QT prolongation; cap citalopram at 20 mg.
- **Activity score:** 0 = PM, 0.5 = IM, 1 to 2 = NM, above 2 = UM (CPIC/Gaedigk).
- **HLA-B*15:02:** carbamazepine-induced SJS/TEN; common in Han-Chinese and South/South-East Asians; screen before starting; cross-risk with oxcarbazepine and phenytoin.
- **HLA-A*31:01:** carbamazepine hypersensitivity (SJS/TEN, DRESS) across broader ancestries.
- **TPMT (and NUDT15):** poor-metaboliser variants cause severe azathioprine myelosuppression; screen before thiopurines.
- **HTR2A, ANK3:** candidate pharmacodynamic response signals; ANK3 is a robust bipolar GWAS locus; response evidence preliminary, not actionable.
- **Atomoxetine in CYP2D6 PM:** levels peak about 10-fold higher (FDA-labelled).
- **Resources:** CPIC and DPWG (dosing guidelines), PharmGKB (variant-drug annotations), PharmVar (CYP star-allele catalogue).
- **GeneSight:** 8-gene combinatorial panel (PK: CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4, CYP2D6; PD: HTR2A, SLC6A4); weak, mixed RCT evidence, decision-support only.
- **PRS for treatment response:** the pharmacogenomic frontier; explains little variance, not clinically recommended; South-Asian under-representation limits portability.

Discriminate

13 · Discriminate: match the finding to the right design and read a pedigree

These notes have walked through every genetic method one at a time. The examinable skill, and the reason this topic exists, is the opposite move: given a clinical or research *question*, name the **study design** that answers it, and given a family drawn on paper, read the **pedigree** correctly. Vivas and single-best-answer stems rarely ask "define a twin study"; they ask "which design would tell you whether the aggregation is genetic or environmental?" and expect you to say twin study without hesitation. This is a discrimination drill, not a definitions list.

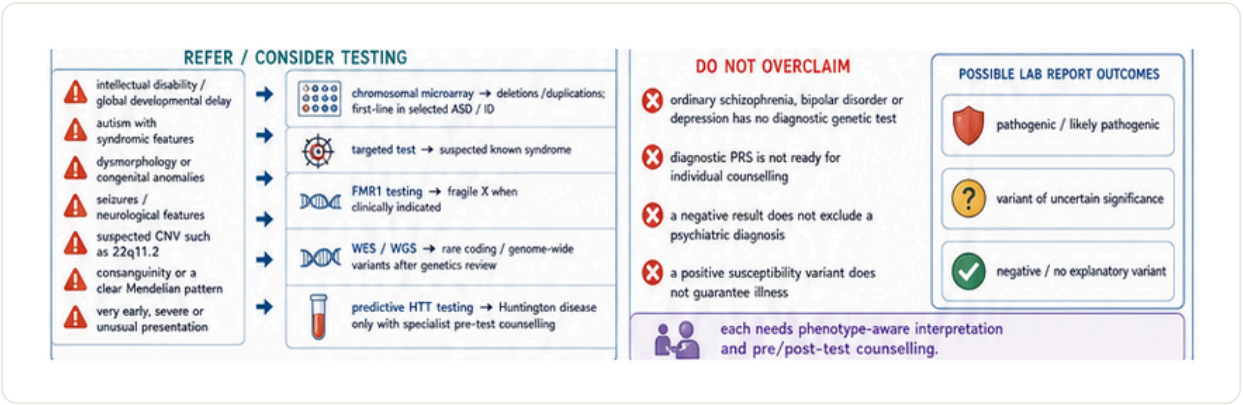


Fig 3.23 When genetic testing helps, and when it does not.

The whole set of notes collapses into one decision tree that Kaplan and Sadock frame as a logical progression of five questions (Kaplan & Sadock 2024): does it run in families, how much is genes versus environment, how is it transmitted, roughly where is the gene, and which specific variants. Bolt on to that the modern clinical add-ons (rare-variant testing, aggregate risk prediction, drug-response prediction) and the classic reading errors that trap the unwary, and you can answer any permutation the paper throws at the material. Then the second half: the standard **pedigree** and **genogram** symbols, recognising an inheritance pattern from them, and turning a family drawing into a recurrence-risk estimate.

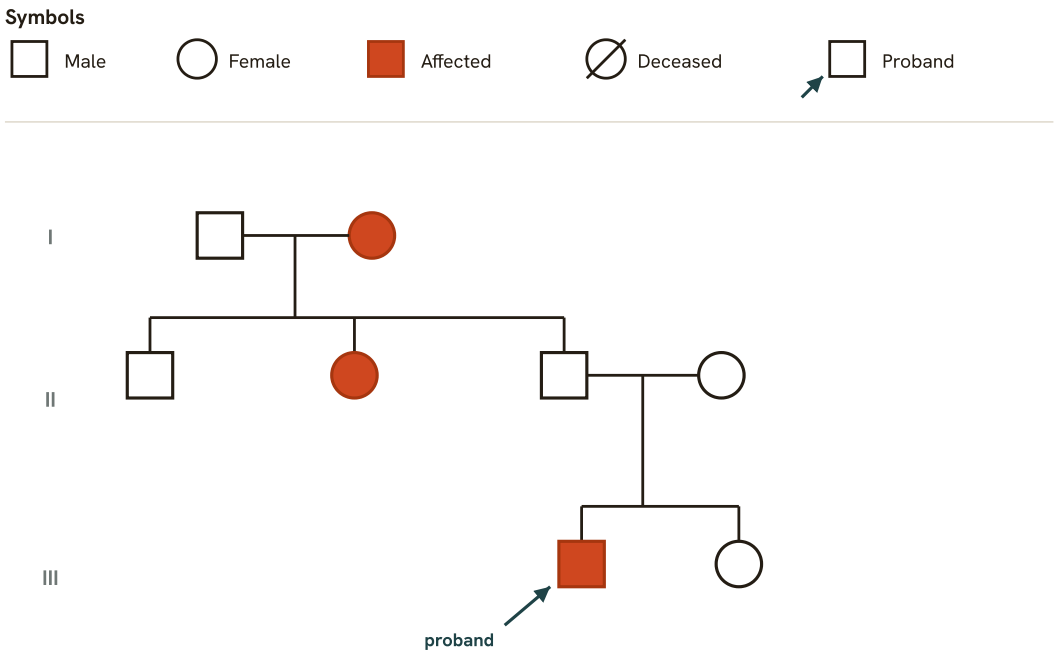


Fig 3.24 Reading a pedigree. The legend gives the standard symbols: squares are male, circles female, a filled symbol is affected, a slash marks deceased, and the arrow marks the proband, the person through whom the family came to attention. In the worked three-generation pedigree, affected members appear in each generation and in both sexes with no clean skipping, which reads as familial aggregation on a multifactorial background rather than a single-gene Mendelian pattern. Recognising the pattern is the first step in choosing the right study design and estimating recurrence risk in counselling.

13.1 The question drives the design: the five-question spine

Answer the question with the cheapest sufficient tool. Genetic epidemiology proceeds as an ordered sequence, and each rung has exactly one design that answers it (Kaplan & Sadock 2024). "Does the phenotype run in families?" is answered by a **family study** (compare disorder rates in relatives of affected probands versus relatives of controls; if genetic, risk rises with closeness of relationship). Familial aggregation alone cannot separate genes from a shared household, so the next question, "how much is genes versus shared environment?", needs a **twin study** (monozygotic versus dizygotic concordance yields heritability). To strip out the confound that families share both genes and rearing, the **adoption study** separates genetic parents from rearing parents. "How is it transmitted?" is a **segregation analysis** (fit Mendelian and non-Mendelian models to pedigree data). "Roughly where is the gene?" is **linkage analysis**, reported as a LOD score. "Which specific variants?" is an **association study**, at genome-wide scale a GWAS. The trick in choosing which design is to read what the stem asks you to *rule out*.

RULE **Answer the question with the cheapest sufficient tool, and read what the stem asks you to rule out.** "Genes or environment?" is a twin study; add "controlling for rearing" and it becomes an adoption study.

13.2 The discrimination table: research question to correct design

This is the memory anchor for the whole set of notes. Read the question in the left column, commit the design in the middle, and note the single word in the right column that discriminates it from its neighbours. The three classic epidemiological designs (family, twin, adoption) form a nested logic: each is introduced to remove a confound the previous one cannot (New Oxford Textbook of Psychiatry 2020; Kaplan & Sadock 2024).

RESEARCH QUESTION (AS THE STEM PHRASES IT)	CORRECT DESIGN	WHAT ONLY THIS DESIGN SETTLES
Does the disorder run in families?	Family study	**Familial aggregation; risk scales with degree of relationship**
Is the aggregation genes or shared environment?	Twin study (MZ vs DZ concordance)	**Separates genes from environment; yields heritability**
Is it genes or the rearing environment specifically?	Adoption study	**Splits genetic parents from rearing parents**
How is the trait transmitted through generations?	Segregation analysis	Tests goodness-of-fit of Mendelian vs complex models
Roughly where on the chromosomes is the locus?	Linkage analysis (LOD score)	**Coarse chromosomal region via co-segregation in families**
Which common variants raise risk across the population?	Association study / GWAS	**Specific common alleles; unit is the unrelated individual**
Is there a specific rare cause in this one patient?	Chromosomal microarray (CMA) for CNVs; sequencing (WES/WGS)	**Individual molecular diagnosis, not population inference**
What is this patient's aggregate inherited liability?	Polygenic risk score (PRS)	Sums weighted effects of many common SNPs into one score
Will this drug work or harm this patient?	Pharmacogenetic test (e.g. CYP metaboliser status, HLA risk allele)	**Predicts drug response or toxicity, not disease risk**

The decision tree in one grid: match the phrasing of the stem to the design, then check the discriminator that separates it from its nearest rival.

13.3 The two commonest confusions: which design, and which level

Family versus twin, and population versus individual. Two axes trip candidates. First, **which design** along the family-to-molecular axis: a family study proves aggregation but can never separate genes from a shared household, so any stem that says "distinguish genetic from environmental transmission" demands a twin study, and one that adds "controlling for the rearing environment" demands an adoption study. Second, the *level* of inference: family, twin, adoption, linkage and association all make *population-level* statements about a disorder, whereas CMA, sequencing, PRS and pharmacogenetic testing make statements about *this individual patient in front of you*. When a stem is framed clinically ("a 6-year-old boy with autism and dysmorphism", "an antidepressant non-responder"), the answer is almost always an individual-level test

(microarray, sequencing, or a pharmacogenetic panel), not a research design (Kaplan & Sadock 2024).

HOLD THIS

Population design or individual test? A clinical stem means an individual-level test. Family, twin, adoption, linkage and association make population statements; CMA, sequencing, PRS and pharmacogenetic testing speak to the one patient in front of you.

COMMON TRAP

Do not answer "twin study" when the stem asks to separate genetic transmission from the *rearing* environment specifically: that is the adoption study's job, because twins reared together share both genes and household. And do not answer "GWAS" for a single patient's diagnostic workup: GWAS is a population design that discovers common risk alleles, whereas a chromosomal microarray or sequencing panel is what yields a molecular diagnosis in one child.

13.4 Reading a pedigree: the standard symbols

You cannot interpret a family you cannot decode. A pedigree (the clinical drawing is a **genogram** when it also carries relationship and social detail) uses a fixed symbol set that examiners expect you to read on sight. Learn the core glyphs cold; a mislabelled proband or a missed consanguinity line changes the whole interpretation.

Square
Male.

Circle
Female.

Diamond
Sex unknown or unspecified.

Filled (shaded) symbol
Affected individual. A half-filled or dotted symbol conventionally marks a carrier or a milder/subthreshold phenotype.

Open (unfilled) symbol
Unaffected.

Diagonal line (slash) through a symbol
Deceased.

Arrow (with "P")
The proband, i.e. the index case through whom the family was ascertained.

Horizontal line joining two symbols
A mating (partnership).

Double horizontal line
Consanguineous mating (partners are blood relatives): a major clue to autosomal recessive inheritance.

Vertical line down to a horizontal sibship line
Offspring of the mating; siblings hang off the sibship line left to right by birth order.

Roman numerals (I, II, III) down the left margin

Generations, oldest at the top. Individuals within a generation are numbered left to right in Arabic numerals, so "II-3" is a specific person.

13.5 Recognising the inheritance pattern from the drawing

The pattern is in the geometry. Once decoded, the shape of shading across generations suggests the mode of transmission, and this is a favourite viva move. Autosomal dominant: affected individuals in every generation (vertical transmission), roughly half of offspring affected, and male-to-male transmission is possible. Autosomal recessive: affected individuals cluster in a single sibship with unaffected parents (horizontal pattern), and consanguinity (the double line) raises the odds; both sexes affected equally. X-linked recessive: mostly affected males, transmitted through unaffected carrier females, with *no* male-to-male transmission (a father cannot pass his X to a son). X-linked dominant: affected in every generation, but affected fathers transmit to all daughters and no sons. Mitochondrial: transmitted only through the maternal line, all children of an affected mother at risk, no transmission through affected fathers. Psychiatric disorders fit *none* of these cleanly, which is itself the exam point: they are polygenic and multifactorial, so a pedigree shows aggregation without a recognisable Mendelian signature (New Oxford Textbook of Psychiatry 2020).

TRAP Do not force a psychiatric pedigree into a Mendelian pattern: familial aggregation without a clean dominant, recessive or X-linked signature is the expected picture for a polygenic, multifactorial disorder.

13.6 Estimating recurrence risk from the genogram

From drawing to a number for counselling. For a clear single-gene pattern, recurrence risk follows Mendelian arithmetic: autosomal dominant gives about 50% to each child of an affected parent, autosomal recessive about 25% to the next child of two carrier parents (one in four), X-linked recessive gives 50% of sons of a carrier mother affected and 50% of daughters carriers. For the multifactorial psychiatric disorders you actually counsel on, there is no Mendelian fraction; you fall back on **empirical recurrence risks** derived from family studies. For schizophrenia these are the numbers to carry: roughly 5 to 15% for a first-degree relative against a population baseline near 1%, rising steeply with the number of affected relatives and with closeness of relationship (Kaplan & Sadock 2024). Recurrence risk in multifactorial disease also rises with severity of the index case and with the number already affected in the family, and it falls off faster than the Mendelian halving as you move to more distant relatives.

CLINICAL ANCHOR

A CMA (chromosomal microarray) finding of a 22q11.2 deletion in a child reframes the whole pedigree: this single CNV carries an associated risk of roughly 25 to 30% of developing a psychotic disorder (Kaplan & Sadock 2024), a far larger per-carrier effect than any common SNP. It is the standard worked example of why, for an individual patient with intellectual disability or syndromic features, you order a microarray (an individual-level rare-variant test) rather than reasoning from population heritability.

13.7 The classic false conclusions when reading families

Aggregation is not proof of a shared gene. The reason twin and adoption designs exist is that a pedigree can mislead in half a dozen stereotyped ways, and naming these is a reliable viva question. Each is a way a family can look genetic when it is not, or look non-genetic when it is (Kaplan & Sadock 2024; New Oxford Textbook of Psychiatry 2020).

Assortative mating

Affected individuals partner non-randomly with similarly affected partners, concentrating risk alleles in a lineage and inflating apparent aggregation beyond simple transmission.

Phenocopy

An environmentally produced case clinically identical to the genetic form; an affected person in the pedigree who carries none of the family's risk variants, blurring co-segregation.

Incomplete (reduced) penetrance

A gene carrier who never manifests the disorder appears as an unaffected symbol, so the gene seems to "skip" and dominant inheritance is missed.

Variable expressivity

The same variant produces different or milder phenotypes across relatives (a hallmark of many CNVs, e.g. 16p11.2), so the "same" gene looks like different conditions in one family.

Genetic (locus) heterogeneity

Different genes cause the same phenotype in different families; pooling pedigrees dilutes any single linkage signal, a core reason linkage failed in psychiatry.

Shared environment mistaken for shared genes

A common household exposure (diet, toxin, trauma, infection) aggregates in relatives and mimics genetic transmission; only twin and adoption designs can distinguish it.

PEARL

Every one of these six is a reason a pedigree alone cannot prove a genetic cause, which is exactly why the field built twin and adoption designs on top of the family study. Turn the list around at exam time: if asked "why is familial aggregation not sufficient evidence of a genetic cause?", these six confounders (led by shared environment) are your answer.

MNEMONIC

FAMILY - TWIN - ADOPT - SEGREGATE - LINK - ASSOCIATE

Runs it? FAMILY study. Genes or environment? TWIN. Genes or rearing? ADOPT. How transmitted? SEGREGATE. Where is it? LINK (LOD). Which variant? ASSOCIATE (GWAS). The order is also the historical and logical order in which each question can only be asked once the previous is answered.

GOOD TO REMEMBER

- **Family study:** answers "does it run in families?"; proband and relatives vs control relatives; risk scales with degree of relationship (first-degree share ~50% of genes).
- **Twin study:** answers "genes vs environment?"; MZ vs DZ concordance yields heritability.
- **Adoption study:** answers "genes vs rearing environment?"; separates genetic from rearing parents.
- **Linkage analysis:** answers "roughly where?"; LOD +3 = proof (1000:1 odds for), LOD -2 = exclusion.
- **Association / GWAS:** answers "which common variant?"; genome-wide significance threshold p < 5 x 10 to the -8.
- **Schizophrenia empirical recurrence risk:** first-degree relative ~5 to 15% vs population ~1% (Kaplan & Sadock 2024).
- **Schizophrenia twin concordance:** MZ ~40 to 60%, DZ ~10 to 16%; heritability ~80% (Kaplan & Sadock 2024).
- **22q11.2 deletion syndrome:** CNV detectable on CMA; associated psychosis risk ~25 to 30% per carrier (Kaplan & Sadock 2024).
- **16p11.2 CNV:** variable expressivity, linked across ASD, schizophrenia and bipolar disorder (Tasman 2015).
- **PRS for schizophrenia:** best current score explains ~11% of liability; theoretical ceiling ~25% (Kaplan & Sadock 2024).
- **Pedigree symbols:** square male, circle female, filled affected, diagonal deceased, arrow proband, double line consanguinity, generations in Roman numerals.

Apply and consolidate

14 · Genetic counselling in psychiatry

Genetic counselling in psychiatry is the clinical process of helping a patient and family understand the genetic and environmental contributions to a psychiatric disorder, appreciate the chance of recurrence in relatives, and reach their own decisions about reproduction, testing and life planning (Kaplan & Sadock 2024; Austin 2020). It is deliberately distinct from the Mendelian counselling of single-gene disease: psychiatric disorders are complex and polygenic, so recurrence chances are quoted as **empirical risks** derived from family, twin and adoption studies, not from Mendelian ratios. The modern model, well developed in the psychiatric genetic-counselling outcomes literature, treats the encounter as more existential than arithmetical, centred on the question "Why me?" and on relieving guilt, blame and fear rather than on delivering a number (Inglis et al. 2015; Austin 2020).

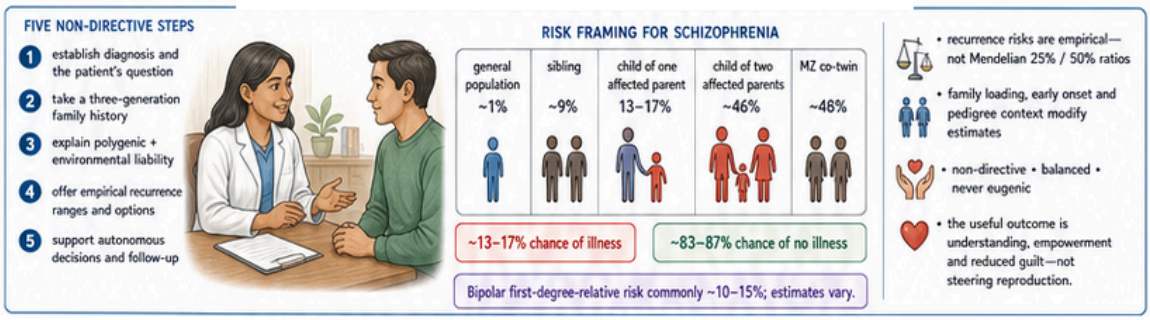


Fig 3.25 Genetic counselling: numbers without destiny.

Why it matters. This is a high-yield exam topic that sits at the junction of genetics, ethics and Indian practice. Examiners reward candidates who can state the standard empirical figures for schizophrenia and bipolar disorder, articulate the **non-directive** stance, know when to refer to clinical genetics, and place the whole discussion inside a consent and capacity framework. The India layer, consanguinity, arranged-marriage disclosure pressure and family-level decision-making, is what turns a textbook answer into a distinction answer. For the underlying consent, capacity and ethics scaffolding, cross-reference paper iii.

14.1 What genetic counselling is, and is not

A communication process, not a verdict. The classic definition frames genetic counselling as a communication process dealing with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family: helping the individual comprehend the medical facts, appreciate how heredity contributes, understand the options for dealing with recurrence, choose the course of action congruent with their goals and values, and make the best adjustment to the disorder (Resta et al. 2006, adapting Fraser). Every clause is about supported autonomous decision-making, not about reducing the incidence of illness.

Not eugenics. A goal of reducing the birth rate of a condition is explicitly eugenic and is not an acceptable aim of counselling; the counsellor must not present any reproductive decision as correct or advantageous for the patient or for society (National Academies consensus). This principle is load-bearing for the ethics viva.

Delivered increasingly by specialists. Reproductive genetic counselling is now largely the province of medical geneticists and certified genetic counsellors rather than psychiatrists, given the pace of testing technology; but the psychiatrist must recognise the situations in which counselling is indicated and make the referral (Harrison et al., Shorter Oxford Textbook of Psychiatry 2018). Dedicated psychiatric genetic-counselling clinics (for example the Adapt clinic, British Columbia) accept both physician referrals and self-referrals (Inglis et al. 2015).

14.2 Non-directiveness: the governing stance

Definition. **Non-directive counselling** means the counsellor provides balanced, accurate information and emotional support but does not steer the patient toward any particular reproductive or testing decision; the choice, and the values that drive it, belong to the patient

(Kaplan & Sadock 2024). It is the declared standard of care for reproductive planning and for counselling around untreatable disorders.

Why psychiatry stresses it. People weigh reproductive risk by their felt ability to cope with an affected child far more than by precise numerical probabilities, and risk perception is shaped by control, treatability, visibility and whether they know an affected person (Lippman-Hand & Fraser). A directive stance overrides exactly the personal calculus that counselling exists to protect.

The realistic caveat. Pure non-directiveness is an ideal; skilled counsellors still shape the frame through which information is presented, so the safeguard is transparency and reflection rather than a pretence of value-neutrality.

RULE **Non-directive, and never eugenic.** Supply balanced information and support, leave the reproductive decision to the patient, and never frame reducing the birth rate of a condition as a goal of counselling.

14.3 Step one: establish the diagnosis and build the pedigree

Diagnosis first. No risk figure is meaningful until the proband's diagnosis is secure, because empirical risks are disorder-specific and the schizophrenia figures differ from the mood-disorder figures. A misassigned diagnosis propagates a wrong risk estimate to the whole family.

The three-generation pedigree. Best-practice psychiatric genetic counselling bases chances on a detailed, systematically taken three-generation family history, then applies empirical data to that specific pedigree rather than quoting a generic textbook number (Austin et al. 2008; Austin 2020). Family loading (number and closeness of affected relatives, early onset) shifts the individualised estimate above or below the population figure.

Contracting. Fewer than half of patients presenting for psychiatric genetic counselling actually want a recurrence number at referral; the counsellor contracts explicitly, discusses aetiology and recovery first, then checks again whether the patient wants specific figures. After that discussion only around 40 percent opt to hear specific chances, and interest often falls once the emotional driver behind the question is addressed (Borle et al. 2018).

14.4 Step two: communicate empirical recurrence risks

Empirical, not Mendelian. Because liability is polygenic and multifactorial, recurrence chances come from observed rates in relatives of probands (corrected for the age of risk, so-called expectancy rates or **morbid risks**), not from Mendelian segregation ratios (Shorter Oxford Textbook of Psychiatry 2018). Figures are best given as absolute risks and frequencies with broad ranges, always anchored against the roughly 1 percent population baseline for schizophrenia (Austin et al. 2008; Borle et al. 2018).

Schizophrenia. Using the pooled lifetime-risk figures (Gottesman, reproduced in Shorter Oxford Textbook of Psychiatry 2018): a sibling of a proband carries about 9 percent, a child of one affected parent about 13 to 17 percent, a child of two affected parents about 46 percent, and the monozygotic co-twin about 48 percent (with twin studies converging on 40 to 50 percent).

Bipolar disorder: the first-degree-relative risk is of the order of 10 to 15 percent in the narrower estimates commonly quoted in counselling, with older broad-liability family studies giving figures as high as 25 to 27 percent for offspring of one affected parent; the monozygotic co-twin concordance is around 60 percent (Shorter Oxford Textbook of Psychiatry 2018). The spread itself is the teaching point: quote a range, name the source, and never imply false precision.

How to frame the number. Present risk in the context of the population rate, avoid framing that inflates dread ("a 13 percent chance of illness" also means an 87 percent chance of no illness), and pair every figure with the reminder that genes set liability while environment and chance decide expression.

RELATIONSHIP TO PROBAND	SCHIZOPHRENIA LIFETIME RISK	BIPOLAR DISORDER RISK
General population (baseline)	~1%	**~1%**
Sibling	~9%	**~5 to 10%**
Child, one affected parent	~13 to 17%	**~10 to 15% (up to ~25 to 27% in broad-liability studies)**
Child, both parents affected	~46%	**markedly higher (broad studies quote up to ~74%)**
Dizygotic co-twin	~17%	**~20%**
Monozygotic co-twin	~48% (range 40 to 50%)	**~60%**

Empirical recurrence risks by relationship: schizophrenia figures from the Gottesman pooled data (Shorter Oxford 2018); bipolar figures span narrow counselling estimates and older broad-liability family studies, hence the ranges.



14.5 When to refer to clinical genetics

The referral triggers. The psychiatrist should refer to a medical geneticist or genetic-counselling service when features suggest a discrete, testable cause rather than ordinary polygenic liability: *dysmorphology* (an unusual facial gestalt or congenital anomalies), *intellectual disability* or global developmental delay accompanying the psychiatric presentation, a *suspected syndromic or copy-number cause* (for example 22q11.2 deletion presenting with psychosis, or fragile X in ID with autism features), and *consanguinity*, which raises the yield of autosomal-recessive and homozygous-variant conditions.

Why it matters clinically. These situations may carry a much larger, sometimes near-Mendelian, individual risk than the polygenic average: an individual with a 3q29 deletion has been estimated to have roughly a one-in-three chance of developing schizophrenia, and chromosomal microarray is now a routine test in selected patients (Shorter Oxford Textbook of Psychiatry 2018; Baker et al. 2014). A syndromic diagnosis also reframes counselling, prognosis and, occasionally, targeted management.

Practical rule. Ordinary schizophrenia or bipolar disorder without dysmorphology, ID or a suggestive family pattern is counselled with empirical risks; add-red-flag features earn a genetics referral and possible cytogenetic or microarray testing.

HOLD THIS

Counsel with empirical, not Mendelian, risks; refer the red flags. Polygenic liability means recurrence comes from family-study rates against the ~1% baseline; dysmorphology, intellectual disability, a suspected CNV or consanguinity earn a clinical-genetics referral.

14.6 Predictive and prenatal testing, and their ethical weight

No clinical predictive test exists for common psychiatric disorders. For schizophrenia and bipolar disorder there is no validated genetic test that predicts who will fall ill; the honest answer to "will it happen again?" is that we cannot predict with certainty (Austin & Peay). Predictive testing in the true sense applies to the rare high-penetrance neuropsychiatric conditions, above all Huntington's disease, where presymptomatic DNA testing is possible and mandates pre-test counselling by a clinical geneticist (Companion to Psychiatric Studies; MacLeod et al. 2013).

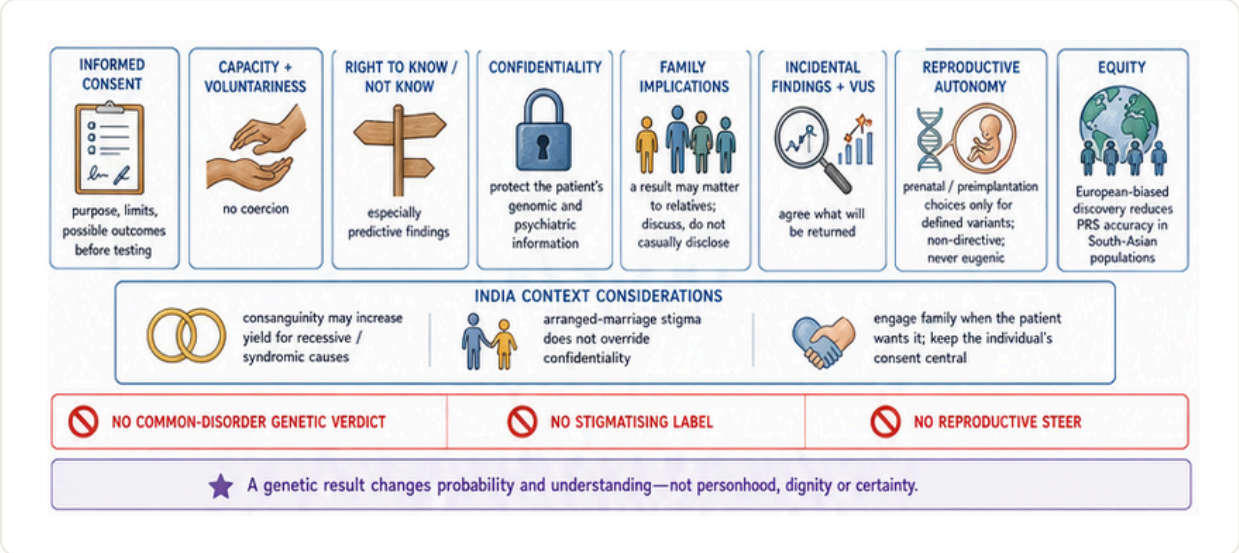


Fig 3.26 Ethics, equity and genomic humility.

The weight of a presymptomatic result. Learning one's status for an untreatable condition carries risks to mood, self-image, reproductive and career decisions and insurability; a positive result has implications for other family members who may not wish to know theirs (New Oxford Textbook of Psychiatry; Kaplan & Sadock 2024). Protocols therefore insist on informed consent, a cooling-off structure, and support before and after disclosure.

Prenatal testing. Prenatal or preimplantation testing is meaningful only for the rare identifiable single-gene or chromosomal causes, not for polygenic psychiatric liability; where offered, non-directiveness and full pre- and post-test counselling are the standard, and the decision to test or to continue a pregnancy is left to the couple (National Academies consensus).

14.7 Incidental findings and the meaning of a "negative"

Incidental (secondary) findings. Broad testing such as chromosomal microarray or exome sequencing can reveal variants unrelated to the presenting complaint, including variants of

uncertain significance and medically actionable secondary findings; consent must cover in advance what will be returned and what the patient wishes to know (Kaplan & Sadock 2024).

The two-sided interpretation trap. Because these are susceptibility not diagnostic tests, many people with a clear psychiatric diagnosis carry no identified variant, and many carriers never fall ill. A "negative" result may wrongly make a patient doubt the validity of their diagnosis or reduce treatment adherence, and may paradoxically increase parental guilt by removing a biological explanation; a positive susceptibility result labels risk without certainty (Kaplan & Sadock 2024). Pre-test counselling must rehearse the meaning of both outcomes.

14.8 Polygenic risk scores: not yet clinical

What a PRS is. A **polygenic risk score** sums the effects of many common risk alleles weighted by GWAS data to estimate an individual's genetic liability to a disorder (Kaplan & Sadock 2024). It captures the en-masse effect of variants that are not individually genome-wide significant.

Why it is not used in counselling. Current PRS modify a family-history-based estimate only marginally, are not definitively predictive, and are far less informative outside populations of European ancestry because the discovery datasets are predominantly European, an equity problem acute for Indian patients (Kaplan & Sadock 2024; Murray et al. 2021; Wray et al. 2021). The consensus through 2026 is that PRS remain a research tool, not a clinical counselling instrument, and should not be quoted as an individual risk to a patient. Communicating a non-definitive score risks being read as higher than warranted or being discounted, in ways that vary with the patient's coping style (Kaplan & Sadock 2024).

INDIA

Consanguinity. Consanguineous marriage is common in parts of India and raises the yield of autosomal-recessive and syndromic causes of intellectual disability, autism and epilepsy that can present with psychiatric features; a consanguineous pedigree is itself a trigger to consider a clinical-genetics referral rather than to quote polygenic empirical risks alone. **Disclosure pressure.** In the arranged-marriage context a family history of mental illness carries heavy stigma, and families may face pressure either to conceal a psychiatric diagnosis during matchmaking or to demand disclosure from the other party. The counsellor's duty is to the patient's confidentiality and autonomy: information about a proband is shared only with the patient and, where relevant, guardians of a dependent child, never volunteered to grandparents or prospective in-laws (Borle et al. 2018). Framing risk to reduce stigma, and resisting any eugenic or "don't marry / don't have children" steer, matters more here than anywhere. **Family-level decisions.** Reproductive and marital choices are frequently made at the level of the extended family rather than the individual, so non-directive counselling in India often means engaging the family unit while still protecting the individual patient's consent and confidentiality. See paper iii for the consent, capacity and confidentiality framework these tensions sit within.

COMMON TRAP

Quoting Mendelian ratios (25 percent, 50 percent) for schizophrenia or bipolar disorder. These are polygenic conditions; recurrence is given as *empirical* risk from family and twin studies, corrected for age of risk. A "25 percent" answer for a first-degree relative may coincidentally resemble a broad-liability figure for bipolar disorder, but the reasoning (autosomal-dominant segregation) is wrong and loses marks.

PEARL

The best-evidenced *outcome* of psychiatric genetic counselling is increased patient empowerment and reduced guilt, not changed reproductive decisions, and the largest gains occur in people who initially wanted a recurrence number but changed their mind after discussing aetiology and recovery (Borle et al. 2018; Inglis et al. 2015). The number is often the ticket in, not the therapeutic ingredient.

CLINICAL ANCHOR

A 28-year-old woman with schizophrenia (ICD-11 6A20; DSM-5-TR schizophrenia) asks what chance her future child has of the illness. You secure the diagnosis, take a three-generation pedigree (no other affected relatives), and, after contracting, offer an empirical figure of roughly 13 percent for a child of one affected parent against a population baseline near 1 percent, framed non-directively and alongside the 87 percent chance of no illness. No PRS is quoted. Because there is no dysmorphology, intellectual disability or consanguinity, no clinical-genetics referral is needed.

MNEMONIC

DR PACE

Diagnosis confirmed, **R**ecords and three-generation pedigree, **P**opulation-anchored empirical risk (not Mendelian), **A**utonomy and non-directiveness, **C**onsent for predictive or prenatal testing (and paper iii capacity/ethics), **E**motional support and follow-up. The steady pace of psychiatric genetic counselling: diagnosis before numbers, support around the numbers.

GOOD TO REMEMBER

- **Schizophrenia, sibling of proband:** ~9% lifetime risk (Gottesman, Shorter Oxford 2018).
- **Schizophrenia, child of one affected parent:** ~13 to 17% (classic Gottesman figure ~13%; Shorter Oxford table lists 17%).
- **Schizophrenia, child of two affected parents:** ~46%.
- **Schizophrenia, monozygotic co-twin:** ~48% (twin-study range 40 to 50%); dizygotic co-twin ~17%.
- **Schizophrenia population baseline:** ~1%.
- **Bipolar disorder, first-degree relative / child of one parent:** ~10 to 15% in narrow counselling estimates; older broad-liability family studies give up to ~25 to 27%.
- **Bipolar disorder, monozygotic co-twin concordance:** ~60%; dizygotic ~20%.
- **3q29 deletion:** ~1-in-3 (~33%) chance of developing schizophrenia, an example of a high-risk CNV warranting clinical-genetics referral.
- **22q11.2 deletion:** syndromic cause of psychosis; a referral trigger when psychosis co-occurs with dysmorphology or developmental features.
- **Huntington's disease:** the exemplar of true presymptomatic (predictive) DNA testing, mandating pre-test genetic counselling.
- **Polygenic risk score (PRS):** sums many common GWAS alleles; NOT clinically actionable in counselling as of 2026, and less valid in non-European (including Indian) populations.

15 · Apply: four genetics vignettes

The whole set of notes converges here. Psychiatric genetics earns its exam marks only when a family history, an ancestry, a dysmorphic phenotype or a metaboliser report is made to *predict* a clinical consequence and then force a first move. These four vignettes are deliberately drawn from four corners of the discipline, so the discriminator in each is a different genetic tool: an **empirical recurrence risk** read off polygenic familial data, a **pharmacogenomic HLA test** that averts a fatal skin reaction, a **copy-number variant** hunted with a cytogenetic assay, and a **pedigree read alongside a CYP genotype**. Each runs to the three-beat rhythm the examiners reward: the **presentation**, then the **genetic reasoning** that alone explains it, then the **counselling, testing or dosing action** the genetics forces.

Read each as a reasoning drill, not a fact to memorise. If you can name the tool the moment the stem lands, whether the answer is a probability given non-directively, an allele screened before a drug, an assay ordered before a referral, or a study design chosen to match a transmission pattern, the response is already written. Numbers that carry weight are given only where a canonical source verifies them, and any figure to confirm against a current guideline or formulary before quoting is flagged (Kaplan & Sadock 2024; New Oxford 2020; Maudsley 2021). A hard rule threaded through all four: give population-level probabilities without implying determinism, and never name a diagnosis to a family in a way that stigmatises the proband or an unaffected relative.

15.1 Vignette 1: a couple ask about their child's risk when one partner has bipolar disorder, the empirical-risk counselling drill

CLINICAL ANCHOR

Case: a couple attend for pre-conception advice. The husband has an established diagnosis of bipolar type I disorder (ICD-11 6A60; DSM-5-TR bipolar I disorder), well controlled on lithium. The wife has no psychiatric history and no affected relatives. They ask, directly, what the chance is that a future child will develop the same illness, and whether they should have children at all.

Reasoning. Bipolar disorder is the single most heritable major psychiatric disorder (heritability around 0.85, rising toward 0.9 for narrowly defined bipolar-I; MZ co-twin concordance conventionally around 60 percent against a DZ rate an order lower), yet its inheritance is *polygenic and non-Mendelian*: it does not segregate in simple ratios, so there is no single-gene calculation to offer (Kaplan & Sadock 2024; McGuffin 2003). What counselling uses instead is the **empirical recurrence risk**, the observed rate of illness in relatives of probands read straight off family-study data. For a child with one affected parent the empirical risk of bipolar disorder is of the order of 10 to 15 percent, several-fold above the roughly 1 to 2 percent population baseline; the risk of any mood disorder (including unipolar depression) in that child is higher still, and the figure climbs further, toward 40 to 50 percent, if both parents are affected (verify the exact figures against a current text before quoting). Recurrence risk in this model rises with the severity of the index case and with the number of affected relatives, the same liability-threshold logic that governs all the common disorders.

Counselling action (non-directive). The mechanism dictates the manner. Genetic counselling here is **non-directive**: you supply the empirical probability as a probability, frame it against the population baseline so it is neither minimised nor catastrophised, and explicitly leave the reproductive decision to the couple rather than advising for or against childbearing. Add the constructive counterweight that most children of an affected parent do *not* develop bipolar disorder, that no prenatal or predictive genetic test exists for a polygenic condition of this kind, and that early recognition and treatment of any future illness improves outcome. Where relevant, fold in the separate, drug-specific reproductive-safety discussion (lithium and first-trimester exposure) as its own strand, and route the detailed peri-conception medication protocol to the clinical psychiatry chapters (Paper II).

COMMON TRAP

Do not quote a Mendelian fraction (a "one in four" or "one in two") for a polygenic psychiatric disorder: that arithmetic belongs to single-gene conditions and misrepresents the biology. And do not drift into directive advice ("you shouldn't have children") or false reassurance ("it won't be passed on"). The examinable failure modes are the Mendelian-ratio error and the loss of non-directiveness; the correct answer is an empirical percentage, delivered neutrally, with the decision left to the couple.

15.2 Vignette 2: carbamazepine in a patient of Han-Chinese or South-Asian ancestry, the HLA-B*15:02 screen before starting

CLINICAL ANCHOR

Case: a 30-year-old man of Han-Chinese ancestry (the same caution applies across South-East and South Asian populations, including Thai and many Indian groups) is to be started on carbamazepine, whether for a mood-stabilising indication in bipolar disorder or for trigeminal neuralgia or epilepsy. He is treatment-naive to the drug. Before writing the prescription, the question is what to check.

Reasoning. Carbamazepine can precipitate the life-threatening severe cutaneous adverse reactions **Stevens-Johnson syndrome** and **toxic epidermal necrolysis (SJS/TEN)**. The susceptibility is pharmacogenomic and strongly ancestry-linked: the class I HLA allele **HLA-B*15:02** is the established risk marker for carbamazepine-induced SJS/TEN, and its carrier frequency is substantial in Han-Chinese, Thai and many South and South-East Asian populations while being rare in Europeans (Kaplan & Sadock 2024). The mechanism is immunogenetic, not metabolic: the risk allele shapes the HLA-restricted T-cell response to the drug, so this is a pharmacodynamic pharmacogenetic marker of a hypersensitivity reaction rather than a dose-handling problem. Because the reaction is idiosyncratic and severe, the genetic test is deployed *pre-emptively*, before the first dose, in the at-risk ancestry groups.

Testing action. Screen for **HLA-B*15:02** before initiating carbamazepine in patients of the relevant ancestry, and if the patient is positive, *avoid carbamazepine* and choose an alternative agent unless the benefit clearly outweighs the risk. Two examinable refinements: HLA-B*15:02 positivity also flags cross-risk with other aromatic antiepileptics that cause SJS/TEN, notably phenytoin and oxcarbazepine, so phenytoin is *not* a safe substitute in a positive patient; and a distinct allele, HLA-A*31:01, is linked to a broader spectrum of carbamazepine hypersensitivity (including DRESS and maculopapular eruption) across other ancestries including Europeans. Genotyping does not replace clinical vigilance: counsel every starter about the early rash and mucosal warning signs and the instruction to stop and present immediately (verify current screening thresholds and the exact at-risk populations against a live guideline; Kaplan & Sadock 2024; Maudsley 2021).

INDIA

This vignette is squarely an Indian-practice issue: HLA-B*15:02 carriage is appreciable across several South Asian groups, so ancestry-based pre-carbamazepine screening is directly relevant to prescribing here, not a Western-only footnote. Where testing is not readily available or affordable, the pragmatic and defensible move is to favour an alternative mood stabiliser or antiepileptic in a patient from a high-frequency background, and to document an explicit informed discussion of the SJS/TEN risk and the early warning signs.

15.3 Vignette 3: developmental delay, dysmorphism and later psychosis, recognising 22q11.2 and ordering the right assay

CLINICAL ANCHOR

Case: a young person carries a history of developmental delay and learning difficulty from childhood, with subtle dysmorphic features, a history of a congenital cardiac anomaly and recurrent infections, and a characteristically nasal quality to the speech. In late adolescence he now presents with a first episode of psychosis (ICD-11 6A20 schizophrenia; DSM-5-TR schizophrenia). The task is to recognise the pattern and act on it.

Reasoning. The constellation of developmental delay, dysmorphism, a conotruncal cardiac lesion, immune and palatal features, and a markedly elevated risk of psychosis is the signature of the **22q11.2 deletion syndrome** (velocardiofacial syndrome / DiGeorge syndrome), a microdeletion on the long arm of chromosome 22. It is the single best-characterised and highest-yield copy-number variant in psychiatric genetics: it is a large recurrent deletion that confers one of the strongest known monogenic-scale risks of schizophrenia, with a substantial minority of 22q11.2-deletion carriers developing a schizophrenia-spectrum psychosis, which is why the deletion has focused attention on genes in that region as predisposing to psychosis in general (New Oxford 2020; Shorter Oxford 2018). Unlike a single-nucleotide polymorphism, a CNV of this size behaves like a miniature chromosomal abnormality of high penetrance, so recognising the somatic phenotype behind the psychosis is what converts a routine first-episode presentation into a specific genetic diagnosis.

Testing and referral action. Order a genetic test that can detect a submicroscopic deletion: **chromosomal microarray (CMA)** is the first-line genome-wide assay for copy-number variants and is the appropriate broad test when the differential is open, while a *targeted* assay, fluorescence in-situ hybridisation (FISH) for the 22q11.2 locus (or MLPA), confirms the deletion quickly when 22q11.2 is specifically suspected on the phenotype. A standard karyotype will typically *miss* a microdeletion of this size and is the wrong test. Refer to **clinical genetics** for confirmation, cascade family testing and formal genetic counselling, because the deletion is often de novo but can be inherited, and coordinate the multisystem workup (cardiac, immune, endocrine including calcium). The psychiatric management of the psychosis itself follows standard first-episode lines and belongs to the clinical psychiatry chapters (Paper II).

COMMON TRAP

Do not order a conventional karyotype expecting it to find 22q11.2: it resolves whole-chromosome and large structural changes, not a microdeletion of this scale, so a normal karyotype is falsely reassuring. The correct first-line for CNV detection across an undifferentiated developmental-delay-plus-dysmorphism-plus-psychosis picture is chromosomal microarray; FISH (or MLPA) is the fast targeted confirmatory step when the phenotype points specifically at 22q11.2.

15.4 Vignette 4: a three-generation pedigree plus a CYP2D6 poor-metaboliser report, reading the pattern and adjusting the drug

CLINICAL ANCHOR

Case: you are handed a three-generation pedigree of a family with recurrent depressive illness and a laboratory report on the index patient stating she is a **CYP2D6 poor metaboliser** (for example homozygous for a null allele such as CYP2D6*4). She has developed marked adverse effects on a standard dose of a CYP2D6-dependent antidepressant. Two separate questions are embedded: what does the pedigree tell you about study design, and what does the genotype tell you about her drug.

Reasoning, part one: reading the pedigree for a study design. A pedigree with illness appearing across successive generations but *not* segregating in clean Mendelian ratios, affecting both sexes, with variable expression and incomplete penetrance, is the familiar picture of a common, polygenic psychiatric disorder rather than a single-gene trait. The genetic-epidemiology tool matched to that pattern is *not* classical parametric linkage, which assumes a specified single-locus model and a known mode of inheritance and is powerful only for rare monogenic traits; it is the family-based and population approaches suited to complex inheritance: non-parametric linkage or affected-sib-pair methods, and above all association designs (genome-wide association studies) that detect the many small-effect common variants. The reading skill is to let the transmission pattern pick the design: male-to-male transmission excludes X-linkage, a clean vertical dominant or clustered recessive pattern would invite a Mendelian linkage approach, whereas this "familial but not Mendelian" pedigree signals a polygenic architecture and an association or non-parametric strategy (Kaplan & Sadock 2024; New Oxford 2020).

Reasoning, part two, and the dosing action. The **CYP2D6** report is a pharmacokinetic pharmacogenetic result about a hepatic drug-metabolising enzyme. A **poor metaboliser** (two non-functional alleles, activity score 0) clears CYP2D6-dependent drugs slowly, so at a standard dose plasma concentrations run high and dose-related adverse effects and toxicity follow, exactly her picture. The action the genotype forces is to *reduce the dose* of the CYP2D6-substrate antidepressant, or switch to an agent not dependent on CYP2D6, guided by the genotype and by therapeutic drug monitoring where available; the mirror-image caution is the *ultrarapid* metaboliser (gene duplication) who under-responds at standard doses because the drug is cleared too fast. This is the corner of pharmacogenetics closest to immediate clinical translation, with the important honesty that the evidence base for single-gene dose adjustment is stronger than that for combinatorial multi-gene "which drug" panels (Kaplan & Sadock 2024; Maudsley 2021).

PEARL

Keep the two halves of this vignette in separate drawers, because the exam fuses them to test whether you can. The *pedigree* answers a genetic-epidemiology question (which study design fits which inheritance pattern: linkage for Mendelian, association/GWAS for polygenic). The *CYP2D6 report* answers a pharmacology question (poor metaboliser means lower dose; ultrarapid means higher dose or switch). One family, two tools: one reads transmission to choose a design, the other reads an enzyme genotype to choose a dose.

15.5 The four vignettes at a glance: tool, discriminator, first move

The consolidating grid. Read the discriminator column first: in each stem it is the single feature that names the genetic tool and therefore writes the answer.

VIGNETTE	GENETIC TOOL	DISCRIMINATOR IN THE STEM	FIRST MOVE
1. Couple with one bipolar partner ask about a child's risk	Empirical recurrence risk (polygenic, non-Mendelian)	**Bipolar I in one parent, no Mendelian pattern; a probability is requested**	Counsel the empirical offspring risk (~10 to 15% for BD) non-directively; decision left to the couple
2. Carbamazepine in a Han-Chinese or South-Asian patient	Pharmacogenomic HLA screening (immunogenetic)	**At-risk ancestry plus a planned carbamazepine start; SJS/TEN risk**	Screen HLA-B*15:02 before the first dose; if positive, avoid carbamazepine (and phenytoin)
3. Developmental delay, dysmorphism, cardiac anomaly, later psychosis	Copy-number variant detection (cytogenetic)	**Multisystem developmental phenotype behind the psychosis, pointing at 22q11.2**	Chromosomal microarray (or targeted FISH/MLPA for 22q11.2); refer to clinical genetics
4. Three-generation pedigree plus CYP2D6 poor-metaboliser report	Pedigree analysis + pharmacokinetic pharmacogenetics	**Familial-but-not-Mendelian pattern; genotype-confirmed poor metaboliser with toxicity**	Choose association/GWAS for the polygenic pattern; reduce dose or switch off the CYP2D6 substrate

Four tools, four discriminators: an empirical recurrence risk, a pharmacogenomic HLA screen, a copy-number-variant assay, and a pedigree read alongside a CYP genotype. In every row the discriminator names the tool and the tool forces the first move.

HOLD THIS

Name the tool the moment the stem lands and the answer is already written. The discriminator in the stem (a probability requested, an at-risk ancestry, a dysmorphic phenotype, a metaboliser report) names the genetic tool, and the tool forces the first move.

GOOD TO REMEMBER

- **Bipolar disorder (ICD-11 6A60):** most heritable major psychiatric disorder, heritability ~0.85 (up to ~0.9 for narrow BP-I); MZ concordance conventionally ~60%; empirical offspring recurrence risk ~10 to 15% with one affected parent (verify), higher for any mood disorder and ~40 to 50% if both parents affected.
- **HLA-B*15:02:** risk allele for carbamazepine-induced Stevens-Johnson syndrome / toxic epidermal necrolysis; frequent in Han-Chinese, Thai and South/South-East Asian populations, rare in Europeans; screen before starting carbamazepine, avoid if positive; cross-risk with phenytoin and oxcarbazepine.
- **HLA-A*31:01:** linked to a broader carbamazepine hypersensitivity spectrum (DRESS, maculopapular rash) across other ancestries including Europeans.
- **22q11.2 deletion syndrome:** velocardiofacial / DiGeorge syndrome; recurrent microdeletion on chromosome 22q; one of the strongest CNV risks for schizophrenia (a substantial minority of carriers develop psychosis); developmental delay, dysmorphism, conotruncal cardiac lesion, immune and palatal features.
- **Detection assay:** chromosomal microarray (CMA) is first-line for genome-wide CNV detection; FISH or MLPA is the targeted confirmatory test for 22q11.2; a standard karyotype misses microdeletions of this size.
- **CYP2D6 poor metaboliser:** two non-functional alleles (activity score 0, e.g. CYP2D6*4 homozygote); high plasma levels and toxicity at standard dose of CYP2D6-dependent drugs, so reduce dose or switch; ultrarapid metaboliser (gene duplication) under-responds and needs a higher dose or a switch.
- **Counselling principle:** genetic counselling is non-directive, gives population-level empirical probabilities without implying determinism, and never names a diagnosis to a family in a stigmatising way.
- **Study-design rule:** classical (parametric) linkage suits rare Mendelian traits with a known model; association / genome-wide association studies (and non-parametric or affected-sib-pair linkage) suit the common, polygenic, non-Mendelian psychiatric disorders.

16 · Consolidate: mnemonic total, retrieval and synthesis

This closing block is not new material; it is a **consolidation device** for the whole of these notes. The material has run one long circuit through psychiatric genetics: the methods ladder from twins to biobanks, the inheritance models and the liability-threshold idea, the twin and adoption designs, parametric linkage and the LOD score, the GWAS and CNV and polygenic-risk era, the newer sequencing and gene-therapy approaches, epigenetics and imprinting, endophenotypes, the neurodevelopmental and pleiotropy picture that dissolves the Kraepelinian line, the heritability league table across disorders, the worked example of schizophrenia genetics, pharmacogenetics, and finally the counselling clinic where all of it becomes a recurrence-risk figure spoken to a family. **Study by producing, not by re-reading.** Durable learning comes from spaced *active recall* (self-testing from memory) rather than repeated passive review, the testing effect that Roediger and Karpicke (2006) demonstrated directly. The three subtopics below give you the loop to run it: one master mnemonic that chains the smaller mnemonics into a single spine, a set of answer-free retrieval prompts, and a one-page synthesis map to redraw from memory.

Use them in that order. Recite the mnemonic spine to confirm the scaffold is intact, close the notes and work the retrieval prompts aloud, then take a blank sheet and rebuild the whole-day

circuit from method through architecture to the disorders arrayed on it. Where a limb of the map will not come, that gap is the prediction error naming the exact topic to reopen, which is the entire point of the exercise.

HOLD THIS

One architecture of common and rare variation, differing in dose and neurodevelopmental timing, generates the whole spectrum. Recite the mnemonic spine, work the retrieval prompts aloud, then redraw the architecture plane from memory; the gaps name the topics to reopen.

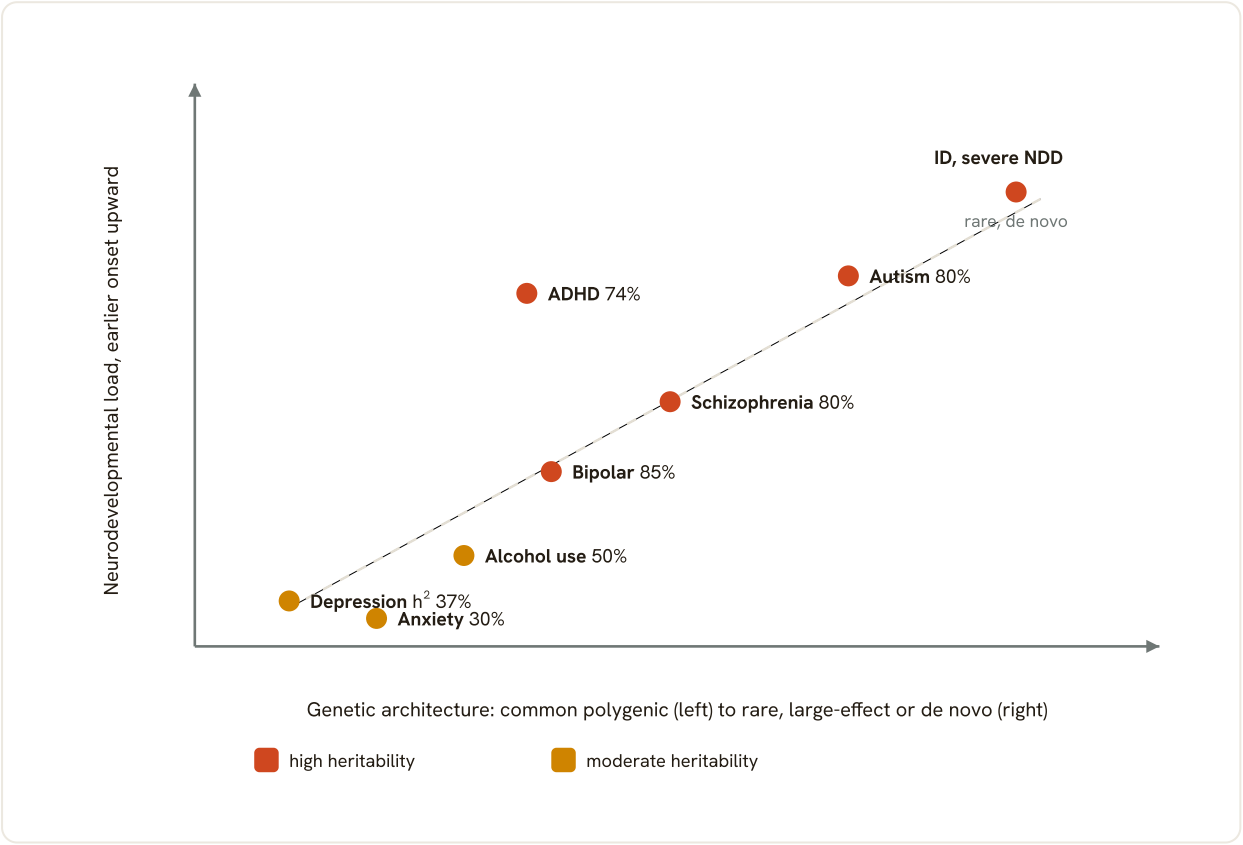


Fig 3.27 The whole subject on one map: major disorders placed by genetic architecture and neurodevelopmental load. Reading left to right, risk shifts from common-variant polygenic (depression, anxiety, much of bipolar and schizophrenia) toward an increasing contribution of rare, large-effect and de novo variants (autism and severe intellectual disability). Reading bottom to top, disorders carry more neurodevelopmental load and earlier onset. Colour marks heritability tier. Redraw this from memory as the synthesis of these notes: for any disorder, you should be able to place it and name the methods that would find its risk.

16.1 Master mnemonic total: chaining the whole subject into one spine

Every topic here already carries its own mnemonic. The problem at revision is not recalling any single one but retrieving the correct one under time pressure and in the right order. The device below is a *mnemonic of mnemonics*: a spine that indexes the methods ladder, the inheritance and threshold logic, the twin and adoption designs, the linkage-to-GWAS mapping tools, the polygenic and copy-number architecture, the newer approaches, epigenetics, endophenotypes, the pleiotropy story, the heritability league, the schizophrenia worked example, pharmacogenetics and counselling, so that recalling the spine pulls each sub-mnemonic up with it. Walk it in the order the material ran, from how we look, through what the architecture is, to what we do with it in clinic.

MNEMONIC

"TWINS LADDER Climb the Threshold, LOD Maps the GWAS-CNV-PRS Triangle, New Genomes Cut and Splice, Marks Above the Genes, Endophenotypes Bridge, Pleiotropy Breaks the Dichotomy, Rank the Heritable, SZ is the Case, CYP-HLA Dose, and Counsel the Family"

TWINS LADDER Climb the Threshold fixes the opening two limbs. The methods ladder runs "Family, Twin, Adoption, Linkage, Association, biobank" as a rising sequence of resolution, each rung answering a sharper question than the last, from is-it-familial to which-variant-and-in-whom. The inheritance limb runs "Mendel is Simple, Psychiatry is Multifactorial: Liability crosses a Threshold": single-gene Mendelian rules give clean segregation ratios, but the common disorders are polygenic and multifactorial, modelled as a normally distributed underlying liability with an abrupt threshold above which the phenotype appears (Falconer). Two threshold corollaries carry exam weight: the more-often-affected sex sits at the lower threshold, so relatives of an affected member of the rarer, higher-threshold sex carry the higher recurrence risk (the Carter effect); and rising recurrence risk with more affected relatives or a more severe proband is the signature of multifactorial, not Mendelian, transmission.

LOD Maps the GWAS-CNV-PRS Triangle chains the mapping and architecture core. Parametric linkage runs on "Three to prove, minus Two to exclude": a LOD (logarithm of odds) of plus 3 (odds of 1000 to 1) proves linkage and minus 2 (odds of 100 to 1 against) excludes it, with the recombination fraction theta running from 0 (never separated, inside the gene) to 0.5 (unlinked). Association then runs on the GWAS threshold "Five times ten to the minus eight" (correcting for about a million independent common variants), and the architecture resolves into a triangle: common SNPs of tiny effect (odds ratios about 1 to 1.2), rare CNVs of large effect (odds ratios about 20 to 100), and the polygenic risk score (PRS) that sums the common alleles into one liability index. The single most useful discriminator for the whole field: "Common is small and many; Rare is large and few", the inverse relationship between allele frequency and effect size.

New Genomes Cut and Splice encodes the novel-approaches limb. Sequencing runs on "Exome for the coding 2 percent, Genome for everything", with trio designs catching de novo mutations that carry large effect (prominent in autism). Therapy runs on "Cut, Splice or Replace": genome editing (CRISPR) cuts, antisense oligonucleotides (ASOs) modify splicing or lower transcript, and viral (AAV) vectors replace a gene, the three exemplified by the spinal muscular atrophy precedents (the SMN2-splice-modifying ASO nusinersen and the AAV SMN1 replacement) and the huntingtin-lowering ASO trials in psychiatry-adjacent neurology.

Marks Above the Genes is the epigenetics line, "Methylation Silences, Acetylation Opens; Imprinting is Parent-of-origin": DNA methylation (laid by the DNMT enzymes) generally silences, histone acetylation generally opens chromatin, and imprinting means expression depends on the parent of origin, the exemplar being the single 15q11-q13 locus that yields Prader-Willi from paternal loss and Angelman from maternal loss (of UBE3A). The gene-by-environment epigenetic mediator to remember is FKBP5, where a risk allele plus childhood trauma demethylates a regulatory element and yields glucocorticoid-receptor resistance (Klengel 2013).

Endophenotypes Bridge, Pleiotropy Breaks the Dichotomy chains two conceptual limbs. Endophenotypes run on the Gottesman and Gould (2003) criteria "Heritable, State-independent,

Co-segregates, seen in unaffected Relatives, and disease-Associated", the measurable intermediate markers (P50 gating, prepulse inhibition, mismatch negativity, antisaccade, smooth pursuit) meant to sit closer to the genes than the diagnosis. Pleiotropy then runs on "One variant, Many disorders": the high cross-disorder genetic correlations (schizophrenia to bipolar rg about 0.68, the highest pair) and shared loci such as CACNA1C and the 22q11.2 deletion collapse the categorical boundaries into a shared cross-disorder architecture, the genetic basis of the p-factor.

Rank the Heritable, SZ is the Case is the quantitative payload. The heritability league runs top to bottom on "Bipolar and Autism High, Schizophrenia and ADHD Next, Depression and Anxiety Low": bipolar about 0.85 and autism about 0.80 at the top, schizophrenia about 0.80 and ADHD about 0.75 next, major depression about 0.37 and the anxiety and stress disorders about 0.30 at the floor. Schizophrenia is then the worked case that ties it all together: high heritability but a polygenic architecture (108 loci in the 2014 PGC GWAS), the MHC / complement C4A signal driving excess synaptic pruning, DRD2 closing the genetics-to-pharmacology loop, and the 22q11.2 deletion as the single largest known genetic risk.

CYP-HLA Dose, and Counsel the Family closes on the two clinical limbs. Pharmacogenetics runs on "CYP for the Dose, HLA for the Danger": the CYP2D6 and CYP2C19 metaboliser phenotypes (poor to ultrarapid, captured as an activity score) set drug exposure and dose, while the HLA alleles flag life-threatening reactions, HLA-B*15:02 for carbamazepine-induced Stevens-Johnson syndrome (screen in Han-Chinese and South and South-East Asian ancestry) and HLA-A*31:01 across broader ancestries. Counselling then runs on "Empiric risk, Non-directive, Genetics-clinic referral for the syndromic and the predictive": most psychiatric counselling gives empiric recurrence figures non-directively, reserving formal clinical-genetics referral for syndromic CNVs (22q11.2, 3q29) and true presymptomatic testing (the Huntington disease model), with PRS explicitly not yet clinically actionable and less valid in non-European (including Indian) populations.

The table restates the spine so you can quiz yourself on any single link. Cover the right two columns and recall the sub-mnemonic and its content from the cue phrase alone.

SPINE LINK	SUB-MNEMONIC	WHAT IT UNLOCKS
Methods ladder	Family, Twin, Adoption, Linkage, Association, Biobank	**Rising resolution: is-it-familial to which-variant-in-whom; twins give heritability, adoption separates genes from rearing**
Inheritance / threshold	Mendel Simple, Psychiatry Multifactorial; Liability crosses a Threshold	Polygenic liability model; Carter effect (rarer-sex relatives higher risk); rising risk with load signals multifactorial
Linkage / LOD	Three to prove, minus Two to exclude; theta 0 to 0.5	**LOD +3 = 1000:1 for linkage, -2 = 100:1 against; recombination fraction; DISC1 from a translocation breakpoint**

SPINE LINK	SUB-MNEMONIC	WHAT IT UNLOCKS
GWAS / CNV / PRS	Five times ten to the minus eight; Common small, Rare large	Genome-wide significance; the frequency-effect-size triangle; PRS sums common alleles into one liability index
Novel approaches	Exome coding 2 percent, Genome everything; Cut, Splice, Replace	**WES vs WGS; de novo trios; CRISPR / ASO / AAV therapy, exemplified by the SMA and Huntington precedents**
Epigenetics	Methylation Silences, Acetylation Opens; Imprinting parent-of-origin	DNMTs and histone marks; 15q11-q13 gives Prader-Willi vs Angelman; FKBP5 gene-by-trauma mediator
Endophenotypes	Heritable, State-independent, Co-segregates, in Relatives, Associated	**Gottesman-Gould criteria; P50, prepulse inhibition, mismatch negativity, antisaccade, smooth pursuit**
Pleiotropy / cross-disorder	One variant, Many disorders	SCZ-BD rg about 0.68; CACNA1C and 22q11.2 shared; p-factor and the collapse of the Kraepelinian dichotomy
Heritability league	Bipolar and Autism High, SZ and ADHD Next, Depression and Anxiety Low	**BD about 0.85, ASD about 0.80, SCZ about 0.80, ADHD about 0.75, MDD about 0.37, anxiety about 0.30**
Schizophrenia case	High heritability, polygenic; C4A prunes, DRD2 loops, 22q11.2 biggest	108 PGC loci; complement-driven pruning; genetics-pharmacology loop; largest single CNV risk
Pharmacogenetics	CYP for the Dose, HLA for the Danger	**CYP2D6 / CYP2C19 metaboliser phenotype and activity score; HLA-B*15:02 and HLA-A*31:01 for carbamazepine reactions**
Counselling	Empiric risk, Non-directive, Genetics-clinic referral	Empiric recurrence figures given non-directively; syndromic-CNV and predictive-testing referral; PRS not yet actionable

The twelve-link master spine for this chapter, each row a cue phrase pointing to a topic mnemonic; recall the middle and right columns from the left cue alone.

16.2 Active-recall prompts: cover the page and answer aloud

These are retrieval questions, not a summary. They are deliberately answer-free, so that they force you to generate the answer from memory, which is where the testing effect does its work; printing a model answer here would defeat the device. This is the *retrieval practice* set for these notes: cover everything below the label, answer each aloud in a full sentence, then reopen the relevant topic only for the prompts you could not complete.

RETRIEVAL PRACTICE, COVER THE ANSWERS

1. State the six rungs of the genetic methods ladder in ascending order of resolution, and say precisely what question the twin design and the adoption design each answer that a family study cannot.
2. Define the liability-threshold model, explain the Carter effect in one sentence, and give the two features of a recurrence-risk pattern that point to multifactorial rather than Mendelian inheritance.
3. Write Falconer's formula for heritability from twin correlations and the ACE model, and explain the equal-environments assumption and why it is the design's load-bearing weakness.
4. Give the LOD score thresholds for proving and for excluding linkage with the odds each represents, and define the recombination fraction theta with its two limiting values.
5. State the GWAS genome-wide significance threshold and what it corrects for, then contrast the effect sizes of common SNPs against rare CNVs and state the general frequency-to-effect-size rule.
6. Explain what a polygenic risk score is, roughly how much schizophrenia liability it currently captures, and two reasons it is not yet used in clinical counselling.
7. Distinguish whole-exome from whole-genome sequencing, and explain why the trio design is the efficient way to detect the de novo mutations that matter in autism.
8. Name the three gene-therapy modalities (edit, splice-modify, replace) with one clinical exemplar each, and say which spinal muscular atrophy agent represents which modality.
9. Contrast the effects of DNA methylation and histone acetylation on transcription, then explain how a single imprinted 15q11-q13 locus produces two different syndromes.
10. State the five Gottesman and Gould criteria for an endophenotype, and name one candidate endophenotype together with the gene or receptor most associated with it.
11. Give the schizophrenia-to-bipolar genetic correlation and explain what such high cross-disorder correlations imply for the Kraepelinian dichotomy and the p-factor.
12. Rank bipolar disorder, autism, schizophrenia, ADHD, major depression and generalised anxiety by twin heritability from highest to lowest with an approximate figure for each.
13. For schizophrenia, name the most robust common-variant locus and its proposed synaptic mechanism, the locus that closes the genetics-pharmacology loop, and the single largest known genetic risk factor.
14. Distinguish the poor, intermediate, normal and ultrarapid metaboliser phenotypes, name the two CYP enzymes most relevant in psychiatry, and give one dosing consequence of each extreme.
15. Name the HLA allele that must be screened before carbamazepine and the ancestry group it is common in, and state what reaction it predicts.
16. Outline the principles of non-directive psychiatric genetic counselling, name two situations that warrant clinical-genetics referral, and state why polygenic risk scores are not yet part of counselling.

If more than a third of these will not come cleanly, do not push through the list a second time the same day; space the next attempt, because retrieval spaced across days is what builds durable

memory (Roediger and Karpicke 2006).

16.3 Synthesis map: the one page to redraw from memory

The final consolidation step is to build a single **synthesis map** and *redraw from memory* the whole of psychiatric genetics as one two-axis plane. Draw the **genetic-architecture plane**: the horizontal axis running from common-polygenic (many small-effect common variants) on the left to rare-large-effect (single CNVs and de novo mutations) on the right, and the vertical axis carrying neurodevelopmental load from low at the bottom to high at the top. Then place the major disorders onto it from memory: autism and intellectual disability high and toward the rare-large-effect right (de novo and CNV enriched, high neurodevelopmental load); schizophrenia high on neurodevelopmental load but sitting across the middle of the horizontal axis, with both a dense common-polygenic component (108 loci) and a rare tail (22q11.2, NRXN1); bipolar disorder mid-height, mostly common-polygenic and sharing much of its architecture with schizophrenia; ADHD toward the neurodevelopmental top but common-polygenic; and major depression and the anxiety and stress disorders low on both axes, common-polygenic with modest heritability. Annotate the plane with the frequency-to-effect-size gradient along the bottom (common small, rare large), the pleiotropy links drawn as arcs between the disorders that share loci (the schizophrenia-bipolar arc the thickest), and the clinical endpoints in the margin (PRS for the common-polygenic pole, clinical-genetics referral for the rare-large-effect pole, pharmacogenetic CYP and HLA testing as the treatment overlay). Redraw it once from memory, then check it against the figures above and fill only the gaps; the act of reconstructing the plane, not admiring a finished one, is what fixes the central claim, that a single architecture of common and rare variation, differing in dose and in neurodevelopmental timing, generates the whole spectrum of psychiatric disorder. The figure to rebuild is that two-axis plane, common-polygenic to rare-large-effect against neurodevelopmental load, with the disorders placed as points and the shared-locus pleiotropy drawn as connecting arcs. [FLAG concept_svg CF6]

Previously asked

Real long-essay (25-mark) and short-note (10-mark) questions from the genetics territory.

LONG ESSAYS (25 MARKS)

- Describe the role of genetics, biological and psychological factors in the development of personality. MUHS 2018

SHORT NOTES (10 MARKS)

- Role of psychopharmacogenetics in psychiatry. MUHS 2013
- Gene mapping. MUHS 2012
- Neurogenetics. MUHS 2011

Genetics is a compact but recurring examiner favourite: pharmacogenetics, gene mapping and the broad "neurogenetics" note all appear, and genetics features inside integrative essays on personality and on individual disorders (schizophrenia genetics is the most examinable long answer). Prepare the methods well enough to define any one in three lines and to name the key findings.

Quick review

The whole picture in one table	
THE GENETICS TOOLKIT	An evidence hierarchy, each method one question: family (does it run in families?), twin (genes vs shared environment?), adoption (genes vs rearing?), linkage (roughly where?), GWAS (which common variants?), CNV and sequencing (rare large-effect variants?), polygenic risk score (aggregate burden?). Risk is mostly common-variant polygenic plus a minority of rare large-effect variants; much heritability is still missing; risk is read out through neurodevelopment.
MODES OF INHERITANCE	Mendelian (autosomal dominant, autosomal recessive, X-linked) vs non-Mendelian (mitochondrial, genomic imprinting, anticipation via trinucleotide repeats). Psychiatric disorders are polygenic and multifactorial. The multifactorial-threshold (liability) model: liability is normally distributed, disease appears above a threshold; relatives are shifted right, so recurrence exceeds prevalence. Sex-specific thresholds give the Carter effect.
TWIN, FAMILY AND ADOPTION STUDIES	MZ vs DZ concordance; heritability approximately 2 times (rMZ minus rDZ); the ACE model splits variance into additive genetic, common environment and unique environment; the equal-environments assumption is the main critique. Adoption designs (adoptee, adoptee's-family, cross-fostering; Heston 1966; the Danish studies). Quantitative methods: segregation analysis, path analysis, variance-components. Gene-environment interaction and correlation.
LINKAGE, LOD SCORE, GENE MAPPING	Linkage tracks co-segregation within families; markers ran RFLP to microsatellite to SNP. LOD (logarithm of the odds) of 3 or more is significant, minus 2 excludes; affected sib-pair is the model-free version. Positional cloning, genetic vs physical maps, fine-mapping. Linkage largely failed for polygenic psychiatric traits (Lander and Kruglyak thresholds), which drove the move to genome-wide association.
GWAS, CANDIDATE GENES, CNVS, PRS	Candidate-gene studies (COMT, 5-HTTLPR, DISC1) mostly did not replicate. GWAS: genome-wide significance 5 x 10 to the minus 8, the Psychiatric Genomics Consortium, sample size the key. Schizophrenia: the complement C4 / MHC signal (Sekar 2016), 108 then 287 loci (Trubetskoy 2022). CNV syndromes: 22q11.2 (largest single risk), 16p11.2, 1q21.1, NRXN1. Polygenic risk scores sum common variants but are not yet individually predictive. Missing heritability.
NOVEL APPROACHES AND GENE THERAPY	Whole-exome and whole-genome sequencing; rare-variant burden; de novo mutations (paternal-age effect, large in autism). SCHEMA named ten genes (SETD1A, GRIN2A, others; Singh 2022). Functional genomics (eQTL, TWAS), iPSC neurons and organoids, Mendelian randomization, biobanks. Gene therapy (antisense oligonucleotides, AAV,

The whole picture in one table	
	CRISPR) is real in monogenic neurological disease but not in polygenic psychiatric disorders.
EPIGENETICS	Stable change in expression without a sequence change: DNA methylation, histone modification, non-coding RNA. Genomic imprinting (Prader-Willi vs Angelman, 15q11-13). Early-life programming: FKBP5 demethylation with childhood trauma (Klengel 2013), Dutch-famine methylation (Heijmans 2008). Epigenetic clock (Horvath 2013) and accelerated ageing. Valproate is a histone-deacetylase inhibitor.
ENDOPHENOTYPES	Heritable intermediate traits closer to gene action. Gottesman and Gould (2003) criteria: associated with illness, heritable, state-independent, co-segregates in families, present in unaffected relatives. Examples: P50 sensory-gating deficit, prepulse inhibition deficit, smooth-pursuit and antisaccade abnormalities, mismatch negativity, working memory. They often proved no simpler genetically than the disorder (Flint and Munafo).
NEURODEVELOPMENTAL GENETICS AND PLEIOTROPY	Risk genes are enriched for synaptic, chromatin and FMRP-target functions and for early expression: risk acts through neurodevelopment. A continuum runs from intellectual disability through autism and ADHD to schizophrenia. De novo mutations and the paternal-age effect. Cross-disorder pleiotropy and the genetic p-factor: shared common-variant risk across disorders (Cross-Disorder PGC).
HERITABILITY ACROSS DISORDERS	Twin-based heritability (population variance ratio, not an individual statement, not immutable): schizophrenia about 80%, bipolar about 85%, autism about 80%, ADHD about 74%, major depression about 37%, generalised anxiety about 30%, alcohol use about 50%, OCD higher in child-onset. SNP-based heritability is lower than twin heritability (part of missing heritability).
SCHIZOPHRENIA GENETICS (FLAGSHIP)	Heritability about 80%; architecture is highly polygenic plus rare CNVs and de novo variants. GWAS and the C4 / synaptic-pruning story; 22q11.2 deletion the largest single risk; candidate-gene history (COMT, DISC1, NRG1, DTNBP1); endophenotypes (P50, PPI); gene-environment interaction (cannabis, urbanicity, migration, obstetric complications, paternal age); neurodevelopmental model; polygenic risk scores; genetic overlap with bipolar.
PHARMACOGENETICS AND PHARMACOGENOMICS	Pharmacogenetics is single-gene, pharmacogenomics is genome-wide drug response. CYP2D6 and CYP2C19 metaboliser phenotypes (poor, intermediate, normal, ultrarapid): CYP2D6 for risperidone, aripiprazole, tricyclics; CYP2C19 for escitalopram, clozapine. Immune-mediated: HLA-B*15:02 and carbamazepine Stevens-Johnson syndrome (screen first; frequent in South-East Asian and some Indian groups), HLA-A*31:01. Guidelines: CPIC, DPWG.

The whole picture in one table	
DISCRIMINATE: DESIGN AND PEDIGREE	Match the question to the design: familial? family study; genes vs shared environment? twin; genes vs rearing? adoption; roughly where? linkage; which common variants? GWAS; a rare cause in this patient? chromosomal microarray or sequencing; predict aggregate risk? polygenic score; drug response? pharmacogenetic test. Read a pedigree (squares male, circles female, filled affected, arrow proband). Pitfalls: assortative mating, phenocopy, incomplete penetrance, genetic heterogeneity.
GENETIC COUNSELLING	Non-directive; use empirical recurrence risks, not Mendelian ratios: offspring of one parent with schizophrenia about 10 to 13%, both parents about 40 to 46%, sibling about 9%; bipolar offspring about 10 to 15%. Refer to clinical genetics for dysmorphism, intellectual disability or a suspected CNV. Predictive and prenatal testing carry ethical weight; polygenic scores are not yet clinical. India: consanguinity, disclosure pressure, stigma.
APPLIED VIGNETTES	Counsel a couple (one parent with bipolar) with the empirical offspring risk, non-directively. Screen HLA-B*15:02 before carbamazepine in a patient of South or East Asian ancestry. A child with developmental delay, dysmorphism and later psychosis: order chromosomal microarray, consider 22q11.2, refer. Read a pedigree plus a CYP2D6 poor-metaboliser report and adjust.
CONSOLIDATE	The master mnemonic chains it all together. The retrieval prompts are answer-free (cover and recall). The synthesis map places each disorder on the genetic-architecture plane: common-polygenic to rare-large-effect on one axis, neurodevelopmental load on the other. For any disorder you should be able to place it and name the methods that would find its risk.

References

These notes are grounded in the standard texts (the source hierarchy below); landmark, contested and numeric claims carry a PubMed-verified journal citation. Every PMID here was checked against PubMed this build, and citations whose identifier did not resolve to the cited paper were corrected or dropped.

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PART IV

IV

General & Developmental Psychology

The mind studied as theory: perception, memory, thought and motivation, and how children become who they are.

01 Foundations

02 General psychology

03 The three depth-psychology schools

04 Developmental psychology

05 Discriminate

06 Apply and consolidate

General & Developmental Psychology

Six sections · 23 topics · one complete notes document

Psychology is a Paper-1 staple because examiners test the *logic of the theories*, not just their conclusions. These notes are built to make each theory tell its own story: for every cognitive and affective topic you get the same shape, so the structure itself becomes a memory aid.

Learn how the idea evolved, not just where it landed. First the schools of thought as a map, then the general-psychology functions (perception, memory, thinking and intelligence, motivation, emotion, consciousness, creativity, emotional intelligence, the mind-body question), each told as a history: the early theory, what the next theory fixed and what it still argued about, the mechanism now accepted, its neural correlate and a worked example. Then the three great depth-psychology schools (Freud, Adler, Jung) and the developmental theorists (Erikson, Piaget, Kohlberg, attachment, temperament, Mahler, milestones), and finally the payoff figure that lays the stage theories side by side down one shared age axis. The examinable skill throughout is discrimination: telling James-Lange from Cannon-Bard, Piaget from Vygotsky, Freud from Jung, and reading a child by stage.

HOW TO USE THESE NOTES

Every general-psychology topic follows one fixed flow: the idea in brief, then the **theories in the order they appeared** (what each fixed, what stayed debated), then the **currently accepted mechanism**, then its **neural correlate**, then a worked example. Figures declare one axis and code it in colour and shape: **petrol** marks structure and the neutral relay, **coral** marks conflict, pathology or the point of debate, and **marigold** highlights the accepted answer. Watch for the boxes marked **Good to remember**: they gather every named theorist, stage, age and hard classification in one place so the reference facts sit apart from the reasoning.

Foundations

1 · Orientation: the schools of psychology as a map

General and developmental psychology begins with a single most useful thing to fix before any of the detail, the **map**: psychology is not one theory of the mind but a small set of competing **lenses,** each of which explains behaviour by looking at a different **unit of analysis**. A biologist looks at the brain, a cognitivist at information flow, a behaviourist at the observable response, a psychodynamicist at the unconscious, a humanist at the striving self. The paper does not usually ask you to pick which school is *correct*; it asks you to recognise which lens a given claim, therapy, or experiment belongs to, and to know whose name sits under it. Almost every later topic on these notes (perception, memory, thinking, motivation, emotion, then the developmental theorists) is a special case of one or more of these lenses (Kaplan & Sadock 2024).

The second orienting idea, and the spine that recurs across these notes, is that the schools appeared in a **historical sequence** in which each usually fixed a gap the last one left open. Introspection could not be verified, so behaviourism banished the inner world and studied only

stimulus and response; behaviourism could not explain language or memory, so the cognitive revolution reopened the mind as information processing; none of the laboratory schools spoke to meaning or suffering, which is where the psychodynamic and humanistic traditions had always lived. Hold that as an *evolution of theories*, because most functions on these notes are best learned as the theory that came first, what it fixed, what it left debated, then the currently accepted account and its neural correlate. This orientation topic lays out the five lenses and previews the developmental theorists; the topics that follow pay them off.

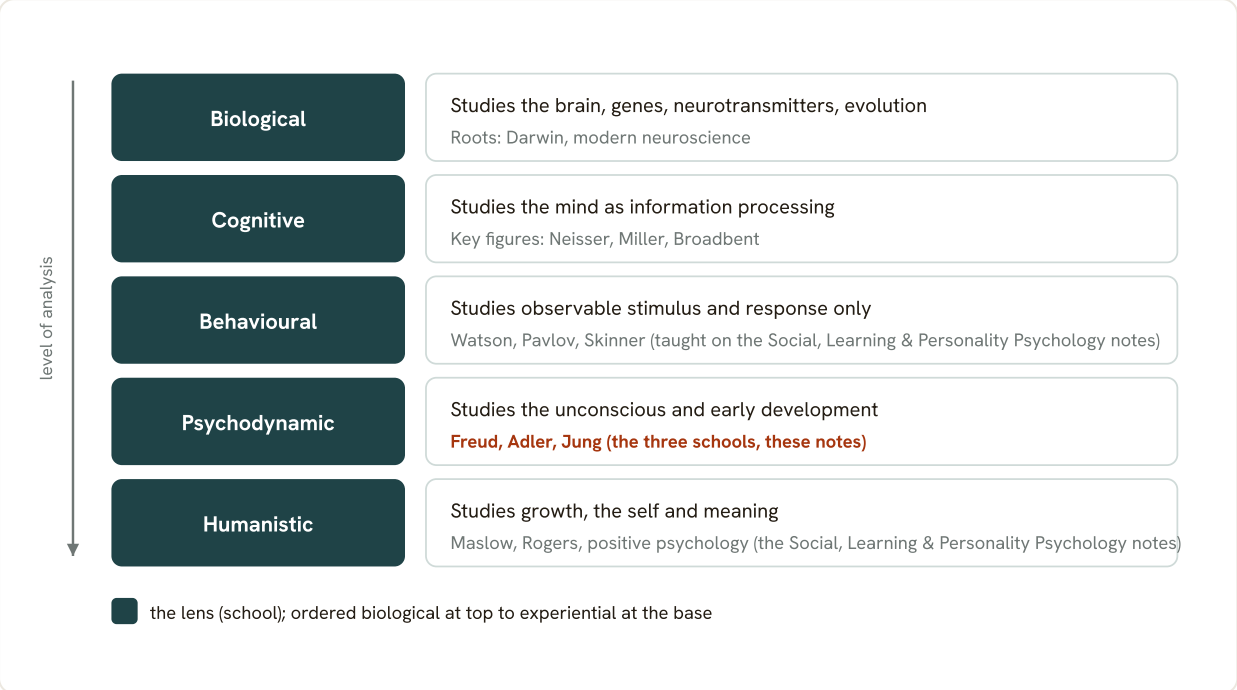


Fig 4.1 The five schools of psychology as one map. Each lens defines its own unit of analysis and answers a different question about the same mind, and each historically arose partly to fix what the previous lens left out: behaviourism against introspection, the cognitive revolution against radical behaviourism, humanistic psychology against both. These notes teach the three depth-psychology schools (Freud, Adler, Jung) in full and the developmental theorists; behaviourism, social psychology and the rest of personality theory are the Social, Learning & Personality Psychology notes.

1.1 Why a map, not a list: the mind through competing lenses

Each school is defined by its unit of analysis. The reason five schools coexist rather than one replacing all others is that they answer different questions about the same behaviour, and each is strongest exactly where the others are silent. A useful discipline for the viva is to ask, of any statement about the mind, "at what level is this explanation pitched?": molecules and circuits (biological), representations and computations (cognitive), observable contingencies (behavioural), unconscious conflict and early development (psychodynamic), or growth, agency and meaning (humanistic). The same clinical fact, say a patient's low mood, is a serotonergic and limbic-circuit story to the biological lens, a negative cognitive schema to the cognitive lens, a loss of reinforcement to the behavioural lens, an unresolved loss turned inward to the psychodynamic lens, and a blocked need for self-actualisation to the humanistic lens. None is wholly wrong; the exam skill is naming the lens (Kaplan & Sadock 2024; Companion to Psychiatric Studies 2010).

1.2 The five lenses as a map

Bind each school to its unit of analysis and its key figures. This is the schema for the whole set of notes: read the school, hold its unit of analysis (what it counts as data), and attach the names examiners expect. Behaviourism gets its full treatment on the Social, Learning & Personality Psychology notes (learning theory, social and personality psychology); the humanistic school and its modern descendant, positive psychology, are also opened deeper on the Social, Learning & Personality Psychology notes.

Biological (biopsychology)

Unit of analysis: the mind *as brain*. Behaviour is explained by genes, neurotransmitters, hormones, neural circuits, and evolutionary pressures. Data are physiological. This lens underwrites the whole of the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes and the Psychiatric Genetics notes (neuroanatomy, neurochemistry, genetics) and the neural-correlate step of every function. Key roots: Darwin (evolution), Sherrington and the neurophysiologists; in psychiatry it is the dominant explanatory frame.

Cognitive

Unit of analysis: the mind *as information processing*. The mind takes input, encodes, stores, retrieves and transforms it, and produces output, on the deliberate analogy of a computer (the **computer metaphor**). Key figure: Ulric Neisser, whose *Cognitive Psychology* (1967) named and consolidated the field. Underwrites perception, attention, memory, thinking and language, and the cognitive model of therapy.

Behavioural

Unit of analysis: *only observable stimulus and response*. The inner mind is treated as a black box; learning is the lawful change in behaviour produced by conditioning. Key figures: John B. Watson (who launched behaviourism in 1913 and demanded psychology study only observable behaviour) and B. F. Skinner (operant conditioning). Fuller treatment on the Social, Learning & Personality Psychology notes.

Psychodynamic

Unit of analysis: *unconscious drives and early development*. Behaviour is driven by conflict among unconscious forces laid down in childhood. Key figures: Sigmund Freud (psychoanalysis, the structural and psychosexual models), Alfred Adler (individual psychology, inferiority and striving), Carl Jung (analytical psychology, the collective unconscious and archetypes). Underwrites psychodynamic formulation and defence mechanisms.

Humanistic

Unit of analysis: *growth, meaning and the self*. The person is an agent striving toward self-actualisation, studied from the inside (phenomenology) rather than reduced to reflexes or drives. Key figures: Abraham Maslow (hierarchy of needs, self-actualisation) and Carl Rogers (client-centred therapy, unconditional positive regard). Its modern scientific descendant is **positive psychology** (Martin Seligman), which studies well-being, strengths and flourishing. Deeper on the Social, Learning & Personality Psychology notes.

RULE **Name the lens, not the verdict.** The paper rarely asks which school is correct; it asks which unit of analysis a given claim, therapy or experiment belongs to, and whose name sits under it.

HOLD THIS

Five lenses, five units of analysis, five images. Biological = brain, cognitive = computer, behavioural = black box, psychodynamic = iceberg, humanistic = growing self. Attach the right image and lead name and you have placed the school.

PEARL

The five lenses in one line: the biological lens sees a *brain*, the cognitive lens sees a *computer*, the behavioural lens sees a *black box*, the psychodynamic lens sees an *iceberg*, and the humanistic lens sees a *growing self*. If you can attach the right image and the right lead name to a claim, you have placed the school.

1.3 The schools appeared in order, each fixing the last one's gap

Read the schools as an evolution, not a menu. The historical arc is itself examinable and it explains why the field looks as it does. The earliest scientific psychology (Wundt's 1879 Leipzig laboratory, and the introspectionism and structuralism of Wundt and Titchener) tried to catalogue conscious experience by trained self-report; it foundered because introspection could not be independently verified. Behaviourism (Watson 1913, then Skinner) fixed that by refusing to talk about the unobservable mind at all and studying only stimulus and response, which bought rigour at the cost of ignoring meaning, memory and language. The **cognitive revolution** of the 1950s to 1960s (crystallised by Neisser 1967) reopened the black box, arguing that the mind can be studied scientifically *as* information processing without abandoning rigour. Running alongside the laboratory tradition, the psychodynamic school (Freud, from the 1890s) had always addressed the unconscious and development, and the humanistic school (Maslow and Rogers, mid-twentieth century) arose as an explicit "third force" reacting against both behaviourism's mechanism and psychoanalysis's pessimism, insisting on agency and growth. Positive psychology (Seligman, from 1998) is the humanistic impulse rebuilt on empirical method (Kaplan & Sadock 2024).

1.4 The developmental theorists, previewed side by side

Four stage theorists run down one age axis. The second half of this material is developmental psychology, and its core is a small set of theorists who each carved the lifespan into stages, but along *different dimensions*. Previewing them together now prevents the commonest error, which is blurring one theorist's stage into another's at the same age. Freud staged **psychosexual** development by the body zone of libidinal focus; Erikson restaged the whole lifespan as **psychosocial** crises, each a tension to be resolved; Piaget staged **cognitive** development by how the child constructs knowledge; Kohlberg extended Piaget into **moral** reasoning. They share an age scaffold but measure different things, and the discriminate topic later on makes you place a described behaviour with the correct theorist. Attachment (Bowlby and Ainsworth), temperament (Thomas and Chess), and separation-individuation (Mahler) sit alongside them as the relational and constitutional strands.

ROUGH AGE	FREUD (PSYCHOSEXUAL)	ERIKSON (PSYCHOSOCIAL)	PIAGET (COGNITIVE)	KOHLBERG (MORAL)
Infancy (0 to ~1.5 yr)	**Oral**	Trust vs mistrust	**Sensorimotor**	(pre-moral)
Toddler (~1.5 to 3 yr)	**Anal**	Autonomy vs shame and doubt	Sensorimotor into preoperational	Preconventional
Preschool (~3 to 6 yr)	**Phallic (Oedipal)**	Initiative vs guilt	**Preoperational**	Preconventional
School age (~6 to 11 yr)	Latency	Industry vs inferiority	**Concrete operational**	Conventional
Adolescence (~12 yr on)	Genital	**Identity vs role confusion**	**Formal operational**	Postconventional
Adulthood	Genital (mature sexuality)	**Intimacy, then generativity, then integrity**	(formal operational persists)	Postconventional

The developmental theorists on one age axis: same scaffold, different dimensions (body zone, social crisis, cognition, moral reasoning). Exact stage boundaries and full descriptions are paid off in the developmental topics; here, hold the parallelism.

1.5 How these notes is wired to the rest of the paper

Know where each thread is finished. This orientation deliberately opens more than it closes, so keep the cross-references straight. Behaviourism (classical and operant conditioning, learning theory), social psychology and personality theory are given full treatment on the Social, Learning & Personality Psychology notes; the humanistic school and positive psychology also go deeper there. Psychological testing, intelligence measurement and the psychometric properties of scales are the Psychometry, Assessment and Descriptive Psychopathology notes. In these notes, the general-psychology functions (perception, memory, thinking and intelligence, motivation, emotion) each run as an evolution of theories ending in the currently accepted mechanism and its neural correlate, and the developmental theorists each run as a stage model ending in a good-to-remember box. Treat this topic as the index page you flip back to whenever a later claim needs placing on the map.

MNEMONIC

Big Cats Bite Prey Hungrily

The five lenses in appearance-and-argument order: **B**iological, **C**ognitive, **B**ehavioural, **P**sychodynamic, **H**umanistic. Big (Biological, the brain) Cats (Cognitive, the computer) Bite (Behavioural, the black box) Prey (Psychodynamic, the iceberg) Hungrily (Humanistic, the growing self). This is the master mnemonic for these notes: every general-psychology function can be interrogated through these five, in this order, and the letters also seed the structure of the material.

GOOD TO REMEMBER

- **Biological lens:** unit = the brain (genes, neurotransmitters, circuits, evolution); roots in Darwin and neurophysiology; the dominant frame in psychiatry.
- **Cognitive lens:** unit = information processing; the computer metaphor; Ulric Neisser, *Cognitive Psychology* (1967).
- **Behavioural lens:** unit = observable stimulus and response; John B. Watson (behaviourism launched 1913) and B. F. Skinner (operant conditioning); full treatment the Social, Learning & Personality Psychology notes.
- **Psychodynamic lens:** unit = unconscious drives and early development; Sigmund Freud (psychoanalysis), Alfred Adler (individual psychology, inferiority), Carl Jung (analytical psychology, archetypes).
- **Humanistic lens:** unit = growth, meaning and the self; Abraham Maslow (hierarchy of needs) and Carl Rogers (client-centred therapy); modern descendant = positive psychology (Martin Seligman); deeper the Social, Learning & Personality Psychology notes.
- **Positive psychology:** Seligman, from 1998; empirical study of well-being, strengths and flourishing.
- **Historical arc:** Wundt's first psychology laboratory, Leipzig 1879; introspection to behaviourism (Watson 1913) to the cognitive revolution (Neisser 1967); humanistic school as the "third force".
- **Freud (psychosexual):** oral, anal, phallic, latency, genital; staged by body zone of libidinal focus.
- **Erikson (psychosocial):** eight stages of paired crises across the whole lifespan (e.g. trust vs mistrust in infancy, identity vs role confusion in adolescence).
- **Piaget (cognitive, 1896 to 1980):** sensorimotor, preoperational, concrete operational, formal operational.
- **Kohlberg (moral):** preconventional, conventional, postconventional; an extension of Piaget into moral reasoning.
- **Relational and constitutional strands:** attachment (Bowlby and Ainsworth), temperament (Thomas and Chess), separation-individuation (Mahler).

General psychology

2 · Perception and attention

Perception is the exam's most philosophically loaded psychological function, and the one whose theory maps most directly onto psychopathology. The theme of the whole topic is a single argument that runs across a century: whether what we perceive is *read off* the world (data-driven, **bottom-up**) or *constructed* by the brain from expectation (concept-driven, **top-down**), a debate that resolves, in the currently accepted view, into perception as a prediction. That resolution is not academic trivia; it is the mechanistic spine of the modern account of the **hallucination**, which is why this topic carries a dedicated theories-of-hallucinations block at its close. **Learn the debate, and the hallucination theories fall out of it.**

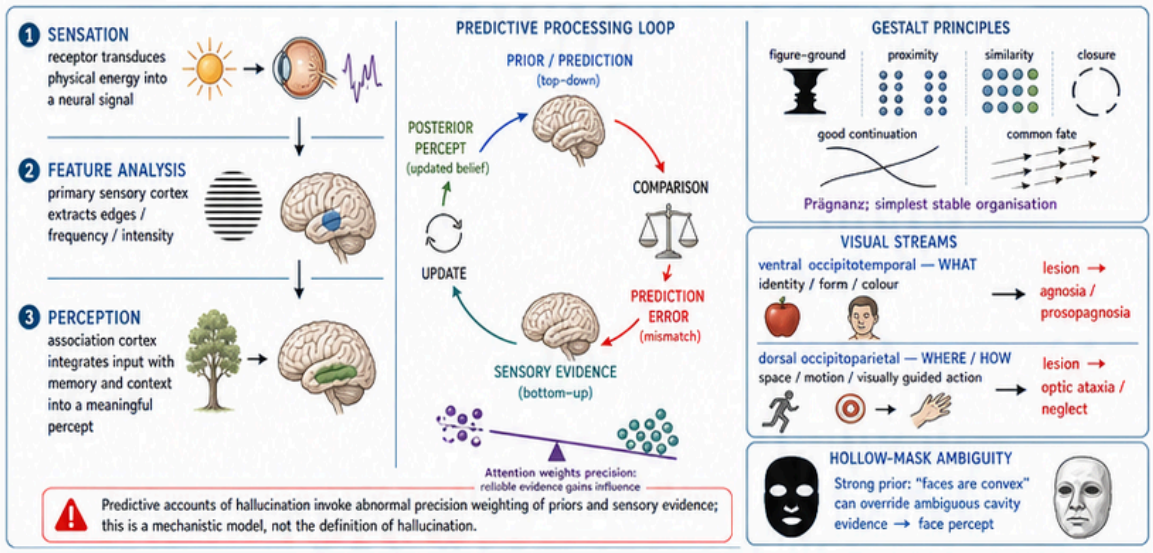


Fig 4.2 Perception: the brain's best constrained guess.

The topic follows the standard evolution-of-theories flow: first the psychophysics that quantified sensation, then the perceptual theories in the order they appeared, each fixing a flaw in the last, then the currently accepted predictive account, its neural correlate in the sensory-association cortex and the two visual streams, a worked example, and finally the parallel evolution of hallucination theory. Attention is folded in as its own theory-sequence, because in the modern view attention is precisely the mechanism that weights bottom-up against top-down. Ground text is Kaplan and Sadock (2024) and the New Oxford Textbook of Psychiatry for the descriptive scaffold.

2.1 Sensation versus perception: the two-stage definition

Sensation. Sensation is the transduction of physical energy at a receptor into a neural signal: light on the retina, pressure on the skin, molecules at the olfactory epithelium. It is bottom-up by definition and largely passive. **Perception** is the active organisation and interpretation of those raw sensations into a meaningful representation of objects and events. The classic exam line is that *sensation is what the sense organ registers, perception is what the mind makes of it*. The distinction matters clinically because the disorders divide along it: a sensory deficit (deafness) sits at the sensation stage, whereas an illusion or hallucination is a disorder of the perceptual stage with the sensory apparatus often intact (Kaplan and Sadock 2024).

Sensation

Receptor-level transduction of a physical stimulus into a neural signal; passive, bottom-up, modality-specific.

Perception

Active organisation and interpretation of sensory data into meaningful percepts; combines bottom-up input with top-down knowledge.

Percept

The finished mental representation of an object or event, the output of perception.

2.2 Psychophysics I: absolute and difference thresholds, Weber-Fechner

Psychophysics, founded by Gustav Fechner in 1860, is the quantitative study of the relation between physical stimulus magnitude and perceived sensation. Two thresholds anchor it. The **absolute threshold** is the smallest stimulus intensity detectable 50 per cent of the time (the criterion of half the trials is the examinable detail, since detection is probabilistic, not all-or-none). The **difference threshold**, or just-noticeable difference (JND), is the smallest change in a stimulus that can be detected 50 per cent of the time.

Weber's law (1834). Ernst Weber found the JND to be a constant fraction of the baseline stimulus, not a fixed absolute amount: the ratio of the change to the baseline (delta-I over I) equals a constant k, the Weber fraction, specific to each sensory dimension. Adding 50 grams to a 1 kg weight is just noticeable; on a 100 gram weight the same 50 grams is glaring, because the fraction, not the absolute amount, governs detection. **Fechner's law** then integrated Weber's law to state that sensation grows as the logarithm of stimulus intensity, so equal ratios of stimulus produce equal steps of sensation. The examinable refinement is **Stevens's power law (1957)**, which replaced the logarithm with a power function that fits a wider range of modalities, expanding for pain and contracting for brightness. What Weber-Fechner fixed was the naive assumption of a linear stimulus-to-sensation map; what it left debated was whether a fixed threshold even exists, a question signal detection theory answered next.

2.3 Psychophysics II: signal detection theory, d-prime and criterion

Signal detection theory (Green and Swets 1966) is the single most important quantitative idea in this topic and a recurring exam favourite, because it dissolves the notion of a fixed threshold. Its claim is that every detection is a decision made against a noisy background, so performance factors into two independent components: *sensitivity* and *bias*. On each trial the observer's internal signal falls somewhere on a continuum; the observer sets a decision **criterion** and says "signal present" whenever the internal evidence exceeds it. This yields the four-cell outcome that must be reproducible on demand: a *hit* (signal present, said yes), a *miss* (present, said no), a *false alarm* (absent, said yes), and a *correct rejection* (absent, said no).

MEASURE	WHAT IT CAPTURES	MOVED BY
d-prime (d')	**Sensitivity: the separation between the signal and noise distributions, a pure measure of the perceptual system's discriminability**	Stimulus strength, acuity, attention, fatigue; NOT by motivation
Criterion (beta or c)	**Response bias: where the observer places the yes/no cut-off, independent of sensitivity**	Payoffs, expectations, base rates; a liberal criterion raises hits and false alarms together, a conservative one lowers both

The two orthogonal parameters of signal detection theory: d-prime is what the system can discriminate, criterion is how willing the observer is to say yes.

The clinical payoff is large. A patient who reports faint voices may have a genuine perceptual change (raised d-prime for that content) or merely a lowered criterion (a bias to say "yes, I hear

it"), and the two demand different formulations. Signal detection theory fixed the fixed-threshold error of classical psychophysics and, crucially, was the first framework to make the perceiver's *expectation and bias* a formal, measurable part of perception, prefiguring the top-down and predictive theories that follow.

TRAP d-prime is **sensitivity** (moved by stimulus strength, acuity, attention, not motivation); criterion is **response bias** (moved by payoffs, expectations, base rates). Do not let a lowered criterion be mistaken for a genuine perceptual change.

2.4 Theory era 1: Wundt, structuralism and introspection

Scientific perception research begins with Wilhelm Wundt's Leipzig laboratory (1879) and the school of **structuralism** (formalised by his student Titchener). Its method was *introspection*: trained observers reported the elementary sensations, images and feelings composing a conscious experience, on the assumption that perception could be decomposed into atomic sensory elements, much as chemistry decomposes compounds. What structuralism fixed was the pre-scientific vagueness of the mind, giving psychology a laboratory method. What it left fatally debated was reliability and reductionism: introspective reports could not be verified between observers, and, more damagingly, perception plainly showed properties that were not present in any of the parts, an objection the Gestalt school turned into a whole movement.

2.5 Theory era 2: Gestalt organisation, the whole over the parts

Gestalt psychology (Wertheimer, Kohler and Koffka, from 1912) is the highest-yield perception theory for the exam and must be reproducible with its laws. Its founding claim, against structuralism, is that *the whole is different from the sum of its parts*: a percept is an emergent, integrated configuration (a Gestalt) that the brain organises spontaneously by self-organising field forces. The master principle is the **law of Prägnanz** (the minimum principle): the perceptual system settles into the simplest, most stable, most regular organisation the stimulus allows. From it descend the grouping laws.

Figure-ground

The visual field is split into a bounded figure and a receding ground; the reversible Rubin vase shows the split is perceptual, not in the stimulus.

Proximity

Elements near one another are grouped together.

Similarity

Elements alike in colour, shape or size are grouped together.

Closure

The system completes incomplete contours into whole, closed figures.

Good continuation

Elements arranged along a smooth line or curve are grouped as a continuous form.

Common fate

Elements moving together in the same direction are grouped together.

What Gestalt fixed was structuralism's atomism, establishing that perception is actively organised and that organisation follows lawful rules. What it left debated was mechanism: the "global field forces" were never specified and the minimum principle could not be quantified or made to yield testable predictions, so the school declined through the 1950s and 1960s. The unresolved question, then, was the source of the organising rules, and it split into two opposed answers: are they built into the incoming stimulation (Gibson) or imposed by the brain's knowledge (Gregory)? That is the bottom-up versus top-down fork, and it is the heart of the topic.

2.6 Theory era 3a: Gibson's direct, bottom-up perception (affordances)

James Gibson's **ecological theory of direct perception** (1966, 1979) is the purest **bottom-up**, data-driven position. Gibson argued that the optic array reaching the eye is already so rich in structure (texture gradients, optic flow, invariants that stay constant as the observer moves) that perception needs no inference, no hypothesis and no stored knowledge: the information is *directly picked up* from the environment. His signature concept is the **affordance**, the action possibility an object offers an organism directly and without deliberation: a chair affords sitting, a handle affords grasping, a cliff-edge affords falling. What Gibson fixed was the poverty-of-the-stimulus assumption that had made perception seem to require guesswork; he showed the ambient array is information-rich and that behaviour in the natural world is often immediate. What he left debated was the equally obvious fact that perception is frequently wrong, ambiguous or illusory, that we can see two things in one figure, and that expectation demonstrably shapes what we see, all of which a purely direct theory struggles to explain.

2.7 Theory era 3b: Gregory's constructivist, top-down perception (perception as hypothesis)

Richard Gregory's **constructivist theory** (1970, 1980) takes the opposite, **top-down**, concept-driven view, reviving Helmholtz's nineteenth-century idea of perception as *unconscious inference*. Gregory's claim is that the retinal image is impoverished and ambiguous, so perception must be an active construction: the brain forms a *perceptual hypothesis*, its best guess about the distal cause, using prior knowledge and expectation, and the percept is that hypothesis, not the raw data. His strongest evidence is precisely the phenomena Gibson could not handle: visual illusions (the Müller-Lyer, the Ponzo, the hollow-mask illusion where a concave face is seen as convex because faces are always convex in experience), and the way a percept flips when the hypothesis changes. What Gregory fixed was the inability of direct perception to explain error, ambiguity and the manifest influence of knowledge on seeing. What he left debated was the reverse problem: if perception is all hypothesis, why is it so fast, so accurate and so stable in the ordinary rich world where Gibson is clearly right? The enduring debate, bottom-up data versus top-down concept, is not resolved by choosing a side but by combining them, which is the modern answer.

2.8 Attention: the theories in time, from early filter to capacity

Attention is the selection and prioritisation of some information for deeper processing at the expense of the rest, and its theory ran a parallel evolution over exactly where in the processing stream selection happens. The exam wants the four models in order with their author and their locus of selection.

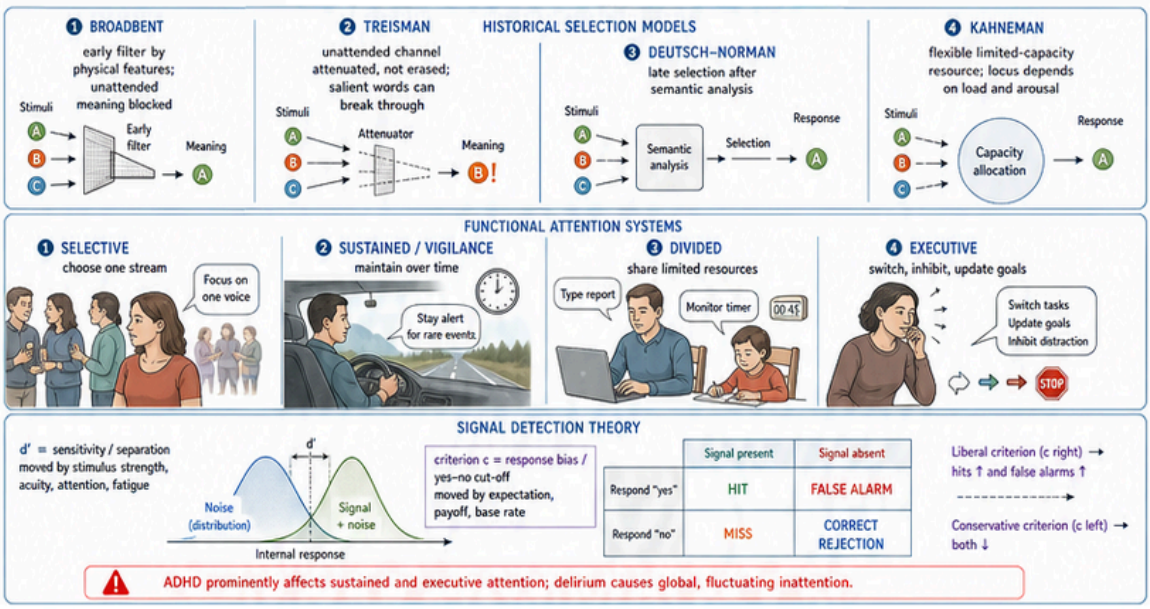


Fig 4.3 Attention: filter, resource and decision.

MODEL (AUTHOR, YEAR)	LOCUS OF SELECTION	WHAT IT FIXED / LEFT OPEN
Broadbent early-filter (1958)	**Early, before meaning: a bottleneck filters by physical features (ear, pitch) and unattended input is blocked before semantic analysis**	Explained selective listening; could not explain why your own name breaks through from the unattended channel (the cocktail-party effect)
Treisman attenuation (1964)	**Early but graded: the filter attenuates rather than blocks the unattended channel; high-salience words with low thresholds still get through**	Fixed Broadbent's leak; left unclear how much late semantic processing really occurs
Deutsch and Norman late-selection (1963, 1968)	**Late, after meaning: all input is analysed for meaning, and selection happens only at the response/memory stage**	Accounted for semantic breakthrough; criticised as metabolically wasteful and hard to reconcile with clear early limits
Kahneman capacity/resource (1973)	**Not a fixed locus at all: attention is a limited pool of mental effort flexibly allocated; selection is early or late depending on load and arousal**	Dissolved the early-late war into a resource question; foreshadowed load theory (Lavie)

The attention sequence: the debate migrated from where the filter sits (Broadbent to Deutsch-Norman) to how much resource is available (Kahneman), the modern framing.

The clinical taxonomy of attention layered on top: *selective* attention (focusing on one stream and ignoring distractors, the cocktail party), *divided* attention (splitting resources across tasks, degraded by load), and *sustained* attention or vigilance (holding focus over time, the deficit probed by the Continuous Performance Test and impaired in ADHD and delirium). In the predictive framework below, attention is reconceived as the mechanism that sets the *weight* given

to incoming sensory evidence relative to prior expectation, which ties the attention story directly into perception.

2.9 Currently accepted: perception as prediction (predictive processing)

The **currently accepted** account, predictive processing or the Bayesian-brain framework (Friston 2010; Clark 2013), synthesises the whole century of debate. The brain is a hierarchical prediction machine: higher levels continuously generate *top-down predictions* (priors) about the causes of sensory input, these predictions are compared against the actual *bottom-up sensory signal*, and only the mismatch, the **prediction error**, is passed up to revise the model. Perception is the brain's best hypothesis (Gregory) constrained by the rich sensory array (Gibson), settling on the interpretation that best explains the data with the least error (a formalisation of Gestalt's Prägnanz as maximising the Bayesian posterior). The relative influence of prior and evidence is set by their *precision* (reliability), and precision-weighting is exactly what attention does: attending to a stimulus raises the precision, and therefore the gain, of its sensory prediction error. This single framework absorbs signal detection theory (criterion is the prior, d-prime is precision-weighted evidence), the bottom-up/top-down fork (both, hierarchically combined), and the attention models (precision allocation), which is why it has become consensus.

RULE **Perception is precision-weighted prediction.** The brain balances bottom-up evidence against top-down priors, and attention is exactly the precision-weighting that sets which one wins.

2.10 Neural correlate: primary versus association cortex, the two streams

The **neural correlate** of the sensation-to-perception pipeline maps cleanly onto the cortical hierarchy. *Primary sensory cortex* (striate cortex V1 for vision, Heschl's gyrus A1 for hearing, postcentral gyrus S1 for touch) performs the first, feature-level, bottom-up analysis: orientation, edges, frequency. *Association (secondary and higher) cortex* integrates these features across modalities and with memory into meaningful percepts; a lesion here produces an *agnosia*, a failure to recognise with intact primary sensation. Above V1 the visual pathway splits into the two anatomically and functionally distinct streams first described by Ungerleider and Mishkin (1982):

Ventral "what" stream

Occipitotemporal, V1 to inferotemporal cortex: object identity, recognition, form and colour. Its damage yields visual agnosia and prosopagnosia.

Dorsal "where/how" stream

Occipitoparietal, V1 to posterior parietal cortex: spatial location, motion, and the visual guidance of action. Its damage yields optic ataxia and, with wider parietal injury, hemispatial neglect.

In the predictive scheme, feedforward connections up the hierarchy carry prediction error while feedback connections carry top-down predictions, and the salience network (anterior insula and dorsal anterior cingulate) with striatal dopamine sets the precision or salience assigned to signals, the node that fails in psychosis (Kaplan and Sadock 2024).

2.11 Worked example: the hollow-mask and a footstep on the stairs

Two everyday demonstrations make the predictive account concrete. **The hollow-mask illusion.** Look at the concave (hollow) back of a face mask and you see it as a normal convex face bulging toward you. The bottom-up sensory data (shading, disparity) correctly specify a hollow surface, but the lifelong prior that "faces are convex" is so strong and high-precision that it overrides the evidence: perception goes with the hypothesis, a direct visualisation of top-down priors winning. The examinable clinical hook is that people with schizophrenia are notably *less* susceptible to this illusion, seeing the true hollow shape, consistent with weakened perceptual priors, which is the mechanism the hallucination theories exploit. **The footstep at night.** Home alone, expecting no one, a creak on the stairs is heard as footsteps and a heart-pounding percept of an intruder; the same creak by day is nothing. Identical sensory input, different prior (and a lowered criterion under fear, in signal detection terms), yielding a different percept, which is perception as prediction in one sentence.

2.12 Theories of hallucinations and their evolution

A **hallucination** is a percept arising without a corresponding external stimulus, experienced with the full force and clarity of a true perception and located in external (objective) space. The full descriptive taxonomy of the disorders of perception (illusions, the pseudohallucination, functional, reflex, extracampine and autoscopic phenomena, and the modality-specific patterns) belongs to the Psychometry, Assessment and Descriptive Psychopathology notes and is treated there in detail (cross-ref: Descriptive Psychopathology, Disorders of Perception). What belongs *here*, as the culmination of the perception theories above, is the mechanism and how the explanation of the hallucination evolved, each theory fixing a defect in the last, ending in the same predictive framework that closed the perception debate.

1. Perceptual-release theory (Hughlings Jackson 1889; West 1962). The oldest neurological account. John Hughlings Jackson proposed a hierarchy in which higher centres normally inhibit lower ones; when higher control is lost (release), lower-level activity is disinhibited and emerges into consciousness. Louis JWest (1962) developed this into the perceptual-release hypothesis: normally, a steady stream of sensory input suppresses stored perceptual traces (memories, images) from reaching awareness; when either sensory input falls (sensory deprivation, eye disease, deafness) or arousal-gating fails, these stored images are *released* and experienced as hallucinations. It elegantly explains the Charles Bonnet hallucinations of the blind, hypnagogic imagery, sensory-deprivation and peduncular hallucinations. What it fixed was the naive idea that a hallucination needs an abnormal stimulus. What it left debated was the specifically psychotic hallucination, where sensory input is intact, and the question of *why* a released image is misattributed to the outside world.

2. Source-monitoring failure (Frith 1992). The cognitive account for psychosis. Christopher Frith proposed that the auditory verbal hallucination is inner speech (subvocal self-talk) that the patient fails to recognise as self-generated. The failure is one of *source monitoring*: a breakdown of the efference-copy or corollary-discharge signal by which the brain normally tags its own motor and cognitive acts as self-produced, so that self-generated inner speech is misattributed to an

external agent. This is why the classic hallucinated voice is in the second or third person and often commenting: it is the patient's own thought, disowned. What it fixed was perceptual release's silence on intact-input psychosis, giving a specific self-versus-other mechanism. What it left debated was the emotional charge and the compelling reality of the voice, and it fit awkwardly with non-verbal and visual hallucinations.

3. Dopaminergic aberrant salience (Kapur 2003). The neurochemical bridge from biology to phenomenology. Building on the finding that midbrain dopamine neurons code reward prediction error and thereby assign *incentive salience* to stimuli (Schultz 1997), Shitij Kapur proposed that in psychosis dysregulated striatal dopamine fires chaotically and assigns **aberrant salience** to internal and external stimuli that do not merit it. Neutral events, thoughts and percepts become urgently, inexplicably significant; hallucinations are the direct experience of aberrant salience attached to a percept, and delusions are the cognitive effort to explain that unbidden significance. It powerfully unifies the pharmacology (antipsychotics are D2 blockers), the prodromal "delusional mood," and the salience of psychotic symptoms. What it fixed was the mechanistic gap between the dopamine hypothesis and lived experience. What it left debated was the finer computational question of *why* salience becomes aberrant, answered by the next account.

4. Predictive-coding / predictive-processing account (Fletcher and Frith 2009; Corlett, Powers, Sterzer, and colleagues, 2010s). The **currently accepted**, integrative mechanism, and the one to lead with. Within the Bayesian-brain framework of 2.9, a hallucination is a percept dominated by an *over-weighted prior*: when top-down predictions are given excessive precision relative to bottom-up sensory evidence, the brain "hears" or "sees" what it expects even in the absence of, or against, the sensory data. Powers and Corlett's conditioned-hallucination experiments demonstrate this directly, showing that people prone to hallucinations over-rely on priors. This single account subsumes its predecessors: perceptual release is the special case where *weak* sensory input lets priors dominate; source-monitoring failure is a miscomputed prediction about the agency of self-generated signals (a failed forward model); and aberrant salience is aberrant precision-weighting of prediction errors driven by dopamine. The hollow-mask finding (2.11), reduced illusion susceptibility in schizophrenia, is the same story seen from the perceptual side. Perception is prediction; the hallucination is prediction unmoored from evidence.

- **Perceptual release** - Hughlings Jackson 1889, West 1962; reduced input plus lost gating releases stored images.
- **Source-monitoring failure** - Frith 1992; inner speech misattributed as external via failed efference copy.
- **Aberrant salience** - Kapur 2003; dysregulated dopamine assigns undue salience; antipsychotics are D2 blockers.
- **Predictive coding** - Fletcher and Frith 2009; over-weighted priors override evidence; the currently accepted account that unifies the earlier three.

HOLD THIS

The hallucination is an over-weighted prior overriding sensory evidence. The four theories are a historical progression (perceptual release, source-monitoring failure, aberrant salience, predictive coding), not rivals, and predictive coding unifies them.

COMMON TRAP

Do not conflate the four hallucination theories as rivals to be chosen between; the exam rewards showing they are a *historical progression* that the predictive-coding account finally unifies. Also keep the two "Friths" straight in your head: the source-monitoring model is Christopher Frith's cognitive theory; the predictive-coding synthesis is Fletcher and Frith (2009), same Chris Frith, later work. And note perceptual release predicts hallucinations from *reduced* input (blindness, deafness), the opposite of what a naive "overstimulation" guess would say.

PEARL

The whole topic is one idea told twice. In normal perception the brain balances bottom-up evidence against top-down priors, weighted by precision (attention). In hallucination that balance tips toward the prior. Every theory on the page, from signal detection's criterion to Kapur's aberrant salience, is a statement about where that balance sits and what moves it. If you can say "perception is precision-weighted prediction, and psychosis is a precision failure," you can reconstruct the rest.

GOOD TO REMEMBER

- **Fechner (1860):** founded psychophysics; absolute threshold = detected 50% of the time.
- **Weber (1834):** JND is a constant fraction of the baseline stimulus (delta-I / I = k, the Weber fraction).
- **Fechner's law:** sensation grows as the logarithm of stimulus intensity; Stevens (1957) refined it to a power law.
- **Signal detection theory (Green and Swets 1966):** d-prime = sensitivity; criterion = response bias; hit / miss / false alarm / correct rejection.
- **Wundt (1879), Titchener:** structuralism, introspection, elementary sensations; failed on reliability and reductionism.
- **Gestalt (Wertheimer, Kohler, Koffka, 1912):** whole differs from the sum of parts; law of Prägnanz; figure-ground, proximity, similarity, closure, good continuation, common fate.
- **Gibson (1966/1979):** direct, bottom-up perception; affordances; optic array is information-rich.
- **Gregory (1970):** constructivist, top-down perception; perception as unconscious inference and hypothesis; explains illusions.
- **Broadbent (1958):** early-filter attention (physical features, before meaning).
- **Treisman (1964):** attenuation (unattended channel dampened, not blocked).
- **Deutsch and Norman (1963/1968):** late selection (all input analysed for meaning, selection at response).
- **Kahneman (1973):** capacity/resource model of attention (limited effort, flexibly allocated).
- **Attention types:** selective (cocktail party), divided (load-limited), sustained (vigilance, CPT, ADHD/delirium).
- **Predictive processing (Friston 2010; Clark 2013):** currently accepted; hierarchical priors vs prediction error, precision-weighting = attention.
- **Neural correlate:** primary sensory cortex (V1/A1/S1) = features; association cortex = meaning (lesion = agnosia); ventral "what" (occipitotemporal) vs dorsal "where/how" (occipitoparietal), Ungerleider and Mishkin (1982).
- **Perceptual release (Hughlings Jackson 1889; West 1962):** lost higher inhibition + reduced sensory input releases stored images (Charles Bonnet, sensory deprivation).
- **Source-monitoring failure (Frith 1992):** inner speech misattributed as external via failed efference copy.
- **Aberrant salience (Kapur 2003):** dysregulated dopamine assigns undue salience; delusion explains it; antipsychotics = D2 block.
- **Predictive-coding hallucination (Fletcher and Frith 2009; Corlett, Powers, Sterzer):** over-weighted priors override sensory evidence; unifies the earlier three.

3 · Memory: types, processes and forgetting

Memory is the set of processes by which experience is **encoded**, held over time (**storage**), and later brought back into use (**retrieval**). It is not one faculty but a family of dissociable systems, and the history of the field is the story of that family being progressively subdivided: from Ebbinghaus measuring one homogeneous "memory" as a decaying trace, to the boxes-and-arrows stores of the multi-store model, to the componential working memory that replaced the single short-term box, to Tulving's taxonomy of long-term systems that a single amnesic brain can double-dissociate. **Read the topic as an evolution, not a list.** Each model is best understood by what it fixed in its predecessor and what it left unsettled for the next, and the whole argument is anchored in one patient whose surgery in 1953 proved the divisions are real in tissue.

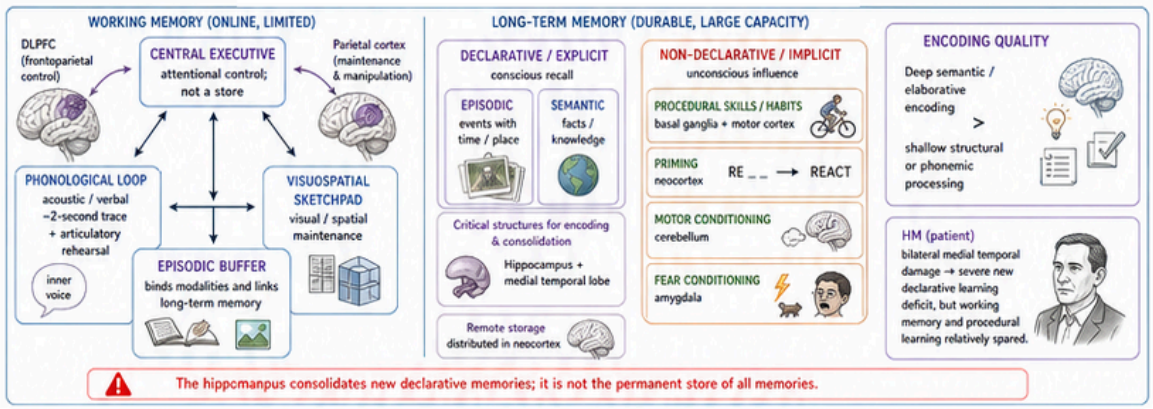


Fig 4.4 Memory is plural: workspace, systems and brain.

For the exam, the payload is fourfold: the ordered theories with their named authors and the specific findings that forced each revision; the taxonomy of long-term memory (episodic, semantic, procedural; declarative versus non-declarative; explicit versus implicit); the four mechanisms of forgetting plus the modern twist that retrieval itself destabilises a memory (reconsolidation, the misinformation effect); and the neural correlate that maps each memory system onto a distinct structure. The functions cross-refer directly to the Functional Neuroanatomy & Neurophysiology notes synaptic plasticity: the cellular basis of the encoding described here is long-term potentiation in the hippocampus.

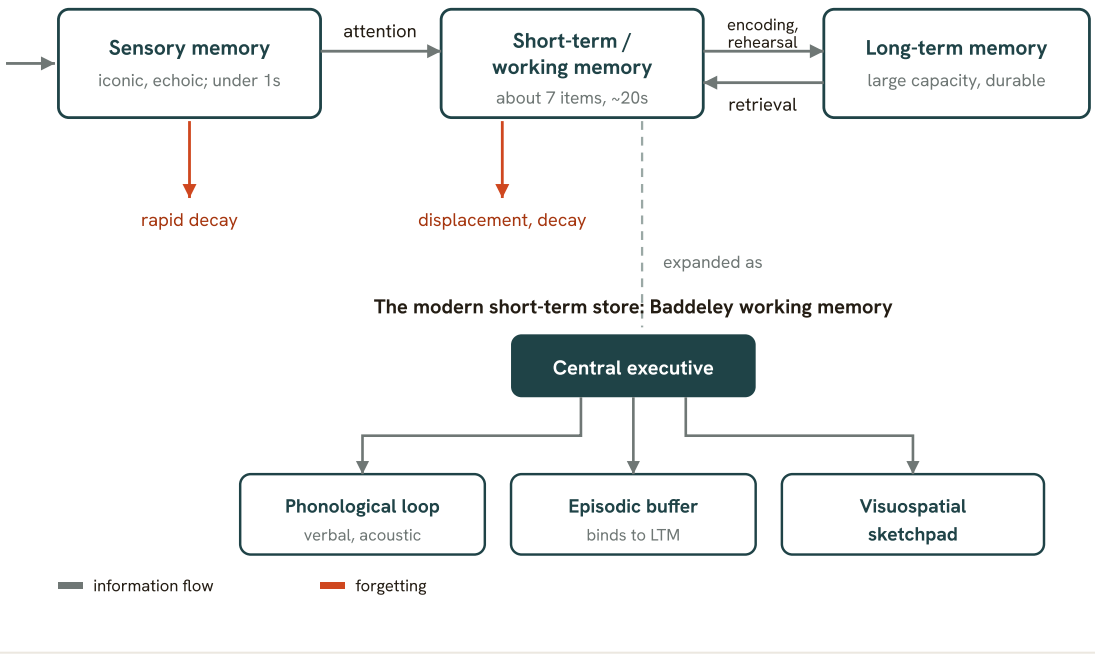


Fig 4.5 The memory system: the Atkinson-Shiffrin multi-store model (top) reads left to right, with attention passing sensory traces into a limited short-term store and rehearsal encoding them into a durable long-term store, from which material is retrieved back. Information is lost by rapid decay from sensory memory and by displacement or decay from the short-term store (coral). Baddeley and Hitch reconceived the short-term store as working memory (below): a central executive directing a phonological loop, a visuospatial sketchpad and an episodic buffer that binds information and links to long-term memory.

3.1 Ebbinghaus: forgetting as a measurable curve, and the savings method

The first quantitative theory. Hermann Ebbinghaus (1885), experimenting on himself with lists of meaningless three-letter *nonsense syllables* (chosen to strip out prior meaning), turned memory into a measurable quantity for the first time. His two enduring contributions are the **forgetting curve**, showing that retention falls steeply in the first hours after learning and then flattens into a long slow tail, and the **savings method**, his index of retention: even when a list can no longer be recalled, relearning it to the original standard takes fewer trials than learning it fresh, and that saving in trials quantifies the memory that survives below the threshold of conscious recall. He also first described the *spacing effect* (learning distributed over time beats massed cramming) and the *serial position* advantage. **What it fixed.** It replaced philosophical introspection about memory with a reproducible curve. **What it left debated.** It treated memory as one undifferentiated store decaying with time, so it could describe the rate of forgetting but said nothing about its architecture or its cause, the very questions the next century answered (Kaplan and Sadock 2024).

3.2 Atkinson and Shiffrin: the multi-store (modal) model and its three stores

The boxes-and-arrows model. Atkinson and Shiffrin (1968) proposed the **multi-store** model (the "modal model") in which information flows sequentially through three structurally separate stores, gated by attention and rehearsal. Incoming stimulation first enters **sensory memory**, a modality-specific register of very large capacity and sub-second duration (iconic for vision, echoic for hearing); whatever is *attended* passes into **short-term** store; and material that is *rehearsed* is transferred into **long-term** store. The stores differ on three axes: encoding, capacity, and duration. Short-term store holds roughly seven items (Miller's 7 plus or minus 2, 1956) for about 15 to 30 seconds and codes mainly acoustically; long-term store is effectively unlimited in capacity and duration and codes mainly semantically. Crucially, Atkinson and Shiffrin distinguished the fixed *structural* stores from flexible *control processes* (rehearsal, coding, retrieval strategies) that the person deploys within them.

What it fixed. It gave forgetting an architecture, explaining why a phone number vanishes in seconds yet a childhood address lasts decades, and it accounted for the serial-position curve: the primacy effect reflects rehearsed items already in long-term store, the recency effect reflects the last items still sitting in short-term store (Glanzer and Cunitz 1966 abolished only the recency limb with a filled delay). **What it left debated.** Two weaknesses forced the next models. First, it treated short-term store as a single passive holding box, yet neuropsychological patients showed the box had parts. Second, it made rehearsal the sole route into long-term memory, which is empirically false: depth of meaning matters more than repetition, the gap that levels-of-processing filled (Kaplan and Sadock 2024).

<2 s	7 ± 2	15 to 30 s
SENSORY MEMORY	SHORT-TERM ITEMS (MILLER)	SHORT-TERM DURATION

3.3 Baddeley and Hitch: working memory replaces the single short-term box

From passive store to active workspace. Baddeley and Hitch (1974) showed that the unitary short-term box could not be right: participants could hold a string of digits *and* simultaneously reason or comprehend prose, which is impossible if a single limited store does both. They replaced it with **working memory**, a multi-component system for the temporary holding *and manipulation* of information. In the model, a limited-capacity *central executive* (an attentional controller, not a store) supervises two modality-specific slave systems: the *phonological loop* for speech-based and acoustic material (a store that decays in about two seconds unless refreshed by articulatory rehearsal) and the *visuospatial sketchpad* for visual and spatial material. Baddeley (2000) later added a fourth component, the *episodic buffer*, a general store that binds information across the two slave systems and links it to long-term memory, explaining how we integrate what we see and hear into a single remembered scene.

What it fixed. It explained dual-task performance (two tasks in the same code interfere, two in different codes do not) and made rehearsal optional rather than the only mechanism, and it mapped cleanly onto brain lesions in a way the single box never did. **What it left debated.** The central executive stayed a poorly specified "homunculus," and the number and independence of the components remained contested, so rival accounts followed (Cowan's embedded-processes model treats working memory as the activated portion of long-term memory plus a focus of attention). This is where the field currently sits (Kaplan and Sadock 2024).

3.4 Craik and Lockhart: levels of processing, from structure to depth

Not where you store it, how deeply you process it. Craik and Lockhart (1972) attacked the multi-store assumption that retention depends on *how long* an item sits in a store. They argued instead that durability depends on the *depth* of processing at encoding along a shallow-to-deep continuum: *shallow* structural processing (the word's typeface) and phonemic processing (its sound) leave weak traces, whereas *deep* semantic processing (its meaning, its links to what you already know) leaves durable ones. This reframed Atkinson and Shiffrin's rehearsal: mere *maintenance rehearsal* (rote repetition) keeps material available briefly but transfers little to long-term memory, whereas *elaborative rehearsal* (giving it meaning and associations) is what actually encodes it. **What it fixed.** It explained the store-model's key failure, why meaningful material is remembered far better than repeated-but-meaningless material, and it grounds every effective study technique. **What it left debated.** "Depth" was circular (we call processing deep because it is well remembered), and the framework describes encoding without specifying the storage systems themselves, which Tulving supplied (Kaplan and Sadock 2024).

RULE **Depth of meaning beats duration in a store.** Elaborative (semantic) rehearsal encodes; maintenance (rote) rehearsal only holds material briefly and transfers little to long-term memory.

3.5 Tulving: the taxonomy of long-term memory

Long-term memory is plural. Tulving (1972, 1985) subdivided long-term store into dissociable systems, the taxonomy the exam tests most heavily. The master division is **declarative** (explicit) memory, available to conscious recollection and expressible in words, versus **non-declarative**

(implicit) memory, expressed through performance without conscious access. Declarative memory splits into *episodic* memory (personally experienced events tagged with time and place, "remembering") and *semantic* memory (context-free general facts and knowledge, "knowing"). Non-declarative memory is a heterogeneous family: *procedural* memory (motor and cognitive skills and habits, riding a bicycle), *priming* (facilitated processing of a recently encountered stimulus), simple *classical conditioning*, and *non-associative* learning (habituation, sensitisation). The defining claim is that these are separable in the brain, not merely conceptual labels.

CLINICAL ANCHOR

The declarative/non-declarative line is the single most useful memory distinction in clinical work. Amnesia (from medial temporal or diencephalic damage) devastates declarative memory while leaving non-declarative memory intact, which is why an amnesic patient can learn a mirror-drawing skill perfectly across days yet swear each morning they have never done it. The mirror image is Alzheimer disease, where declarative (especially episodic) memory fails first because the pathology begins in the medial temporal lobe.

3.6 The four mechanisms of forgetting

Why memories fail. Four classical mechanisms are distinguished, and they are not mutually exclusive.

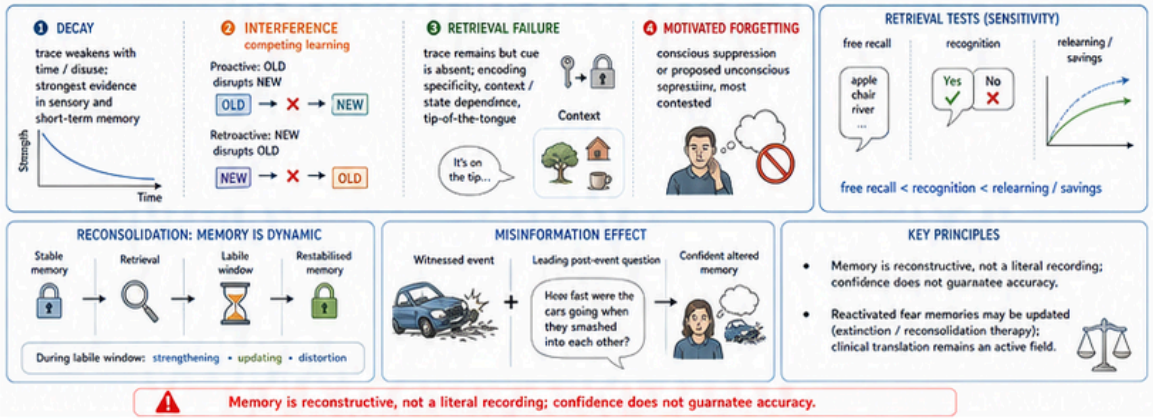


Fig 4.6 Why we forget, and why recall can change memory.

Decay (trace decay)

The memory trace fades with the mere passage of time if not used (Thorndike's law of disuse). Best supported for sensory and short-term stores; heavily disputed for long-term memory, where critics (McGeoch; Nairne 2002) argue it is the intervening events, not time itself, that cause the loss.

Interference

Other learning competes with the target memory. *Proactive* interference: older learning disrupts newer (your old phone number intrudes on the new one). *Retroactive* interference: newer learning disrupts older (learning Spanish erodes your French). The single commonest cause of everyday long-term forgetting.

Retrieval failure (cue-dependent forgetting)

The trace is intact but inaccessible because the right retrieval cue is absent; the memory returns when the cue is restored. The tip-of-the-tongue state is the everyday case; encoding-specificity and context-dependent and state-dependent recall are its corollaries. Recall (cue-free) is the most sensitive retrieval test, recognition easier, relearning (savings) the most sensitive of all.

Motivated forgetting

Emotionally threatening material is kept out of awareness, whether by active suppression or by unconscious repression (the psychodynamic account). Invoked for the amnesia of trauma; the most theoretically contested of the four.

TRAP **Pro**active interference = **old** learning disrupts new (old phone number intrudes); **retro**active interference = **new** learning disrupts old (Spanish erodes French). The prefix names what is disrupted, not what does the disrupting.

3.7 Reconsolidation and the misinformation effect: memory as reconstruction

Retrieval changes the memory. The modern correction to every box model is that a stored memory is not a fixed recording played back unchanged. On retrieval a consolidated memory returns to a labile state and must be restabilised, a process called *reconsolidation*, during which it can be updated, strengthened, or corrupted before it is re-fixed. This makes memory reconstructive rather than reproductive, and it is the mechanism behind Loftus's **misinformation effect**: post-event information, especially a subtly leading question, is incorporated into the original memory so that eyewitnesses confidently report details they never saw (Loftus and Palmer 1974 showed the verb in "how fast were the cars going when they smashed / hit each other" shifted both speed estimates and later false memories of broken glass).
Why it matters. It undermines the reliability of confident eyewitness testimony and recovered memories, and reconsolidation is now an active treatment target, using the reactivation window to weaken maladaptive fear memories in PTSD (Kaplan and Sadock 2024).

3.8 The currently accepted synthesis

A componential working memory feeding a distributed, systems-organised long-term memory. The *currently accepted* account is not any single historical model but their integration. A limited-capacity working memory (a componential attentional workspace, whether framed as Baddeley's components or as the activated portion of long-term memory in Cowan's embedded-processes model) selects and manipulates incoming information; material processed deeply and elaboratively is *consolidated* into long-term memory, a hippocampus-dependent process that gradually transfers the memory to distributed neocortical stores where it becomes independent of the hippocampus (systems consolidation). Long-term memory is not one store but the parallel taxonomy of dissociable systems (declarative and non-declarative), and forgetting is chiefly cue-dependent retrieval failure and interference rather than passive decay, with retrieval itself capable of updating the trace through reconsolidation (Kaplan and Sadock 2024).

3.9 The neural correlate: one structure per memory system

The systems map onto tissue. The strongest evidence that Tulving's taxonomy is biologically real is that each system has a distinct **neural correlate** and can be lost in isolation.

MEMORY SYSTEM	CRITICAL STRUCTURE(S)	EVIDENCE / NOTE
Declarative encoding and consolidation	**Hippocampus and the wider medial temporal lobe (entorhinal, perirhinal, parahippocampal cortex); medial diencephalon (mammillary bodies, dorsomedial thalamus)**	Bilateral MTL damage causes anterograde amnesia (HM, EP); CA1-restricted lesions give milder amnesia (RB); diencephalic version is Korsakoff. Cellular basis is hippocampal LTP (cross-ref the Functional Neuroanatomy & Neurophysiology notes).
Working memory	**Prefrontal cortex (dorsolateral PFC for manipulation, ventrolateral for maintenance), with parietal cortex**	Frontal lesions impair manipulation, monitoring and retrieval strategy; fMRI shows PFC engagement scaling with memory load.
Procedural / skill and habit learning	**Basal ganglia (striatum), with cerebellum and motor cortex**	Preserved in MTL amnesia; degraded in Parkinson and Huntington disease.
Classical conditioning of motor responses	**Cerebellum (deep nuclei and cortex)**	Cerebellar lesions abolish the conditioned eyeblink response while sparing the reflex.
Emotional (fear) conditioning	**Amygdala (with hippocampus for context)**	Amygdala attaches affect to stimuli; model for anxiety disorders. PFC drives extinction.
Remote consolidated memory	**Distributed neocortex**	Old memories survive hippocampal loss (temporally graded retrograde amnesia); slow-wave sleep aids declarative consolidation via hippocampal replay.

The double dissociation across these rows, declarative lost while procedural is spared, is the anatomical proof that "memory" is plural.

COMMON TRAP

Do not equate "short-term memory" with "working memory," and do not call the hippocampus the store of memories. The hippocampus is required to *encode and consolidate* new declarative memories, not to store old ones: consolidated remote memories live in distributed neocortex, which is why HM kept childhood memories while forming no new ones. Working memory (an active PFC workspace) is a superset of the older passive short-term store.

3.10 Worked example: patient HM and the amnesic dissociation

The case that founded the field. Henry Molaison (patient HM) underwent bilateral medial temporal lobectomy by William Scoville in 1953 for intractable epilepsy, removing much of both hippocampi and adjacent cortex. The result, documented over decades by Brenda Milner, was a clean dissociation that no single-store model could accommodate. HM had a dense *anterograde amnesia*: he could not form new declarative memories, failing to learn new facts or events and never recognising his caregivers or learning that his parents had died. Yet three functions were

preserved, and each proves a separate system. His *short-term / working memory was intact* (he could hold a number in mind and converse normally), proving short-term and long-term stores are separate. His *remote memories from before surgery were largely spared*, proving the hippocampus is needed to *form* declarative memories, not to *store* consolidated ones. And most strikingly, he could *learn new motor skills* (mirror-drawing improved across sessions) while insisting each time he had never attempted the task, proving non-declarative (procedural) memory is independent of the medial temporal lobe. **One patient, three dissociations.** HM is the empirical bridge from the abstract boxes of Atkinson and Shiffrin to the tissue-level taxonomy of Tulving, and Atkinson and Shiffrin themselves cited his profile to justify the short-term versus long-term split (Kaplan and Sadock 2024).

HOLD THIS

HM proves memory is plural: one patient, three dissociations. Intact short-term memory (STM separate from LTM), spared remote memory (hippocampus forms but does not store declarative memory), and preserved mirror-drawing (procedural memory is independent of the medial temporal lobe).

GOOD TO REMEMBER

- **Ebbinghaus (1885):** forgetting curve (steep early loss then a tail) and the savings method (relearning is faster); used nonsense syllables; also the spacing effect.
- **Atkinson and Shiffrin (1968):** multi-store / modal model, three stores: sensory, short-term, long-term; attention gates the first transfer, rehearsal the second; structural stores versus control processes.
- **Sensory memory:** modality-specific, huge capacity, under about 2 seconds; iconic (visual) and echoic (auditory).
- **Short-term store:** about 7 plus or minus 2 items (Miller 1956), about 15 to 30 seconds, mainly acoustic coding.
- **Long-term store:** effectively unlimited capacity and duration, mainly semantic coding.
- **Baddeley and Hitch (1974) working memory:** central executive (attentional controller) plus phonological loop and visuospatial sketchpad; episodic buffer added by Baddeley (2000).
- **Craik and Lockhart (1972):** levels of processing; depth (semantic) beats shallow (structural/phonemic); elaborative rehearsal beats maintenance rehearsal.
- **Tulving (1972, 1985):** declarative (explicit) = episodic + semantic; non-declarative (implicit) = procedural, priming, conditioning, non-associative.
- **Serial position:** primacy (long-term store, rehearsed) plus recency (short-term store); recency abolished by a filled delay (Glanzer and Cunitz 1966).
- **Four types of forgetting:** decay, interference (proactive = old disrupts new; retroactive = new disrupts old), retrieval failure / cue-dependent, motivated forgetting (suppression/repression).
- **Loftus (misinformation effect):** post-event leading information corrupts the memory; basis of unreliable eyewitness testimony; mechanism is reconsolidation of a labile trace on retrieval.
- **Neural correlates:** hippocampus and medial temporal lobe = declarative encoding (LTP, the Functional Neuroanatomy & Neurophysiology notes cross-ref); prefrontal cortex = working memory; basal ganglia and cerebellum = procedural; cerebellum = conditioned motor responses; amygdala = fear conditioning; distributed neocortex = remote consolidated memory.
- **Patient HM (Henry Molaison):** bilateral medial temporal lobectomy, Scoville 1953, studied by Milner; dense anterograde amnesia with intact short-term memory, spared remote memory, and preserved procedural (mirror-drawing) learning.

4 · Thinking, problem-solving and intelligence theories

This topic pairs the two ends of higher cognition the exam most reliably tests together: the *process* of thinking (how the mind forms concepts, reasons, and solves problems, and how that process fails through bias) and the *capacity* for it (intelligence, and the century-long fight over whether it is one thing or many). The first half is a toolkit of named effects (heuristics, biases, mental set, insight) that recur in cognitive psychology, in cognitive-behavioural therapy, and in the psychopathology of thought. The second half is a clean evolution-of-theories story, from Spearman's single **g** to the modern **CHC** consensus, that rewards the candidate who can lay the models out in time and say what each one fixed. **One process, one capacity, one debate: is intelligence unitary or plural?**

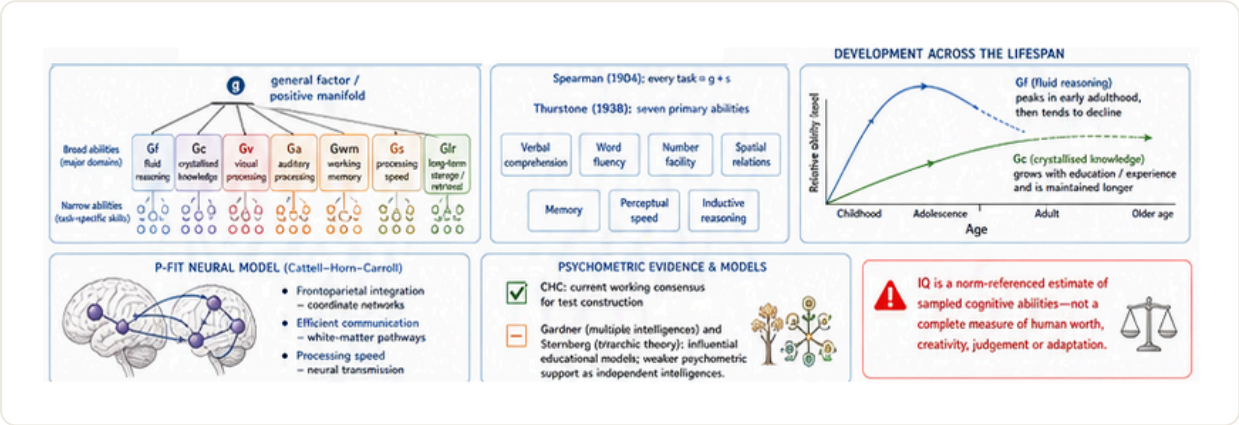


Fig 4.7 Intelligence: one general factor, many broad abilities.

The intelligence half follows the standard evolution-of-theories flow: a definition, then the theories in the order they appeared, each fixing a flaw in the last, then the currently accepted model (CHC), its neural correlate (the parieto-frontal integration theory and processing speed), and a worked example. Note the deliberate split from the Psychometry, Assessment and Descriptive Psychopathology notes: the theories of intelligence are taught here, but the instruments that operationalise them (Binet-Simon, the Wechsler scales, deviation IQ, the diagnostic bands) are taught on the Psychometry, Assessment and Descriptive Psychopathology notes (cross-ref: Psychometry and assessment, IQ testing). Ground text is Kaplan and Sadock (2024) and the New Oxford Textbook of Psychiatry, with the historical chronology cross-checked against the standard intelligence literature (Carroll 1993; Warne 2023).

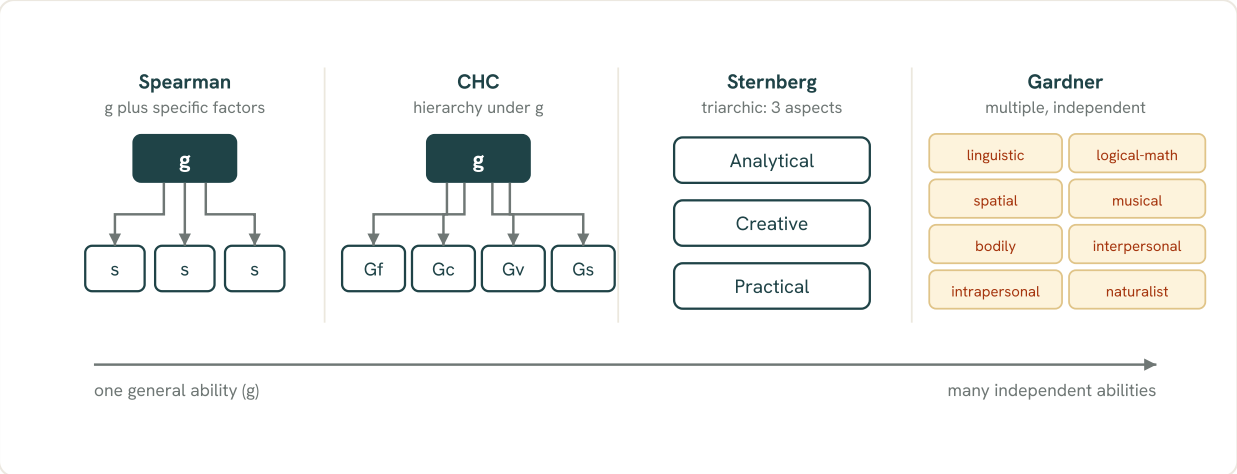


Fig 4.8 The theories of intelligence read as one argument: is intelligence a single thing or many? Spearman's positive manifold pointed to a general factor g with task-specific factors; the Cattell-Horn-Carroll model keeps g but organises the broad abilities (fluid Gf, crystallised Gc, visual Gv, processing speed Gs and more) beneath it, and is the modern working consensus. Sternberg's triarchic model and Gardner's multiple intelligences push toward the plural end, valuing abilities that classic IQ tests miss. Intelligence testing itself is taught on the Psychometry, Assessment and Descriptive Psychopathology notes.

4.1 Thinking and concept formation: the units of thought

Thinking is goal-directed mental manipulation of internal representations (images, words, concepts, propositions) to reach a conclusion, form a judgement, or solve a problem. Its basic unit is the **concept**, a mental category that groups objects, events, or ideas by shared features, letting the mind treat many particulars as one kind and so economise on cognitive effort. **Concept formation** proceeds in two classic ways. On the *classical* view a concept is defined by a set of necessary and sufficient features (a bachelor is unmarried and male and adult). On the more psychologically accurate *prototype* view (Rosch 1975), a concept is organised around a best example or prototype, and membership is graded by family resemblance: a robin is a more prototypical bird than a penguin, and the mind classifies faster the closer an instance sits to the prototype. Clinically, the breakdown of concept formation, the loss of the capacity to abstract and a slide into concrete, over-inclusive, or literal categorisation, is a core sign in schizophrenia and in the frontal and organic states, and is probed by proverb interpretation and card-sorting.

4.2 Reasoning: deductive and inductive

Reasoning is thinking directed at drawing a conclusion from premises, and it comes in two forms the exam contrasts. **Deductive reasoning** moves from general premises to a specific, logically certain conclusion: if all premises are true and the form is valid, the conclusion *must* be true (all humans are mortal; Socrates is human; therefore Socrates is mortal). It is truth-preserving but adds no new content. **Inductive reasoning** moves the other way, from specific observations to a general, probable conclusion: every swan I have seen is white, so swans are probably white. It is content-expanding but not certain, since a single black swan refutes it, and it is the engine of hypothesis-generation and everyday learning. Human reasoning departs systematically from formal logic, as the Wason selection task shows (people fail abstract logical versions but succeed on concrete social ones), which sets up the study of the biases that follow.

4.3 Problem-solving: algorithms versus heuristics

Problem-solving is the sequence of operations that moves a start state to a goal state, and it runs on two contrasting strategies. An **algorithm** is an exhaustive, step-by-step procedure that is *guaranteed* to find the solution if one exists (checking every permutation of a lock, following long division): it is reliable but often slow and effortful, sometimes computationally impossible for large problems. A **heuristic** is a mental shortcut or rule of thumb that reduces a hard problem to a manageable one and usually delivers a good-enough answer fast, at the cost of no guarantee and a systematic vulnerability to error (working backward from the goal, means-ends analysis, hill-climbing). The trade-off is the whole point: algorithms buy certainty with effort, heuristics buy speed with the risk of bias. The specific heuristics Tversky and Kahneman identified are the bridge to the next subtopic.

Algorithm

Exhaustive rule-based procedure guaranteeing a solution; reliable but slow and effortful.

Heuristic

Shortcut or rule of thumb; fast and low-effort but not guaranteed and prone to systematic bias.

Means-ends analysis

A heuristic that repeatedly reduces the difference between the current state and the goal by setting subgoals.

4.4 The Tversky and Kahneman heuristics and biases

The **heuristics-and-biases programme** (Tversky and Kahneman 1974) is the single most examinable block in this half of the topic, because the same biases reappear as cognitive distortions in CBT and as reasoning errors in delusion and depression. The claim is that judgement under uncertainty is governed by a few economical heuristics that are usually useful but produce predictable, replicable errors. Three are core.

HEURISTIC	THE SHORTCUT	THE BIAS IT PRODUCES
Availability	**Judge probability by how easily instances come to mind**	Vivid, recent, or emotionally charged events are over-estimated (fear of plane crashes over car crashes; a doctor over-diagnoses the condition last seen)
Representativeness	**Judge probability by resemblance to a prototype, ignoring base rates**	The base-rate fallacy and the conjunction fallacy (the "Linda problem"); a shy tidy man judged more likely a librarian than a farmer despite farmers being far more numerous
Anchoring and adjustment	**Start from an initial value (the anchor) and adjust insufficiently**	Estimates stay pulled toward an arbitrary starting number, even a plainly irrelevant one; the basis of negotiation and pricing effects

The three core Tversky and Kahneman heuristics: each is a serviceable shortcut whose failure mode is a named, reproducible bias.

Two allied effects round out the block and are worth naming. **Framing**: the same option is chosen or rejected depending on whether it is described in terms of gains or losses (the surgery "90 per cent survive" versus "10 per cent die"), a violation of the invariance that rational choice requires and a cornerstone of prospect theory (Kahneman and Tversky 1979). **Confirmation bias**: the tendency to seek, weight, and recall evidence that supports a prior belief and to discount evidence against it, the reasoning engine behind the maintenance of delusions and the negative schemas of depression.

TRAP **Availability** judges by ease of recall (vivid/recent events over-estimated); **representativeness** judges by resemblance to a prototype and ignores base rates (the Linda / base-rate fallacy). Do not swap them.

4.5 Dual-process theory: System 1 and System 2

The heuristics-and-biases findings are organised by **dual-process theory** (Stanovich and West 2000; popularised as *Thinking, Fast and Slow*, Kahneman 2011), the currently dominant framework for reasoning. It holds that two systems generate judgements. **System 1** is fast, automatic, effortless, parallel, emotional, and unconscious: it runs the heuristics and produces intuitions and snap judgements. **System 2** is slow, deliberate, effortful, serial, logical, and conscious: it can monitor and override System 1 but is lazy and capacity-limited, so it often endorses System 1's output unchecked. Most biases are System 1 intuitions that System 2 failed to catch. The clinical resonance is direct: CBT can be read as training System 2 to interrupt and re-appraise the automatic, System 1 negative thoughts that drive emotional disorder.

4.6 Barriers to problem-solving: mental set, functional fixedness, insight

Three classic obstacles and their resolution are high-yield, drawn from the Gestalt tradition of problem-solving. **Mental set** (Einstellung) is the tendency to persist with a strategy that worked before even when a simpler or better one is available, demonstrated by Luchins's water-jar problems, where subjects keep using a laborious learned formula after a one-step solution appears. **Functional fixedness** is a special case: the inability to see that an object can be used for a function other than its usual one, shown in Duncker's candle problem, where subjects fail to use the tack-box as a candle-holder because they fix on its role as a container. The escape from both is **insight**, the Gestalt phenomenon of a sudden, complete restructuring of the problem, the "aha" experience described by Kohler in his chimpanzees (Sultan stacking boxes to reach a banana): the solution appears abruptly and whole rather than by gradual trial and error, marked by a felt click of comprehension. Insight problems are solved all-at-once; incremental problems are solved by heuristic search.

Mental set (Einstellung)

Persisting with a previously successful strategy when a better one exists (Luchins's water-jar task).

Functional fixedness

Failing to use an object in a novel function because its usual function dominates (Duncker's candle problem).

Insight

Sudden, complete perceptual restructuring of a problem; the Gestalt "aha" (Kohler's apes).

4.7 Intelligence defined, and the one-versus-many debate

Intelligence is the global capacity to think rationally, act purposefully, and deal effectively with the environment (Wechsler's classic definition), or more operationally the aggregate ability to learn from experience, reason abstractly, and adapt to novel and complex situations (Kaplan and Sadock 2024). Every theory below is an answer to one question that has run for over a century and is *still* formally open: is intelligence a single general capacity, or a set of separate abilities? Kaplan and Sadock (2024) state it plainly, that whether intelligence is best regarded as a single general capacity, the **g** proposed by Spearman in 1904, or a range of modular capabilities as first proposed by Thurstone in 1938, remains an open question with no consensus. Hold that debate as the spine: each theorist moves the count of "how many intelligences" and each is judged against one stubborn empirical fact, the *positive manifold*, that scores on almost all cognitive tests are positively correlated.

4.8 Spearman's two-factor theory: g and s, the positive manifold

Charles **spearman** (1904, 1927), inventing factor analysis to do it, made the founding observation: performance on any one mental test correlates positively with performance on almost every other, a pattern he named the **positive manifold**. To explain it he proposed the **two-factor theory**: every cognitive performance draws on a single *general* factor, **g**, common to all tasks and representing overall mental energy or power, plus a *specific* factor, *s*, unique to that particular task. A person high in g tends to do well across the board; the s factors explain why they are nonetheless better at some tasks than others. What Spearman *fixed* was the pre-scientific vagueness of "intelligence," giving it a measurable, statistically derived core (g) and the tool (factor analysis) that all successors would use. What he *left debated* was whether one general factor could really account for the full diversity of human ability, and whether g was a real entity or a statistical artefact of how tests are built.

4.9 Thurstone's primary mental abilities: the plural challenge

Louis L. **thurstone** (1938), using a more advanced (multiple-factor) form of factor analysis, rejected a single dominant g and argued instead for several independent **primary mental abilities**, identifying seven: verbal comprehension, word fluency, number facility, spatial visualisation, perceptual speed, associative memory, and inductive reasoning. On his account an overall IQ score misleads, because a person is a profile of distinct strengths, not one number. What Thurstone *fixed* was Spearman's reductionism, insisting that ability is multidimensional and that the profile matters. What he *left debated*, and eventually conceded, was that his seven abilities were themselves positively intercorrelated and, when factored again, yielded a higher-order g. The debate thus did not resolve so much as move up a level: both a general factor and specific abilities seemed to be real, which is exactly what the hierarchical models would later formalise.

4.10 Cattell and Horn: fluid versus crystallised intelligence

Raymond **cattell** and John Horn (1960s) split g itself into two broad, empirically separable intelligences, the distinction the exam wants most from this era. **Fluid intelligence (Gf)** is the capacity to reason, see relationships, and solve novel problems independent of acquired knowledge, largely biological and content-free (matrix reasoning, novel puzzles). **Crystallised intelligence (Gc)** is the store of acquired knowledge, vocabulary, and skills built up through education and culture (general knowledge, word meanings). Their evidence came from outside factor analysis, in the aging data: the two follow different lifespan trajectories, with **fluid** intelligence peaking in early adulthood and declining from around the third to fourth decade, while **crystallised** intelligence rises through life and is maintained into old age. This dissociation is clinically vital, because it is the basis of "hold" versus "no-hold" tests in dementia assessment: preserved vocabulary (Gc) against declining novel problem-solving (Gf) estimates premorbid ability and flags decline. What Cattell and Horn *fixed* was the monolithic g, showing it fractionates into meaningfully different, differently-ageing components. What they *left debated* was, again, that Gf and Gc are themselves correlated and combine into a general factor, so the one-versus-many question persisted.

RULE **Fluid falls, crystallised holds.** Fluid intelligence (Gf, novel reasoning) peaks in early adulthood and declines from the third to fourth decade; crystallised intelligence (Gc, acquired knowledge) is preserved into old age, which is the basis of "hold" tests in dementia.

4.11 The Cattell-Horn-Carroll (CHC) three-stratum model: the synthesis

John Carroll's survey of over 460 factor-analytic datasets (1993) resolved the century-old dichotomy by making it a hierarchy, and merging with the Cattell-Horn work gave the **chc** (Cattell-Horn-Carroll) theory, the great synthesis. It is a **three-stratum model**: at the top (Stratum III) sits general intelligence, g; the middle (Stratum II) holds around eight to ten *broad abilities* (fluid reasoning Gf, crystallised knowledge Gc, short-term/working memory, long-term retrieval, visual processing, auditory processing, processing speed, and others); the bottom (Stratum I) holds many *narrow abilities* (Thurstone's primary factors sit here). What CHC *fixed* was the false either-or of Spearman versus Thurstone: g and multiple abilities are not rivals but different levels of one nested structure, so the positive manifold (a real g) and profile diversity (real broad and narrow abilities) are both accommodated. It is the model that underlies most modern intelligence tests, which is why they report both a global IQ and index scores. The debate it *leaves* is now a matter of detail (the exact number and boundaries of the broad abilities), not of principle.

4.12 Gardner's multiple intelligences: the outward expansion

Howard **gardner** (1983, *Frames of Mind*) pushed hardest against g, proposing that intelligence is not one or a few abilities but a set of largely *independent* intelligences, each with its own developmental course and neural substrate, and each capable of dissociating (as in savant syndrome or focal brain injury). He named seven, later expanded to eight, with a ninth proposed: linguistic, logical-mathematical, spatial, musical, bodily-kinaesthetic, interpersonal, intrapersonal, and naturalistic (with existential intelligence suggested). What Gardner *fixed*, or tried to, was the

narrowness of the "book-smart" tradition, giving academic status to musical, bodily, and social talents that IQ tests ignore, which is why his theory is so popular in education. What he *left* deeply *debated*, and where the exam expects the critique, is the evidence: his core claim that the intelligences are independent contradicts the single most robust finding in the field, the positive manifold, since these abilities are in fact positively correlated. The "learning styles" industry that grew from his theory is likewise unsupported by research. Gardner is best remembered as the boldest pluralist whose reach exceeded the data.

4.13 Sternberg's triarchic theory: intelligence for real-world success

Robert **sternberg** (1985, *Beyond IQ*) offered a smaller, more defensible pluralism aimed at what predicts success in life, not just in school. His **triarchic theory** names three intelligences. **Analytical** intelligence is the academic, problem-solving ability that traditional IQ tests measure (close to g). **Creative** (experiential) intelligence is the ability to deal with novelty and generate new ideas, the capacity IQ tests neglect. **Practical** (contextual) intelligence is "street smarts," the tacit, unspoken know-how for adapting to, shaping, and selecting real-world environments. What Sternberg *fixed* was the exclusion of creativity and practical adaptation from the concept of intelligence, and he was the first to bring creativity formally inside the tent. What he *left debated* is that practical intelligence has not been shown to be a single unified ability transferring across domains, and traditional IQ (which he cast as merely academic) in fact predicts a wide range of real-world outcomes well, undercutting the sharp separation his theory draws.

4.14 Currently accepted: CHC as the working consensus

The **currently accepted** position in intelligence research is the **chc** (Cattell-Horn-Carroll) model (4.11). It is the mainstream because it is the one framework that honours both halves of the century-old debate: a genuine general factor g at the apex (vindicating Spearman and explaining the positive manifold) sitting above a rich layer of broad and narrow abilities (vindicating Thurstone, Cattell, and Horn and explaining ability profiles). Gardner's and Sternberg's pluralist theories, though influential in education and useful for widening what we value, are held to sit outside the empirical mainstream precisely because they deny or minimise g, which the data will not allow. The practical upshot is that modern tests are built on CHC: they yield a full-scale IQ (the g estimate) alongside index scores that map onto the broad abilities.

> HOLD THIS
>
> **Every intelligence theory lives or dies on the positive manifold.** Because cognitive scores all correlate positively, the pluralist theories that deny g (Gardner, Sternberg) cannot be the consensus, and CHC can, by nesting g over broad over narrow abilities.

4.15 Neural correlate: the P-FIT model and processing speed

The **neural correlate** of general intelligence is captured by the **parieto-frontal integration theory (P-FIT)** (Jung and Haier 2007), the leading neurobiological account and the current consensus on the biology of g. Its claim is that intelligence is not localised to one region but reflects the *efficiency of a distributed network*, chiefly the dorsolateral prefrontal cortex, the inferior and superior parietal lobules, the anterior cingulate, and the white-matter tracts (notably

the arcuate fasciculus) that connect frontal to parietal cortex. On this model, sensory information is elaborated in temporal and occipital cortex, integrated and abstracted in the parietal lobe, evaluated and problem-solved in the prefrontal cortex, with the parieto-frontal loop generating the solution, and the integrity and speed of the connecting white matter set the ceiling on performance. Two robust biological correlates support it: **processing speed** (faster, more efficient neural conduction, indexed behaviourally by reaction time and biologically by white-matter integrity, correlates with higher g) and the *neural efficiency hypothesis* (higher-ability brains recruit *less*, not more, activation for a given task, working more economically). Overall brain volume correlates modestly with IQ (roughly r = 0.3 to 0.4), but network efficiency, not size, is the operative variable (Kaplan and Sadock 2024).

4.16 Worked example: reading the debate in one candidate

Consider a medical student who reasons brilliantly through an unseen clinical problem, has an encyclopaedic command of facts, plays the sitar beautifully, and is socially adept on the ward. Each theory reads her differently, and seeing the same person through each lens fixes the models. **Spearman**: her across-the-board excellence is high g, one general capacity lifting every performance (the positive manifold in a person). **Thurstone**: she is a profile, strong verbal, numerical, and spatial primary abilities. **Cattell and Horn**: her novel problem-solving is fluid intelligence (Gf), her stored medical knowledge is crystallised intelligence (Gc), and if we tested her at seventy the Gc would still be intact while the Gf had slipped. **Gardner**: her sitar is musical intelligence and her ward manner interpersonal intelligence, talents an IQ test would miss, though the critic notes these still correlate with her academic ability. **Sternberg**: her exam ability is analytical, her novel formulations creative, her ward-management practical intelligence. **CHC**: all of it nests, a high g at the apex expressed through strong broad abilities (Gf, Gc, and others). **P-FIT**: the shared substrate is an efficient, fast, well-connected fronto-parietal network. The one candidate, six readings, one nested truth.

COMMON TRAP

Do not present Gardner and Sternberg as the "modern, correct" theories because they feel inclusive and appealing: the exam rewards the opposite, that both sit outside the empirical mainstream because they deny or minimise g, and the currently accepted model is CHC. Equally, do not put IQ testing here: Binet-Simon, the Wechsler scales, deviation IQ, and the diagnostic bands are assessment-day material (cross-ref: Psychometry and assessment). And keep the pairing straight, fluid intelligence *declines* with age while crystallised intelligence is *preserved*, which is the direction that grounds "hold" tests in dementia.

PEARL

The entire intelligence half is one axis: how many intelligences are there, and what does the positive manifold allow? Spearman said one (g), Thurstone said seven, Cattell and Horn said two (Gf and Gc), Gardner said eight or nine, Sternberg said three, and Carroll's CHC said all of them at once by stacking g over broad over narrow abilities. Every theory lives or dies on the positive manifold, the fact that cognitive scores intercorrelate, which is why the pluralist theories that deny g cannot be the consensus and the hierarchical CHC can.

GOOD TO REMEMBER

- **Concept:** mental category grouping particulars; classical (necessary/sufficient features) vs prototype (Rosch 1975, best example).
- **Deductive reasoning:** general to specific, logically certain, truth-preserving. **Inductive:** specific to general, probable, content-expanding.
- **Algorithm:** exhaustive, guaranteed, slow. **Heuristic:** shortcut, fast, not guaranteed, bias-prone.
- **Tversky and Kahneman (1974):** availability (ease of recall), representativeness (resemblance, ignores base rates), anchoring and adjustment (pulled to a starting value).
- **Framing (prospect theory, Kahneman and Tversky 1979):** gain vs loss wording flips choice. **Confirmation bias:** seeking belief-consistent evidence.
- **Dual-process (Stanovich and West 2000; Kahneman 2011):** System 1 fast/automatic/intuitive vs System 2 slow/deliberate/logical.
- **Mental set (Einstellung):** Luchins's water-jars. **Functional fixedness:** Duncker's candle. **Insight:** Gestalt "aha," Kohler's apes.
- **Spearman (1904/1927):** two-factor theory, g (general) + s (specific); positive manifold; invented factor analysis.
- **Thurstone (1938):** seven primary mental abilities (verbal comprehension, word fluency, number, spatial, perceptual speed, memory, reasoning); the plural challenge.
- **Cattell and Horn (1960s):** fluid (Gf, novel reasoning, declines with age) vs crystallised (Gc, acquired knowledge, preserved with age).
- **Carroll / CHC (1993):** three-stratum hierarchy, Stratum III = g, Stratum II = broad abilities, Stratum I = narrow abilities; the synthesis, currently accepted.
- **Gardner (1983):** multiple intelligences, seven then eight (linguistic, logical-mathematical, spatial, musical, bodily-kinaesthetic, interpersonal, intrapersonal, naturalistic); critique: contradicts positive manifold.
- **Sternberg (1985):** triarchic, analytical + creative + practical; brought creativity into intelligence.
- **Currently accepted:** CHC (Cattell-Horn-Carroll), g over broad over narrow.
- **Neural correlate:** P-FIT (Jung and Haier 2007), efficient fronto-parietal network (DLPFC, parietal, anterior cingulate, arcuate fasciculus); processing speed and neural efficiency; brain volume r approx 0.3 to 0.4.

5 · Motivation theories

Motivation is the internal process that *energises*, *directs* and *sustains* goal-directed behaviour: it answers not what an organism can do but why it does it now, in this direction, with this persistence. For the exam the topic is best read as a single argument that runs across the twentieth century, from a purely biological push (behaviour as the discharge of a bodily deficit) to a psychological pull (behaviour as the pursuit of value and meaning), and finally to the

recognition that neither alone suffices and the mind runs several motivational systems in parallel. **Learn the sequence and you can place any scenario stem.**

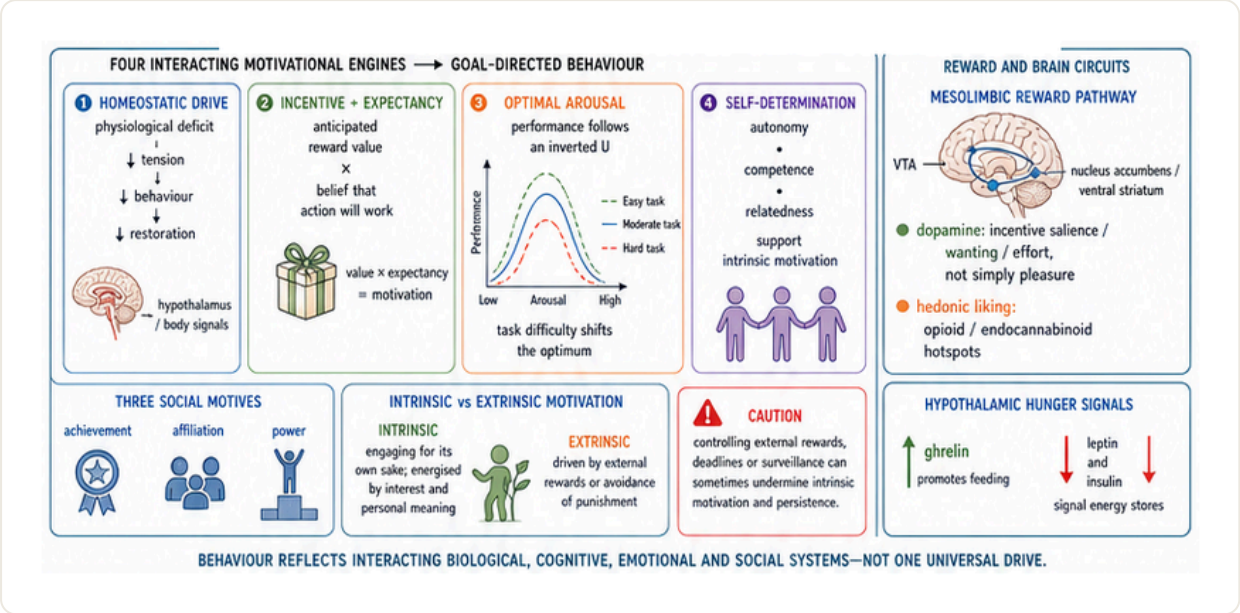


Fig 4.9 Motivation: need, value, control and reward.

The topic follows the standard evolution-of-theories flow: the theories in the order they appeared, each fixing a flaw in the last, from instinct through **drive**-reduction, arousal and **incentive** to the humanistic and cognitive-need theories, then the currently accepted multi-system view, its **neural correlate** in the mesolimbic dopamine reward pathway and the hypothalamic feeding centres, and a worked example. The single organising question is the one drive-reduction could not answer: if all behaviour serves homeostasis, why does a well-fed, safe, warm person still read, explore, climb and strive? Ground text is Kaplan and Sadock (2024), the New Oxford Textbook of Psychiatry, and Tasman (2015) for the developmental placement of Maslow.

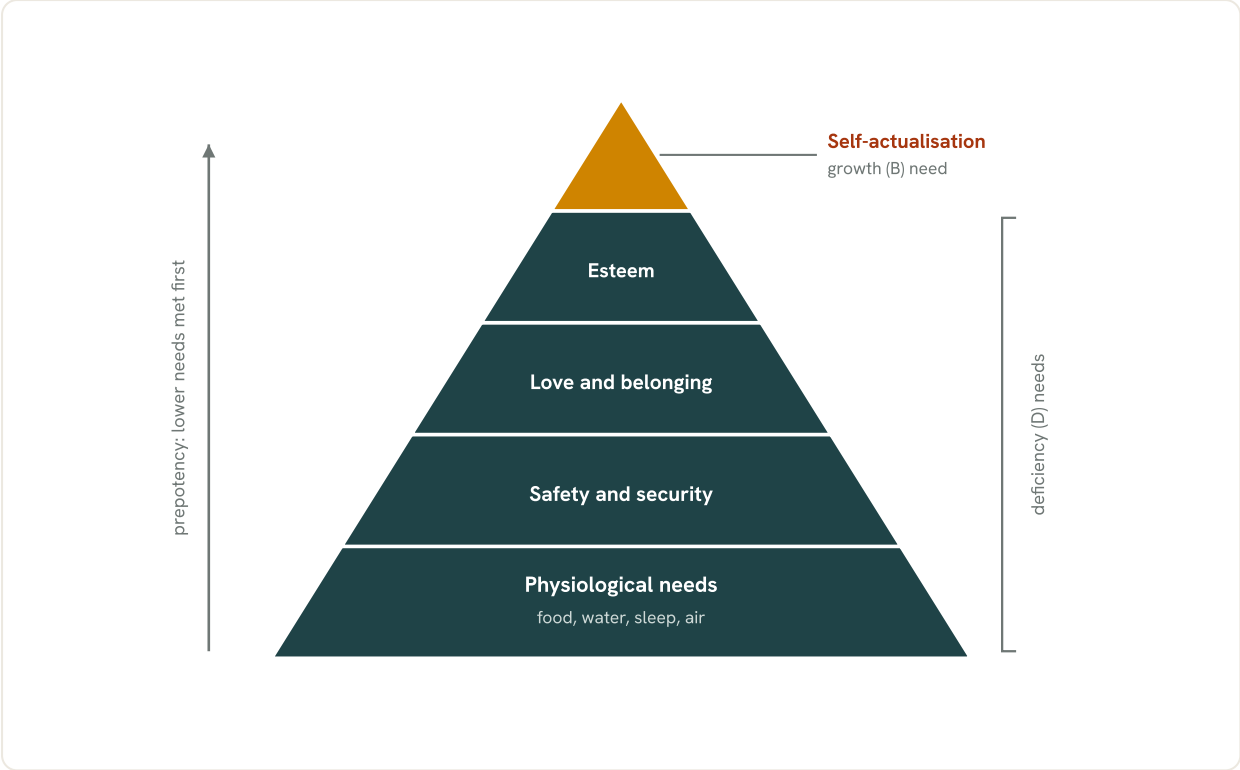


Fig 4.10 Maslow's hierarchy of needs. Needs are arranged by prepotency: the lower, deficiency (D) needs (physiological, safety, belonging, esteem) generally press for satisfaction before the higher growth (B) need of self-actualisation becomes the person's motive. The model captures why homeostatic drive-reduction cannot be the whole story of motivation, since a fed and safe person still strives; later revisions loosen the strict ordering and add cognitive, aesthetic and self-transcendence needs.

5.1 Definition and the three questions motivation must answer

What a motivation theory must deliver. A complete account of motivation must specify three things about a behaviour: its *activation* (what initiates it and how much energy it commands), its *direction* (why this goal and not another), and its *persistence* (why it continues against obstacles). The classic distinction is between the *push* of internal states (a need or drive that shoves behaviour out) and the *pull* of external goals (an incentive that draws behaviour toward it). The whole history below is the field discovering that human behaviour needs both, plus a layer of higher goals that neither push nor pull can capture (Kaplan and Sadock 2024).

Need

A physiological or psychological deficit or requirement (food, safety, belonging).

Drive

The aroused, tension-like internal state that a need produces and that energises behaviour to reduce it; the engine of the "push" theories.

Incentive

An external stimulus or goal whose anticipated value pulls behaviour toward it, independent of any internal deficit.

Motive

A relatively stable, often learned, disposition that gives behaviour a characteristic direction (achievement, affiliation, power).

5.2 Instinct theory: McDougall and the innate-programme account

The first theory. The earliest scientific account, from William James and above all **William McDougall (1908)**, held that behaviour, like animal behaviour, is driven by **instincts**: innate, biologically fixed, purposive dispositions inherited by every member of a species and triggered by specific stimuli. McDougall catalogued human instincts (flight, curiosity, pugnacity, gregariousness, parental care) and argued each carried its own emotion. In the animal literature the same idea became the ethologists' *fixed action pattern* (Lorenz, Tinbergen): a stereotyped, unlearned behavioural sequence released by a sign stimulus, such as the greylag goose rolling any round object back to the nest or the stickleback attacking any red-bellied shape. **What it fixed.** It rooted motivation in biology and made it heritable and species-general, a genuine advance on faculty psychology. **What it left debated.** The list exploded: within two decades psychologists had named thousands of contradictory "instincts" with no unifying principle and no way to falsify any of them, and the theory could not explain the sheer flexibility of human behaviour. Naming an instinct merely re-described the behaviour rather than explaining it, and the school collapsed, though its evolutionary logic survives in modern evolutionary psychology.

5.3 Drive-reduction theory: Hull, homeostasis and the tension model

The homeostatic engine. Clark Hull (1943) replaced the unfalsifiable instinct list with a mechanistic learning theory built on **homeostasis**, the body's tendency to hold its internal milieu at a stable set point (a concept from Cannon and Bernard). A biological need (food deprivation) creates an aversive internal tension, the **drive**; behaviour that reduces the drive is reinforced and learned; once the need is met and homeostasis restored, the drive falls and motivation subsides until the next deficit. Hull distinguished *primary drives*, unlearned and biological (hunger, thirst, sex, sleep, temperature, pain-avoidance), from *secondary drives*, acquired by conditioned association with primary ones (money, status, achievement become motivating because they predict primary reinforcement). His formula made behaviour a multiplicative product of drive and learned habit strength. **What it fixed.** It grounded motivation in measurable physiological need and tied it rigorously to learning and reinforcement, giving the field a testable engine. **What it left debated.** The fatal gap, and the pivot of the whole topic, is that drive-reduction explains only *deficit*-driven behaviour and cannot explain behaviour that *raises* arousal or serves no homeostatic deficit at all: curiosity, exploration, play, sensation-seeking, and the pursuit of achievement. A monkey solves puzzles for no food reward; a sated, safe person reads a novel or rides a rollercoaster, deliberately increasing tension. Homeostasis has no account of this, and its failure spawned the arousal and incentive theories (Kaplan and Sadock 2024).

RULE **The curiosity problem is the pivot of the whole topic.** Drive-reduction explains only deficit-driven behaviour; that a sated, safe person still explores, plays and strives is what forces arousal, incentive and higher-need theories.

5.4 Arousal and optimal-level theory: the Yerkes-Dodson inverted-U

Fixing the curiosity problem. Arousal (optimal-level) theory answered drive-reduction's central failure by proposing that organisms are motivated not to *minimise* arousal but to maintain an *optimal level* of it: too little arousal is aversive (boredom drives us to seek stimulation, which is

why curiosity and exploration exist), and too much is also aversive (we withdraw to calm down). The quantitative core is the **Yerkes-Dodson law (1908)**: performance relates to arousal as an inverted U, rising with arousal to a peak then falling as high arousal degrades performance. The examinable refinement is that the optimum *shifts with task difficulty*: simple, well-learned tasks have a high optimal arousal, whereas complex or novel tasks have a low optimum, so anxiety wrecks a hard exam but barely dents a routine drill. **What it fixed.** It explained the exploratory and stimulation-seeking behaviours that homeostasis could not, and it linked motivation directly to emotion and performance. **What it left debated.** It described the level of arousal sought but said little about the *direction* of behaviour or why a specific goal is chosen, which the pull theories addressed next.

5.5 Incentive and expectancy theory: the pull of anticipated reward

From push to pull. Incentive theory shifted the locus of motivation from an internal deficit to the external goal itself: behaviour is drawn by the anticipated *value* of a reward (or the threat of a punishment), so that a stimulus can motivate even with no bodily need, which is why we eat an appealing dessert when already full. This is the conceptual home of *extrinsic motivation*. **Expectancy theories** then made the pull cognitive: what motivates is not the reward alone but the product of how much the person *values* the outcome and how strongly they *expect* their effort to attain it. Tolman's early work on purposive behaviour and cognitive maps, Vroom's *expectancy-value* model in organisational psychology, and Atkinson's expectancy-value theory of achievement all share this form: motivation equals value multiplied by expectancy, so a prize you cannot realistically win, or a trivial prize you easily could, both fail to motivate. **What it fixed.** It accounted for goal-directedness, choice between goals, and the power of external rewards, and it introduced the person's beliefs and expectations as motivational variables. **What it left debated.** It still treated the person as reactive to external payoffs and said little about the higher, self-generated needs that dominate a secure human life, which the humanistic theory placed at the summit.

5.6 Maslow's hierarchy of needs: deficiency versus growth motivation

The humanistic summit. Abraham Maslow (1943, 1970) interpreted the whole person in motivational terms and arranged human needs in an ascending **hierarchy of needs**, usually drawn as a pyramid, in which lower needs must be reasonably satisfied before higher ones become the salient motivators. The five classic levels, bottom to top, are *physiological* (food, water, sleep, sex), *safety* (security, protection, order), *love and belonging* (affection, intimacy, group membership), *esteem* (self-respect and the respect of others, competence, recognition), and *self-actualisation* (the realisation of one's unique potential) at the apex. The master distinction is between the lower four as **deficiency needs** (D-needs), which are driven by lack and quieten once met, and self-actualisation as a **growth need** (B-need, being-need), which is never sated and grows with fulfilment. Maslow later placed the fleeting, transcendent *peak experience* at the top and argued psychology had been too fixated on pathology, calling for a focus on positive mental health, a direct ancestor of positive psychology. **What it fixed.** It captured the higher, self-generated strivings that push and pull theories miss, and it explained the ordering of human

concerns (the starving man risks danger and ostracism for food, but the well-fed man is dominated by esteem and meaning). Its exam-relevant caveats are that the strict order is not rigidly followed (Maslow himself noted creators who skip lower levels straight to self-actualisation, and in late life the hierarchy can invert per Tasman 2015), and the theory resists tidy empirical test. **What it left debated.** It is a taxonomy of *what* we want, not a mechanism of *how* a need moves behaviour, and its needs are broad classes rather than testable processes, gaps the next two theories addressed.

5.7 Murray's needs and McClelland: achievement, affiliation and power

Making needs measurable. Henry Murray (1938) proposed a long list of *psychogenic needs* and the method to measure them, the *Thematic Apperception Test* (TAT), in which the stories a person tells to ambiguous pictures reveal their dominant motives. **David McClelland (1961)** distilled Murray's list into three learned social motives that account for most individual differences in striving, assessed projectively and each with a characteristic behavioural signature.

Need for achievement (nAch)

The drive to meet standards of excellence and master challenges; high-nAch people prefer tasks of moderate, calculated difficulty (where effort, not luck, decides the outcome) and seek concrete performance feedback.

Need for affiliation (nAff)

The drive for warm, close interpersonal relationships and social acceptance; high-nAff people prioritise harmony and belonging over competition.

Need for power (nPow)

The drive to influence, control or have impact on others; splits into personalised power (dominance for self) and socialised power (influence for collective ends), the latter linked to effective leadership.

What it fixed. It turned Maslow's abstract higher needs into specific, measurable, individually varying motives and showed that these motives are learned and predict real-world behaviour (entrepreneurship, leadership). **What it left debated.** It described the *content* of human motives but not the underlying process that makes any activity feel self-driven versus coerced, the question self-determination theory finally formalised.

5.8 Self-determination theory: Deci and Ryan, intrinsic versus extrinsic

The process of autonomous motivation. **Self-determination** theory (SDT), developed by Edward Deci and Richard Ryan (1985, 2000), is the dominant contemporary framework and the most exam-relevant of the modern theories. Its central claim is that the *quality* of motivation matters more than its quantity, and quality depends on how self-endorsed the behaviour is. SDT distinguishes *intrinsic motivation* (acting for the inherent interest, enjoyment and satisfaction of the activity itself, the "loves the activity for its own sake" pole) from *extrinsic motivation* (acting for a separable outcome such as a reward, grade, or the avoidance of punishment). Crucially, extrinsic motivation lies on a continuum of *internalisation*, from purely external regulation, through introjected and identified regulation, to fully integrated regulation that feels autonomous even though the goal is instrumental. SDT roots all of this in three innate, universal *basic psychological needs*: **autonomy** (a sense of volition and self-authorship), **competence** (feeling

effective and masterful), and **relatedness** (feeling connected to and cared for by others). Contexts that satisfy the three needs foster intrinsic motivation, well-being, persistence and creativity; contexts that thwart them breed control, ill-being and, in the extreme, forms of psychopathology. The signature empirical finding is the *overjustification effect*: paying people to do something they already enjoy can *undermine* their intrinsic motivation, because an external reward shifts the perceived locus of causality from inside to outside. **What it fixed.** It supplied the missing mechanism, why the same behaviour can be vitalising or draining depending on need satisfaction, and it reconciled the earlier incentive theories (extrinsic pull) with the humanistic emphasis on growth (autonomy and self-actualisation), unifying the field's push, pull and higher-need strands.

5.9 Currently accepted: a multi-system view of motivation

The **currently accepted** position is not a single winning theory but an explicitly *multi-system* account, because the century of debate showed each theory captures a genuine and partly separable component. Contemporary affective neuroscience holds that motivation is generated by several interacting systems: *homeostatic drives* that defend biological set points (the truth in Hull), a *reward and incentive-salience* system that assigns motivational pull to cues and goals (the truth in incentive theory, now with a precise neural substrate), and *higher cognitive goal systems* in the prefrontal cortex that pursue self-generated, value-laden aims and can override the lower systems (the truth in Maslow, McClelland and SDT). The modern refinement, from Berridge's work, is the dissociation of *wanting* (the dopaminergic motivational pull toward a reward, incentive salience) from *liking* (the opioid-mediated hedonic pleasure of consuming it), which explains why addicts intensely want a drug they no longer like. Motivation, on this view, is the moment-to-moment arbitration between competing systems, which is why a dieter genuinely wants both the cake (incentive plus homeostatic hunger) and the goal weight (a higher cognitive value), and either can win.

5.10 Neural correlate: mesolimbic dopamine and the hypothalamic centres

The neural correlate of motivation maps onto two levels that mirror the push-versus-pull divide of the theories. The *homeostatic drives* are governed by the **hypothalamus**, and the feeding example is the exam classic: the **lateral hypothalamus** is the "hunger" or feeding-on centre, so its stimulation elicits eating and its lesion produces *aphagia* (the lateral hypothalamic syndrome, animal stops eating and starves), whereas the *ventromedial hypothalamus* is the "satiety" or feeding-off centre, so its lesion produces *hyperphagia* and obesity (the ventromedial hypothalamic syndrome). This dual-centre feeding model is cross-referenced to the hypothalamus and drive states covered on the biological-bases days (cross-ref: the Functional Neuroanatomy & Neurophysiology notes, Neuroanatomy of the hypothalamus; the Neurochemistry, Neuroendocrinology, Neuroimaging & Basic Psychopharmacology notes, Homeostasis and drive states). The *incentive and reward* system, the neural home of "wanting", is the **mesolimbic dopamine pathway**, projecting from the *ventral tegmental area* to the *nucleus accumbens* (ventral striatum), with input to and from the prefrontal cortex and amygdala. Schultz (1997) showed these midbrain dopamine neurons fire in proportion to *reward prediction error* (better-than-

expected outcomes), the teaching signal that assigns **incentive salience** to cues, and Berridge showed this dopaminergic signal codes wanting rather than the pleasure (liking) of reward. This is the same aberrant-salience system implicated in psychosis and the common final pathway hijacked by every drug of addiction, tying motivation directly to psychopathology (Kaplan and Sadock 2024).

HOLD THIS

Lateral hypothalamus = hunger-on (lesion causes aphagia); ventromedial = satiety (lesion causes hyperphagia and obesity). On the reward side, mesolimbic dopamine codes *wanting* (incentive salience), not *liking* (opioid pleasure).

5.11 Worked example: the medical student before the exit exam

A single scenario shows every theory operating at once, and shows how a scenario stem is decoded. A resident revising for the exit exam skips lunch (a **drive-reduction** and homeostatic hunger signal builds, driven by the lateral hypothalamus, and eventually pulls attention off the books). The looming pass or fail is an **incentive** whose motivational force is the product of how much the resident values passing and how much they expect their effort to secure it (**expectancy-value**): a certain pass or a hopeless one both demotivate, moderate odds motivate most. Exam-day anxiety illustrates the **Yerkes-Dodson inverted-U**: a little arousal sharpens recall, but panic past the optimum (low, because the task is complex) collapses performance. In **Maslow's** terms the resident cannot focus on the esteem-level goal of qualifying if safety or belonging needs are unmet, and the drive to master the material is an **achievement** motive (nAch) in McClelland's sense, best sustained on challenges of moderate difficulty. Finally, whether the studying feels vitalising or grinding turns on **self-determination**: a resident who studies because medicine genuinely fascinates them (intrinsic, autonomous, competence-satisfying) persists and performs better than one grinding only to avoid the shame of failure (controlled extrinsic regulation), the practical payoff of the whole topic.

MNEMONIC

"I Drove A Incentive to Maslow's Mountain, Met McClelland, and Self-Determined."

The theories in historical order: **I**nstinct (McDougall), **D**rive-reduction (Hull), **A**rousal (Yerkes-Dodson), **Incentive** and expectancy, **Maslow's** hierarchy, **McClelland** (Murray's needs), and **Self-Determination** (Deci and Ryan). Read the list as push, then pull, then higher needs, then the modern process account.

COMMON TRAP

Do not confuse **drive-reduction** with **arousal** theory: drive-reduction is about *lowering* tension to restore homeostasis after a deficit, so it cannot explain curiosity; arousal theory is about seeking an *optimal* level, which is precisely why it can. Second trap: intrinsic motivation is not always stronger than extrinsic. The *overjustification effect* shows adding a reward to an already-enjoyed activity can *reduce* intrinsic motivation. Third: on the neural correlate, dopamine codes *wanting* (incentive salience), not *liking* (hedonic pleasure), a Berridge dissociation examiners favour.

GOOD TO REMEMBER

- **Instinct theory (McDougall 1908):** behaviour driven by innate, fixed, purposive instincts; animal parallel is the fixed action pattern.
- **Drive-reduction (Hull 1943):** a biological need creates a drive; behaviour reduces it to restore homeostasis; primary vs secondary drives. Cannot explain curiosity.
- **Arousal / optimal-level (Yerkes-Dodson 1908):** organisms seek an optimal arousal; inverted-U of arousal versus performance; optimum is lower for complex tasks.
- **Incentive and expectancy (Tolman; Vroom; Atkinson):** behaviour pulled by anticipated reward value; motivation equals value multiplied by expectancy.
- **Maslow's hierarchy of needs (1943, 1970):** physiological, safety, love/belonging, esteem, self-actualisation; deficiency needs vs the growth need at the apex; peak experience.
- **Murray (1938):** psychogenic needs, measured by the Thematic Apperception Test (TAT).
- **McClelland (1961):** three learned motives, need for achievement (nAch, prefers moderate-difficulty tasks), affiliation (nAff), and power (nPow).
- **Self-determination theory (Deci and Ryan 1985, 2000):** intrinsic vs extrinsic motivation on an internalisation continuum; three basic needs, autonomy, competence, relatedness; overjustification effect.
- **Currently accepted:** a multi-system view, homeostatic drives plus incentive salience plus higher cognitive goals; wanting (dopamine) dissociated from liking (opioid).
- **Neural correlate:** mesolimbic dopamine (ventral tegmental area to nucleus accumbens) for incentive salience and reward prediction error; lateral hypothalamus = hunger/feeding-on centre (lesion causes aphagia); ventromedial hypothalamus = satiety centre (lesion causes hyperphagia and obesity).

6 · Emotion theories and neural circuits

An **emotion** is a brief, intense, object-directed affective response with three coupled components: a felt subjective experience, a physiological (autonomic and endocrine) change, and an expressive-behavioural output, all triggered by an appraised event. It is distinguished from **mood**, which is a more prolonged, less intense, and often objectless affective background. The whole topic is best read as one long argument about *sequence*: given a bear on the path, which comes first, the pounding heart or the fear? **Body-first or cognition-first.** Every named theory is a different answer to that single question, and each one fixed a specific hole in the theory before it.

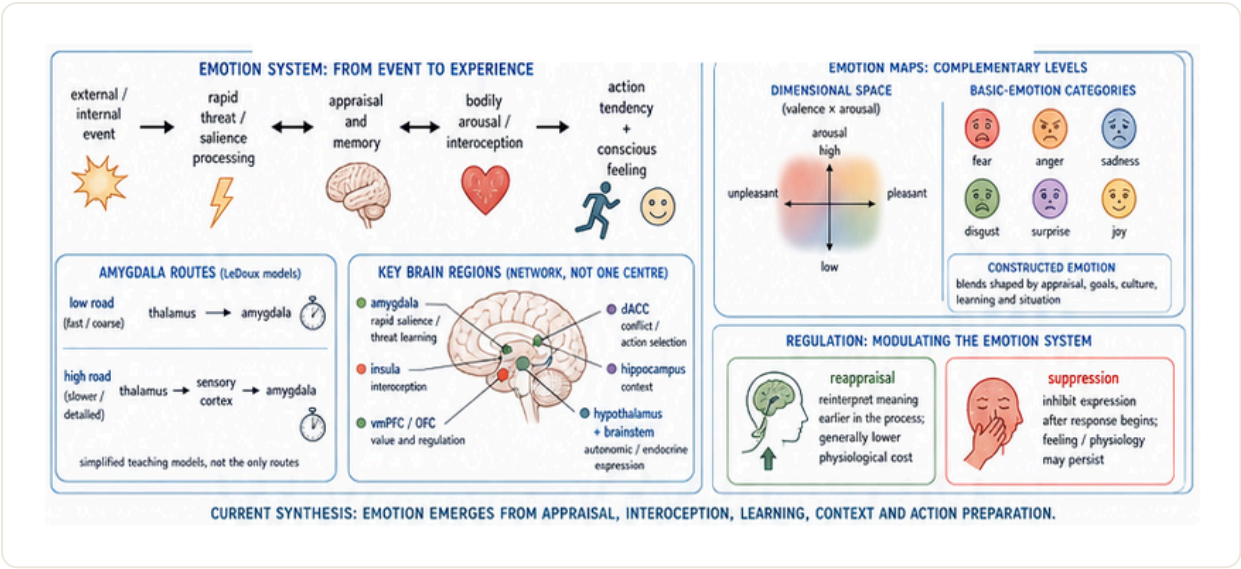


Fig 4.11 Emotion: appraisal, body, action and construction.

For the exam the payload is fourfold: the ordered theories with their authors and the one claim each is remembered for; the body-first versus cognition-first axis that organises them; the currently accepted synthesis (appraisal plus interoception plus construction); and the neural correlate that grounds it all, the limbic system and the Papez circuit, the amygdala with LeDoux's two roads, and the insula for interoception. The anatomy has its deep home in the Functional Neuroanatomy & Neurophysiology notes; here it is the substrate for the psychology. Structure the answer as an evolution, not a list.

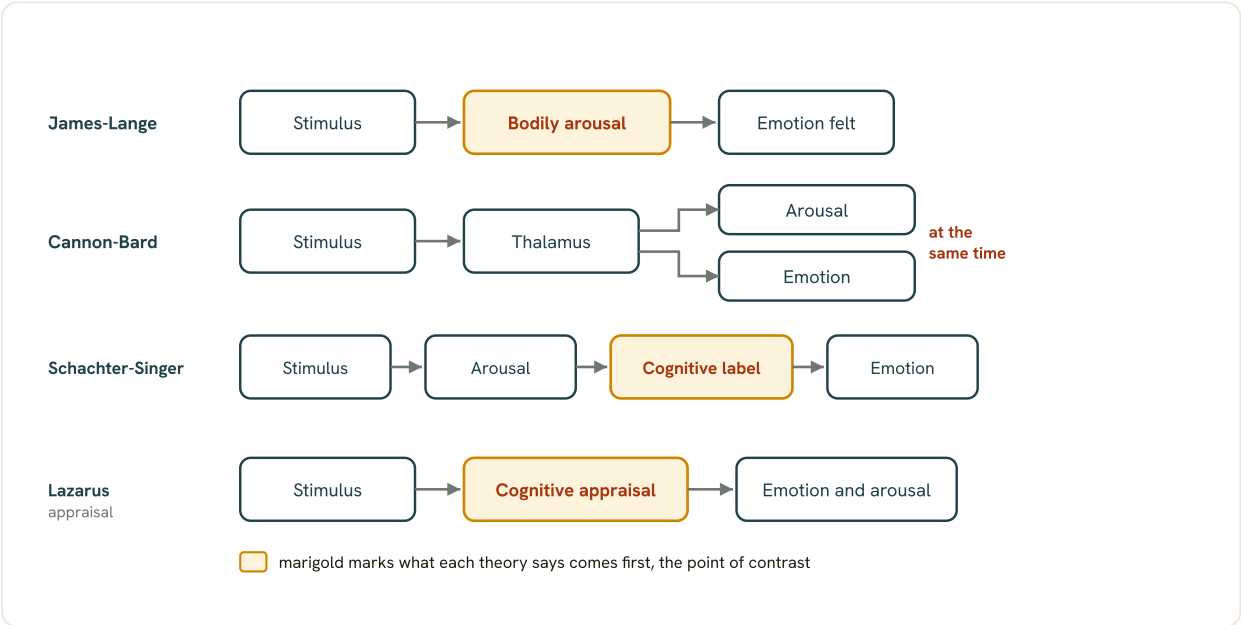


Fig 4.12 The four classic theories of emotion differ over the ORDER of arousal, cognition and feeling. James-Lange puts the bodily change first and reads emotion as the perception of it; Cannon-Bard makes arousal and feeling simultaneous outputs of the thalamus; Schachter and Singer's two-factor theory needs undifferentiated arousal plus a cognitive label; Lazarus makes an appraisal the trigger. The enduring debate is body-first versus cognition-first, which modern appraisal, interoception and constructed-emotion accounts largely reconcile.

6.1 Darwin: emotions as evolved, universal, adaptive expressions

The starting point. Charles Darwin (1872), in *The Expression of the Emotions in Man and Animals*, made the first scientific claim about emotion: that emotional expressions are innate,

evolved, and serve adaptive communicative and preparatory functions, and that the same core expressions (the bared teeth of anger, the recoil of fear) appear across human cultures and are continuous with those of other animals. **What it fixed.** It moved emotion out of philosophy and theology and into biology, framing it as a product of natural selection rather than a moral or spiritual state. **What it left debated.** Darwin described the *output* (the expression) and its evolutionary purpose, but said nothing about the internal *mechanism*: what actually generates the felt emotion inside the organism, and in what order its parts arise. That mechanistic question is what the next century fought over (Kaplan and Sadock 2024).

6.2 James-Lange: the body changes first, emotion is its perception

The bodily-feedback theory. William James (1884) and, independently, the Danish physiologist Carl Lange proposed the counter-intuitive **james-lange** theory: an emotion is not the cause of bodily change but the *perception* of it. James put it in his famous inversion of common sense: we do not tremble because we are afraid, we are afraid because we tremble. In his own words, "we meet a bear, are frightened and run . . . the more rational statement is we feel afraid because we tremble" (James 1884). The sequence is therefore: stimulus, then bodily and autonomic response (racing heart, sweating, fleeing), then perception of that response, which *is* the emotion. A strong prediction follows: each distinct emotion must have a distinct bodily signature, since the feeling is nothing but the read-out of the body. **What it fixed.** It gave Darwin's output an internal mechanism and made emotion an embodied, testable process rather than a disembodied mental event. **What it left debated.** It required different emotions to map onto reliably different visceral patterns, and it made the body the sole source of feeling, both of which the next theory attacked head-on (Kaplan and Sadock 2024).

6.3 Cannon-Bard: body and feeling arise together, driven by the thalamus

The central (thalamic) theory. Walter Cannon (1927), later developed by his student Philip Bard, mounted three empirical objections to james-lange and replaced it with the **cannon-bard** theory. His evidence: surgically isolating the viscera from the brain did not abolish emotional behaviour in animals; artificially inducing visceral changes (for example an adrenaline injection) did not by itself produce a genuine emotion; and autonomic responses are too slow and too uniform to account for the speed and variety of felt emotion. Cannon concluded that an emotional stimulus produces *two parallel outputs*: the thalamus (in modern terms, the thalamus and hypothalamus) simultaneously and independently sends one signal up to the cortex, producing the conscious feeling, and one signal down to the body, producing the autonomic arousal. The sequence is therefore: stimulus, then feeling and bodily change *at the same time*, neither causing the other. **What it fixed.** It broke the requirement for unique bodily signatures and located emotion in the brain rather than the periphery, giving it a neuroanatomical seat. **What it left debated.** By making arousal and feeling wholly parallel and independent, it left no role for how the arousal is *interpreted*, the very gap the next theory exploited (Kaplan and Sadock 2024).

6.4 Schachter-Singer: two factors, arousal plus a cognitive label (the adrenaline study)

The two-factor (arousal-cognition) theory. Stanley Schachter and Jerome Singer (1962) proposed that an emotion requires *two* ingredients: undifferentiated physiological arousal, plus a cognitive **label** that interprets that arousal in light of the situation. The same racing heart is felt as fear in a threatening context and as euphoria in a joyful one; the arousal supplies the intensity, the cognition supplies the identity. Their classic **schachter** experiment tested this: participants were injected with adrenaline (epinephrine) or saline and then placed with a confederate who acted either euphoric or angry. Crucially, some were correctly informed of the drug's arousing effects, some were told nothing, and some were misinformed. Those who had an *unexplained* arousal (told nothing or misinformed) took on the emotion modelled by the confederate, describing themselves as euphoric or angry to match; those who could correctly *attribute* their pounding heart to the injection did not. The arousal was constant; only the available cognitive explanation varied the emotion. This is the origin of *misattribution of arousal*. **What it fixed.** It reconciled james-lange and cannon-bard: the body supplies the arousal (james-lange) but is too undifferentiated to specify the emotion alone (cannon-bard's critique), so cognition does the specifying. **What it left debated.** It treated the cognitive label as a post-hoc read of an already-present arousal, and never fully specified *when* and *how* the appraisal happens, which the next debate addressed (Kaplan and Sadock 2024).

TRAP Schachter-Singer is **not** cognition-first. The undifferentiated arousal comes first and is then labelled by context, so it is body-first with cognition supplying only the identity; the same racing heart is fear beside a threat and euphoria beside joy.

6.5 Lazarus versus Zajonc: does appraisal come before feeling, or can affect be primary?

The cognition-first theory and its challenger. Richard Lazarus (1966, 1991) pushed cognition all the way to the front with the cognitive **appraisal** (cognitive-mediational) theory: an appraisal, an evaluation of the event's meaning for the self, is *necessary and prior*, and it determines both the emotion and the bodily response that follow. The **lazarus** sequence is: stimulus, then appraisal, then emotion (and its physiology) together. He distinguished *primary* appraisal (is this relevant and is it a threat, harm, or benefit to me?) from *secondary* appraisal (can I cope with it?), and it is the appraisal, not the event, that explains why the same lecture invitation delights one student and frightens another. Magda Arnold (1960) had first introduced "appraisal"; Lazarus built the full model. **The counter.** Robert Zajonc (1980, 1984) argued for *affective primacy*: some affect arises fast, automatically, and *independently of, or prior to,* full cognitive appraisal ("preferences need no inferences"), as when we flinch at a sudden loud sound or feel an instant, unexplained liking. This Lazarus-Zajonc debate is the classic exam contrast. **What it fixed and left open.** Lazarus explained individual and cultural differences in emotion to the same event; Zajonc showed appraisal cannot be the whole story because affect can outrun it. The tension between them, fast automatic affect versus slower deliberate appraisal, was resolved neurally rather than psychologically, by LeDoux's two roads (6.8), and both are folded into the modern synthesis (Kaplan and Sadock 2024).

6.6 Basic-emotion versus dimensional and constructed-emotion accounts

The modern structural debate: how many emotions, and are they given or built? Two rival modern camps carry Darwin's legacy forward.

Basic (discrete) emotion: Ekman

Paul Ekman (1970s onward), extending Darwin, holds that a small set of *basic emotions* are innate, biologically hard-wired, and universally recognised from the face across cultures, each with its own program and expression. The classic six are anger, disgust, fear, happiness, sadness, and surprise (later expanded to include contempt and others). Emotions are natural kinds the brain comes equipped with.

Dimensional (circumplex): Russell

James Russell (1980) argued emotions are not discrete categories but points in a continuous two-dimensional space, the *circumplex model*, whose axes are *valence* (pleasant to unpleasant) and *arousal* (activated to deactivated). Fear and excitement share high arousal but differ in valence; contentment and depression share low arousal. Emotion words label regions of this space rather than separate machines.

Constructed emotion: Barrett

Lisa Feldman Barrett (2017) advanced the *theory of constructed emotion*: emotions are not triggered but *constructed* in the moment by the brain, which uses concepts and past experience to make meaning of raw interoceptive and sensory signals (core affect) via predictive processing. The identical churning stomach becomes "hunger" in a bakery and "dread" in a waiting room, depending on the brain's prediction. This is the current cutting edge and directly extends the two-factor idea: arousal is given, the categorising concept builds the emotion.

Ekman says emotions are discrete and given by evolution; Russell and Barrett say they are constructed from underlying dimensions of affect.

6.7 The currently accepted account: appraisal plus interoception plus construction

Not one theory but their integration. The *currently accepted* view is that no single classical theory is right and each captured a real piece. An emotional episode begins when an event is *appraised* for its significance to the self (Lazarus), often through a fast automatic route that can precede conscious appraisal (Zajonc); this appraisal drives an autonomic and endocrine *bodily* response whose sensing, *interoception*, is a genuine constituent of the feeling (the modern vindication of james-lange, via Damasio's *somatic marker hypothesis*, in which bodily signals bias decision-making); and the brain then *constructs* the specific, named emotion by categorising this core affect using learned concepts and context (Schachter-Singer's label, formalised by Barrett's constructed emotion within a predictive-processing framework). In short: appraisal sets it off, interoception gives it its felt body, and conceptual construction gives it its identity. This synthesis dissolves the body-first versus cognition-first war by making both continuously and reciprocally involved (Kaplan and Sadock 2024).

6.8 Neural correlate: the limbic system and the Papez circuit

The historical anatomical model. The neural correlate of emotion begins with the **limbic** system. James **papez** (1937, formalised 1939), building on Cannon's work, proposed that emotion is generated by a specific reverberating circuit, the *Papez circuit*: hippocampus, then via the fornix to the mammillary bodies of the hypothalamus, then via the mammillothalamic tract

to the anterior thalamic nuclei, then to the cingulate gyrus (the seat of conscious emotional experience in his scheme), and back to the hippocampus, closing the loop. Paul MacLean (1949, 1952) extended this into the modern *limbic system* as the "visceral brain," adding the **amygdala**, the septal area, and the orbitofrontal and prefrontal cortex. The Papez circuit's clinical footprint is memory as much as emotion: lesions anywhere along it (classically the mammillary bodies and dorsomedial thalamus in Korsakoff syndrome) produce amnesia, tying this topic to the Functional Neuroanatomy & Neurophysiology notes anatomy (Kaplan and Sadock 2024).

6.9 Neural correlate: the amygdala (LeDoux's low and high roads) and the insula

The fear hub and its two routes. The single most important structure for emotion, especially fear, is the **amygdala**. Joseph LeDoux (1996) mapped how a threat reaches it by two parallel pathways from the sensory thalamus. The *low road* is a fast, direct, "quick and dirty" thalamo-amygdala projection that triggers a defensive response on a crude sketch of the stimulus before the cortex has finished processing it, the neural basis of Zajonc's affective primacy and of jumping at a stick that might be a snake. The *high road* is a slower thalamo-cortico-amygdala route that delivers a detailed cortical analysis which either confirms the threat and sustains the response or cancels it as a false alarm, the neural basis of Lazarus's appraisal. This two-road architecture resolves the appraisal-versus-primacy debate anatomically: both routes are real and run in parallel. The amygdala also tags experiences for emotional memory (why emotionally charged events are remembered vividly) and is hyperresponsive in PTSD and anxiety disorders. Alongside it, the *insula* (insular cortex) is the cortical hub for *interoception*, mapping the internal bodily state, and is the neural home of the james-lange and Barrett strand: it is central to disgust and to the felt bodily quality of emotion. The *orbitofrontal and ventromedial prefrontal cortex* integrate emotion with value and regulate the amygdala (Damasio's somatic-marker substrate); the *ventral striatum and mesolimbic dopamine* system carries reward and positive affect (Kaplan and Sadock 2024, Companion to Psychiatric Studies 2010).

HOLD THIS

LeDoux's two roads settle the appraisal-versus-primacy debate anatomically. The fast low road (thalamo-amygdala) fires before the cortex finishes (Zajonc's primacy); the slow high road (thalamo-cortico-amygdala) delivers the appraisal (Lazarus). Both run in parallel.

CLINICAL ANCHOR

The amygdala model is directly clinical. In PTSD the low road becomes sensitised: trauma reminders drive an exaggerated amygdala response with deficient prefrontal (high-road) regulation, so the fear fires before appraisal can veto it. The Kluver-Bucy syndrome (bilateral amygdala and anterior temporal damage) shows the mirror image: loss of fear and rage, placidity, hyperorality and hypersexuality, proving the amygdala is necessary to attach threat-value to stimuli. Panic disorder and specific phobia are understood as amygdala-centred fear circuits, and exposure therapy works by strengthening prefrontal extinction of that response.

COMMON TRAP

Do not confuse the two "simultaneous" theories with the sequential ones. James-lange is strictly body-first (arousal, then feeling); cannon-bard is simultaneous-and-independent (arousal and feeling together, neither causing the other); schachter-singer is arousal-then-label (body-first but needs cognition to name it); lazarus appraisal is cognition-first (appraisal, then feeling and body together). A frequent error is to call schachter-singer "cognition-first": it is not, the arousal comes first and is then interpreted. Also, Papez proposed the *circuit*; MacLean coined and extended the *limbic system* and added the amygdala.

6.10 Worked example: the snake on the path

One stimulus, read by every theory. You are walking and a coiled shape lunges at your foot. *Darwin:* your face and body throw an evolved, universal fear display (widened eyes, recoil) that readies you and warns others. *James-lange:* your body jerks back and your heart pounds first, and it is your perception of that pounding-and-fleeing body that *is* the fear. *Cannon-bard:* the thalamus fires two signals at once, so you feel fear and your heart races simultaneously and independently. *Schachter-singer:* you feel a surge of undifferentiated arousal and, reading the context (a snake), you label it "fear"; the same surge on a rollercoaster you would label "thrill." *Lazarus appraisal:* a lightning appraisal ("that thing can harm me") comes first and generates both the fear and the racing heart; had you appraised it as a garden hose, no fear would arise. *Zajonc and LeDoux, resolved neurally:* the low road fires the amygdala and yanks your foot back before you consciously know what it is (affective primacy); a heartbeat later the high road delivers the cortex's verdict, "only a rope," and the prefrontal cortex quenches the amygdala and the fear subsides. *Currently accepted synthesis:* the fast appraisal via the amygdala, the interoceptive body-signal sensed by the insula, and the concept "snake-fear" that your brain constructs from context together make the single experience you would call terror. **Same snake, one integrated fear, assembled from appraisal, body, and construction.**

GOOD TO REMEMBER

- **Darwin (1872):** emotional expressions are innate, evolved, adaptive and universal across cultures and species; describes the output, not the mechanism.
- **James-Lange (James 1884, Lange):** body-first; emotion is the *perception* of bodily/autonomic change ("we are afraid because we tremble"); predicts a unique bodily pattern per emotion.
- **Cannon-Bard (Cannon 1927, Bard):** thalamic theory; arousal and feeling occur *simultaneously and independently*; critiqued james-lange (visceral isolation preserves emotion, arousal too slow and uniform).
- **Schachter-Singer (1962):** two-factor = physiological arousal + cognitive label; the adrenaline (epinephrine) and confederate study; origin of *misattribution of arousal*.
- **Lazarus (1966, 1991):** cognitive appraisal (cognitive-mediational) theory; appraisal is prior and necessary; primary appraisal (threat/harm/benefit) and secondary appraisal (coping). Arnold (1960) first named "appraisal."
- **Zajonc (1980):** affective primacy; some affect precedes/bypasses cognition ("preferences need no inferences"); the classic counter to Lazarus.
- **Ekman:** basic (discrete) emotions, innate and universal from the face; classic six = anger, disgust, fear, happiness, sadness, surprise.
- **Russell (1980):** circumplex / dimensional model; two axes = valence (pleasant-unpleasant) and arousal (activated-deactivated).
- **Barrett (2017):** theory of constructed emotion; emotions are built from core affect plus concepts via predictive processing; current cutting edge.
- **Currently accepted:** appraisal (Lazarus) + interoception (james-lange revived; Damasio somatic markers) + construction (Schachter-Singer label, Barrett); dissolves body-first vs cognition-first.
- **Papez circuit (Papez 1937/1939):** hippocampus, fornix, mammillary bodies (hypothalamus), mammillothalamic tract, anterior thalamic nuclei, cingulate gyrus, back to hippocampus. Lesions cause amnesia (Korsakoff). Cross-ref the Functional Neuroanatomy & Neurophysiology notes.
- **MacLean (1949):** named the limbic system ("visceral brain"); extended Papez to add the amygdala, septal area and prefrontal cortex.
- **Amygdala (LeDoux 1996):** fear hub; *low road* = fast thalamo-amygdala (primacy); *high road* = slow thalamo-cortico-amygdala (appraisal); tags emotional memory; hyperactive in PTSD; Kluver-Bucy = its loss.
- **Insula:** interoceptive cortex, felt bodily quality of emotion and disgust; the modern seat of the james-lange/Barrett strand.

7 · Consciousness and altered states

Consciousness is the most slippery construct in the whole of psychology and the one the exam most reliably rewards for clean structure. The single organising move, without which nothing else makes sense, is to split the word in two. **Level versus content.** **Level of consciousness** is *arousal*: the global on-off dimension that runs from alert wakefulness down through drowsiness, clouding, stupor, and coma, and is a property of brainstem and thalamic machinery. **Content of consciousness** is *awareness*: the actual perceptions, thoughts, and feelings present to the mind at a given moment, a property of the cortex. The two are dissociable, which is exactly why the distinction earns its keep: the vegetative-state patient has arousal (eyes open, sleep-wake cycles) with no demonstrable content, while REM-sleep dreaming and vivid hallucination are rich content at a reduced or altered level (Parvizi and Damasio 2001).

For the exam the payload is fourfold and this fragment follows the standard evolution-of-theories spine. First the definitions and the philosophical problem that frames the field. Then the theories *in the order they appeared*, each fixing what its predecessor left unexplained: James's stream, the psychodynamic topography, and the two modern cognitive accounts, Global Workspace and Integrated Information. Then the *currently accepted* position and its **neural correlate**, the ascending reticular activating system, thalamocortical loops, and the default-mode network. Finally the map of **altered states**, from normal sleep and dreaming (sleep architecture proper is the Functional Neuroanatomy & Neurophysiology notes, cross-refer there) through hypnosis, meditation, and drug states to the clinical altered states, delirium, dissociation, and the disorders of consciousness (coma, vegetative and minimally conscious states).

7.1 Definitions: the two axes, and the hard problem

Consciousness has a quantity and a quality. The clinically indispensable framing (Parvizi and Damasio 2001) is that consciousness varies along two orthogonal axes. *Level* (arousal, wakefulness) is the quantitative dimension graded from full alertness to coma; it is generated subcortically and is what a Glasgow Coma Scale measures. *Content* (awareness) is the qualitative dimension, the specific things one is conscious *of*; it is generated by the cortex. Normally the two rise and fall together, but disorders of consciousness are precisely the states where they come apart.

Level (arousal)

The global degree of wakefulness. A single continuum: alert, drowsy, clouded, stuporous, comatose. Subcortical (reticular activating system, thalamus).

Content (awareness)

The set of things present to experience at a moment, the "buzzing, booming stream" (James's phrase, quoted approvingly by Kaplan and Sadock 2024). Cortical, and highly differentiated.

Self-awareness (reflexive)

Awareness that *it is I* who am experiencing: the higher-order sense of a subject. Selectively disrupted in depersonalisation and dissociation.

The "hard problem"

Chalmers's (1995) term for the question that survives every mechanistic advance: why is there *something it is like* to be conscious at all, why does information processing generate subjective experience (qualia)? He contrasted it with the "easy problems" (explaining discrimination, integration, report), which are hard in practice but conceptually tractable. The distinction marks the boundary of what any neuroscience can currently claim to have solved.

RULE **Split the word first: level versus content.** Level is arousal (subcortical, coma-to-alert); content is awareness (cortical). They are dissociable, which is the whole point of the distinction.

7.2 William James: the stream of consciousness

The first psychological description. William James, in *The Principles of Psychology* (1890), gave consciousness its founding characterisation as a **stream of consciousness**, a continuous, ever-changing, personal flow rather than a chain of discrete "ideas." He fixed four properties that still

anchor phenomenological accounts: consciousness is *personal* (always belonging to a self), *continuous* (no gaps felt from within, even across sleep), *constantly changing* (never twice the same state), and *selective* (attention foregrounds some contents and lets the rest fall away). **What it fixed.** It replaced the atomistic "ideas" of the British associationists with a lived, flowing process, and put selective attention at the centre. **What it left debated.** It was pure introspective description with no mechanism and no account of the unconscious, and introspection itself was soon attacked as unreliable, the gap the next tradition filled from the clinic (Kaplan and Sadock 2024).

7.3 The psychodynamic topography: conscious, preconscious, unconscious

Most of the mind is out of view. Freud's topographic model (1900, 1915) reframed consciousness as only the surface of the mind, and did so by dividing mental content by its *accessibility to awareness*. The **conscious** system holds what is in awareness now. The **preconscious** holds material not currently in mind but readily retrievable by directing attention (your mother's name a second before you are asked). The **unconscious** holds material actively barred from awareness by repression, dynamic rather than merely dormant, and knowable only through its derivatives: dreams (the "royal road"), slips of the tongue (parapraxes), symptoms, and free association. **What it fixed.** It gave introspection's blind spots a systematic cause and made the inaccessible mind a legitimate object of study, and it grounds the whole clinical use of dreams and defences. **What it left debated.** The topography was later folded into the structural model (id, ego, superego, the Freud and psychoanalysis topic), and the dynamic unconscious remains empirically contested; cognitive science kept the idea of non-conscious processing while discarding the repression mechanism (Kaplan and Sadock 2024).

7.4 Global Workspace theory (Baars): consciousness as broadcast

Consciousness is a stage that broadcasts. Baars's (1988) **Global Workspace theory** was the first cognitive-science account to specify a *function* for consciousness rather than merely describe it. The mind runs a vast number of specialised, parallel, unconscious processors; most of their work never becomes conscious. A given content becomes conscious when it wins the competition for access to a limited-capacity *global workspace* and is then *broadcast* widely, making it available to all the other processors at once (the "theatre" metaphor: a spotlight of attention on a stage, broadcasting to a dark auditorium of unconscious modules). Consciousness, on this view, is what integration and global availability look like from inside. Dehaene's *global neuronal workspace* (2001 onward) gave it a neural implementation: conscious access corresponds to a sudden, all-or-none "ignition" of long-range fronto-parietal networks. **What it fixed.** It made consciousness a testable information-processing function (global availability) and predicted the empirical signature of conscious versus unconscious stimuli. **What it left debated.** It arguably explains *access* consciousness (report, availability) while sidestepping Chalmers's hard problem of *why* broadcast should feel like anything, the gap the next theory attacks head-on (Kaplan and Sadock 2024).

7.5 Integrated Information theory (Tononi): consciousness as integrated information

Consciousness is how much a system integrates information. Tononi's (2004 onward) **Integrated Information theory** (IIT) inverts the usual approach: it starts from the felt properties of experience and asks what a physical system must be like to have them. Its claim is that consciousness *is* integrated information, quantified as **phi** (the "i"-with-a-line symbol Tononi used), the amount of information a system generates *as a unified whole* over and above the information of its parts considered separately. A system is conscious to the degree that it is both highly *differentiated* (many possible states) and highly *integrated* (irreducible to independent parts). **What it fixed.** It offers, in principle, a measure that explains why the thalamocortical system is conscious while the cerebellum (equally many neurons, but modular and feed-forward) is not, and it motivated the clinically promising perturbational complexity index used to detect covert awareness. **What it left debated.** Phi is effectively incomputable for real brains, and IIT's willingness to attribute graded consciousness to any sufficiently integrated system (a panpsychist flavour) draws sharp criticism; it remains a rival to, not a replacement of, workspace accounts (Kaplan and Sadock 2024).

7.6 The currently accepted position

A pragmatic convergence, not a solved problem. There is no settled theory of consciousness, and the honest exam answer says so. The *currently accepted* working position combines three things. First, the level/content distinction is treated as foundational and clinically decisive. Second, at the mechanistic level the field converges on the idea that conscious content requires *large-scale integration and global availability* across the cortex (Global Workspace and IIT are the two leading, competing formalisations of that single intuition), gated by a functioning arousal system. Third, the "easy problems" of access, report, and integration are regarded as tractable and actively yielding to neuroscience, while Chalmers's hard problem of subjective experience is acknowledged as unresolved. In short: consciousness is operationally split into arousal (a brainstem-thalamic level) plus awareness (a cortical, integrated, globally broadcast content), and that operational split, not any single grand theory, is what current clinical and research practice runs on (Kaplan and Sadock 2024).

7.7 The neural correlate: arousal system, thalamocortical loops, default-mode network

Level and content have different substrates. The neurobiology maps cleanly onto the two axes, which is why the correlates are worth memorising as a pair.

Arousal (level): the ascending reticular activating system

The **ascending reticular activating system** (ARAS), a network of brainstem tegmental nuclei (cholinergic, noradrenergic, serotonergic, and the histaminergic tuberomammillary and orexinergic hypothalamic components) projecting up through the thalamus and basal forebrain to the cortex, sets the global level of wakefulness. Focal damage here, or to the paramedian thalamus it drives, abolishes arousal and produces coma; it is the on-switch for consciousness (the web-cache reviews call it the basic mechanism of awareness).

Content (awareness): thalamocortical loops

Recurrent **thalamocortical** loops, the reciprocal circuits between specific and intralaminar thalamic nuclei and the cortex, are the substrate of conscious content and of its integration. Loss of

thalamocortical integration (deep anaesthesia, slow-wave sleep, vegetative state) abolishes awareness even when some arousal persists; their integrity is what IIT's complexity measures probe.

The self and internal awareness: the default-mode network

The **default-mode network** (medial prefrontal cortex, posterior cingulate and precuneus, and lateral parietal cortex) is most active during rest and internally directed cognition (mind-wandering, self-reference, autobiographical thought). Its activity tracks the self-related, narrative stream of content, is suppressed by demanding external tasks, and is characteristically disrupted in the altered states below (deep meditation, psychedelics, and disorders of consciousness).

7.8 Normal altered states: sleep, dreaming, and the transitional states

The baseline already shifts nightly. Not every altered state is exotic; the ordinary sleep-wake cycle is the reference case. An *altered state of consciousness* is a recognisable, marked departure from the ordinary waking baseline in perception, cognition, emotion, and sense of self (Vaitl 2012). Sleep is the paradigm: *non-REM* sleep is a low-arousal, low-content state, while *REM* sleep pairs a highly activated, "wake-like" brain with vivid, bizarre, poorly-remembered *dreaming*, the classic dissociation of high internal content from external disconnection. Between wake and sleep sit the brief *transitional* states: *hypnagogic* (falling asleep) and *hypnopompic* (waking) imagery, and everyday *daydreaming* and reverie. **Cross-reference.** The detailed sleep architecture, the NREM stages, the REM cycle, the EEG signatures, and the neurobiology of the sleep-wake switch, is covered in the Functional Neuroanatomy & Neurophysiology notes; here it functions only as the exemplar altered state (Kaplan and Sadock 2024).

7.9 Hypnosis: the state versus non-state debate and susceptibility

A trance, or just role and expectancy? Hypnosis is a state of focused, absorbed attention with heightened suggestibility and reduced peripheral awareness, naturally distributed through the population (Tasman 2015 describes it as "a natural state of attentive, focused concentration"). The central theoretical fault-line is whether it is a distinct altered state at all.

POSITION	CORE CLAIM	KEY NAMES / EVIDENCE
State (special-process) theories	**Hypnosis is a genuinely altered state of consciousness, involving a real dissociation of control and monitoring from awareness**	Hilgard's *neodissociation* theory and the "hidden observer"; a divided consciousness in which one stream registers pain the reporting stream denies
Non-state (socio-cognitive) theories	**No special state is needed; effects arise from ordinary suggestion, expectancy, motivation, and role enactment**	Barber, Spanos, Sarbin; hypnotic responses reproducible in motivated non-hypnotised subjects

The debate is unresolved; both camps agree on the phenomena and disagree on whether they require a distinct state.

Susceptibility is the stable, measurable variable. The best-replicated fact about hypnosis is that responsiveness (*hypnotisability* or hypnotic susceptibility) is a trait-like, roughly normally distributed, and stable individual difference, measured by standardised scales, the *Stanford Hypnotic Susceptibility Scales* and the *Harvard Group Scale*. It correlates with the trait of *absorption* (the tendency to become fully immersed in imaginative experience) and predicts

clinical response; a minority are highly hypnotisable, a minority essentially refractory, most intermediate (Tasman 2015; Kaplan and Sadock 2024).

7.10 Meditation and drug-induced states

Two deliberate routes to an altered state. **Meditation** is a family of self-regulation practices that intentionally alter consciousness through the control of attention; the two broad styles are *focused-attention* meditation (sustained concentration on a single object, the breath, a mantra) and *open-monitoring* or mindfulness meditation (non-reactive awareness of whatever arises). Its neural signature centres on altered *default-mode network* activity, reduced self-referential mind-wandering in experienced meditators, alongside changes in prefrontal and insular regulation of attention and interoception. **Drug-induced states** are altered states produced pharmacologically, understood by drug class and shared phenomenology: classic *psychedelics* (LSD, psilocybin, mescaline; serotonin 5-HT2A agonists) disorganise and reduce default-mode network integration, correlating with ego-dissolution; *dissociatives* (ketamine, PCP; NMDA antagonists) uncouple perception from self; sedatives and general anaesthetics collapse thalamocortical integration to abolish awareness. One influential integrative account is *transient hypofrontality* (Dietrich), which explains several altered states (the runner's high, flow, some drug and meditative states) as a temporary down-regulation of prefrontal function (Kaplan and Sadock 2024; ScienceDirect *Encyclopedia of Consciousness* 2009).

- **Psychedelics** - LSD, psilocybin, mescaline; 5-HT2A agonists; reduce default-mode network integration (ego-dissolution).
- **Dissociatives** - ketamine, PCP; NMDA antagonists; uncouple perception from self.
- **Sedatives / anaesthetics** - collapse thalamocortical integration to abolish awareness.

> **INDIA**
>
> The contemplative traditions the exam frames as "meditation" are indigenous to the subcontinent, dhyana and samadhi in the yogic tradition, vipassana in the Buddhist. Transcendental Meditation and mindfulness-based programmes now used clinically are secularised derivatives. Worth naming in a viva both for cultural literacy and because Indian psychiatry has an active research base in yoga-based interventions.

7.11 Clinical altered states: delirium and clouding of consciousness

The commonest pathological altered state on the ward. A reduction in the *level* of consciousness, short of coma, is the core of **delirium** and is described on a graded vocabulary the exam expects verbatim. **Clouding of consciousness** is the mildest: a state ranging from barely perceptible impairment to definite drowsiness in which the person reacts incompletely to stimuli, with impaired attention, concentration, and memory, disturbed orientation, and muddled thinking; it is the *defining feature of delirium* (Shorter Oxford, Harrison et al. 2018). Delirium adds to this clouding an acute onset, a *fluctuating* course (worst at night, "sundowning"), inattention as the cardinal deficit, and perceptual disturbance (illusions and visual hallucinations, which are far more likely when the level of consciousness is reduced). It is the exemplar of an organic altered state and a medical emergency.

COMMON TRAP

"Stupor" is a false friend across specialties. In *psychiatry*, stupor means a state in which the patient is immobile, mute, and unresponsive but appears *fully conscious* (eyes open, following objects, reflexes normal), as in catatonia. In *neurology*, stupor implies an *impairment of the level* of consciousness, a state of reduced arousal from which the patient can be roused only by vigorous stimulation. State which sense you mean (Shorter Oxford, Harrison et al. 2018).

7.12 Clinical altered states: dissociation

A splitting of content, not a lowering of level. **Dissociation** is a disruption of the normal *integration* of consciousness, memory, identity, emotion, perception, and body awareness, with arousal typically preserved. Where delirium lowers the level, dissociation fragments the content: functions that normally stream together, the sense of self, the ownership of memories, the reality of perception, come apart. The clinical forms mark which integration has failed: *depersonalisation* (detachment from one's own self, "as if a robot") and *derealisation* (detachment from surroundings, "as if a film"), dissociative *amnesia* (loss of access to autobiographical memory), and, at the severe end, dissociative *identity* disorder. Trauma is the classic antecedent, and high hypnotisability links dissociation back to 7.9, the same capacity for absorbed, divided awareness underlies both (Kaplan and Sadock 2024).

7.13 Disorders of consciousness: coma, vegetative and minimally conscious states

Where level and content dissociate completely. Severe brain injury produces a graded family of disorders of consciousness that the level/content framework organises perfectly, running from no arousal and no awareness up to fluctuating awareness.

STATE	AROUSAL (LEVEL)	AWARENESS (CONTENT)	HALLMARK
Coma	Absent	**Absent**	Eyes closed, no sleep-wake cycle, unrousable; ARAS or bilateral cortical failure. Time-limited (days to weeks), evolving to recovery, VS, or death.
Vegetative state (unresponsive wakefulness)	Present	**Absent**	Eyes open, sleep-wake cycles return, but no reproducible sign of awareness. The defining dissociation: arousal without content. "Persistent" if prolonged.
Minimally conscious state	Present	**Present but minimal and fluctuating**	Inconsistent but reproducible signs of awareness (command-following, visual tracking, appropriate emotion). Better prognosis than VS.
Locked-in syndrome	Present	**Fully present (not a disorder of consciousness)**	The trap: full awareness and arousal but near-total motor paralysis (ventral pons lesion), often only vertical eye movements. Consciousness is intact; the deficit is output.

Coma is transient; the vegetative state is the pure dissociation of arousal from awareness; locked-in syndrome is intact consciousness misread as unconsciousness.

Level of consciousness at the bedside is quantified by the *Glasgow Coma Scale* (Teasdale and Jennett 1974), scoring eye-opening, verbal, and motor responses to a total of **3** (deepest coma) to **15** (fully alert). Emerging techniques (task-based fMRI, the perturbational complexity index derived from IIT) can now detect *covert* awareness in a subset of behaviourally unresponsive patients, the clinical pay-off of the integration theories above (Kaplan and Sadock 2024).

7.14 Worked example: the vegetative-state patient and the two axes

One bedside picture that makes the whole topic cohere. A young man survives a severe traumatic brain injury. After two weeks in coma (no eye-opening, unrousable, GCS 5) he begins to open his eyes and cycle between sleep and apparent wakefulness, yet he tracks nothing, follows no command, and shows no reproducible response to his family. He is in a *vegetative state*: his ascending reticular activating system has recovered enough to restore *arousal* (level), but his thalamocortical integration has not recovered enough to generate *awareness* (content). This single dissociation, eyes open but no one home, is the clinical proof that level and content are separate axes with separate substrates, and it is why the family's intuitive question ("he's awake, so is he

conscious?") has the counter-intuitive answer "awake is not the same as aware." Months later he begins, inconsistently, to squeeze a hand on request and to smile at his mother: fluctuating, reproducible signs of content have appeared, and he has crossed into the *minimally conscious state*, a better-prognosis category. A task-based fMRI showing him imagining playing tennis on command would be evidence of covert awareness, content detectable by the brain when behaviour cannot express it (Kaplan and Sadock 2024).

HOLD THIS

The vegetative state is the pure dissociation: arousal present, awareness absent. "Eyes open but no one home" is why awake is not the same as aware, and it proves level and content have separate substrates (ARAS versus thalamocortical loops).

GOOD TO REMEMBER

- **Level versus content (Parvizi and Damasio 2001):** level = arousal/wakefulness (subcortical, coma-to-alert); content = awareness (cortical). Dissociable; the master distinction.
- **Hard problem (Chalmers 1995):** why is there subjective experience (qualia) at all, versus the tractable "easy problems" (discrimination, integration, report).
- **William James (1890):** stream of consciousness; four properties: personal, continuous, constantly changing, selective.
- **Freud topographic model (1900, 1915):** conscious / preconscious (retrievable) / unconscious (repressed, dynamic; known via dreams, slips, symptoms).
- **Global Workspace theory (Baars 1988; Dehaene global neuronal workspace):** content becomes conscious by winning access to a limited workspace and being broadcast widely ("theatre/spotlight"); explains access consciousness.
- **Integrated Information theory (Tononi 2004):** consciousness = integrated information, measured as phi; needs differentiation plus integration; explains why cortex is conscious and cerebellum is not.
- **Currently accepted:** no single theory; convergence on integration plus global availability for content, gated by arousal; hard problem unresolved.
- **Neural correlate:** ascending reticular activating system (ARAS, brainstem-thalamus) = arousal/level; thalamocortical loops = content integration; default-mode network (mPFC, posterior cingulate/precuneus, lateral parietal) = self-referential internal content.
- **Altered state (Vaitl 2012):** marked departure from waking baseline in perception, cognition, emotion, self; sleep is the paradigm; hypnagogic/hypnopompic are transitional.
- **Hypnosis debate:** state (Hilgard neodissociation, "hidden observer") versus non-state / socio-cognitive (Barber, Spanos, Sarbin: suggestion, expectancy, role).
- **Hypnotisability:** stable, trait-like, roughly normally distributed; Stanford and Harvard scales; correlates with absorption.
- **Meditation:** focused-attention versus open-monitoring (mindfulness); alters default-mode network activity.
- **Drug states by class:** psychedelics (5-HT2A agonists, reduce DMN integration, ego-dissolution); dissociatives (NMDA antagonists, ketamine/PCP); sedatives/anaesthetics (collapse thalamocortical integration). Transient hypofrontality (Dietrich) as an integrative account.
- **Clouding of consciousness:** mild reduced level with impaired attention/orientation and muddled thinking; the defining feature of delirium; delirium adds acute onset, fluctuating course, inattention, visual hallucinations.
- **Stupor (false friend):** psychiatry = immobile/mute but fully conscious (catatonia); neurology = impaired level, rousable only by vigorous stimulation.
- **Dissociation:** failed integration of content with arousal preserved; depersonalisation, derealisation, dissociative amnesia, dissociative identity disorder; trauma-linked.
- **Disorders of consciousness:** coma (no arousal, no awareness; transient); vegetative/unresponsive wakefulness (arousal present, awareness absent); minimally conscious state (minimal, fluctuating awareness); locked-in syndrome (full consciousness, motor output lost, ventral pons).
- **Glasgow Coma Scale (Teasdale and Jennett 1974):** eye, verbal, motor; total 3 (deepest coma) to 15 (fully alert).

8 · Creativity and divergent thinking

Creativity is the general-psychology topic the exam most often pairs with intelligence, because the two capacities overlap but are not the same, and the discriminator (an intelligent person converges on the one right answer, a creative person generates many) is exactly what a viva examiner wants you to draw. It is worth teaching as its own clean evolution-of-theories story: a

definition, then the models in the order they appeared, each fixing something the last one missed, ending in the currently accepted componential and systems view, its neural correlate, and a clinical anchor. That clinical anchor is the reason creativity earns a place in a psychiatry syllabus at all, the century-old and much-abused "mad genius" question, and specifically the link between the bipolar spectrum and creative achievement, which the modern evidence reframes soberly rather than romantically. **One question runs through the whole topic: what kind of thinking produces something both new and useful, and does it sit near, or apart from, ordinary intelligence and ordinary mental health?**

Ground text for the psychological models is the standard creativity literature (Guilford 1950, 1967; Torrance 1974; Wallas 1926; Sternberg and Lubart 1991; Csikszentmihalyi 1996), synthesised from the general-psychology canon and cross-checked against the Simonton definition used in modern reviews (Simonton 2012). The clinical link is grounded in the DSM-5-TR (2022) and Kaplan and Sadock (2024), and the historical clinical literature (Andreasen 1987; Jamison 1993). The threshold hypothesis and the neuroscience are drawn from the contemporary creativity-neuroscience literature (Guilford; Carson and colleagues 2003; Beaty and colleagues 2016).

8.1 Creativity defined: novel and useful, and the surprise criterion

Creativity is the ability to produce work that is both *novel* (original, statistically rare, not an obvious derivation) and *useful* (valuable, appropriate to the task, or effective as a solution). This two-part definition is the one the exam wants, because either half alone fails: a bizarre response that solves nothing is odd, not creative, and a workable idea everyone already had is competent, not creative. The modern refinement (Simonton 2012), adapted from the three criteria the US Patent Office uses to grant a patent, adds a third quality, *surprise* (the idea should be nonobvious, not a step-by-step deduction from existing expertise). Crucially all three are quantitative, matters of degree with a zero point, and an idea scoring zero on any one criterion has zero creativity: reinventing the wheel is useful but not original, so it is not creative; a parachute made of reinforced concrete is original and surprising but useless, so again not creative. Hold the working definition as *novel and useful*, and add *surprising* for the fuller account.

Novelty (originality)

The idea is statistically rare or unique, low in prior probability; not an obvious derivation.

Usefulness (appropriateness)

The idea is valuable, effective, or fit for the problem; it actually works.

Surprise (nonobviousness)

The idea does not follow step by step from acquired expertise (Simonton 2012, from the patent criteria).

RULE **Creativity needs both novel and useful (add surprising).** Each criterion has a zero point, so a zero on any one means zero creativity: reinventing the wheel is useful but not original; a concrete parachute is original but useless.

8.2 Guilford's turn: divergent versus convergent thinking

The founding move of the scientific study of creativity is J. P. **guilford**'s 1950 American Psychological Association presidential address, which put creativity on the research map and located it in a distinctive kind of thinking. He contrasted two modes. **Convergent thinking** narrows many possibilities down to the single best or correct answer, the mode intelligence tests reward (there is one right response, and speed and accuracy in reaching it are scored). **Divergent thinking** does the opposite: it fans outward from a starting point to generate many varied possibilities, with no single correct answer, and it is the cognitive engine Guilford proposed underlies creative production. What Guilford *fixed* was the prior assumption that creativity was just a by-product of high IQ, giving it a separate cognitive definition (divergent generation) and a way to measure it. What he *left debated* is whether divergent-thinking scores actually predict real-world creative achievement, a validity question that still qualifies every divergent-thinking test.

FEATURE	CONVERGENT THINKING	DIVERGENT THINKING
Goal	Reach the one correct or best answer	**Generate many varied possible answers**
Direction	Narrows inward to a single point	**Fans outward from a starting point**
Right answer?	Yes, one defined solution	**No, an open field of options of varying value**
Measured by	IQ tests; the Remote Associates Test (RAT)	Unusual Uses Task; Torrance Tests (TTCT)
Scored on	Accuracy and speed	Fluency, flexibility, originality, elaboration
Maps to	Intelligence (mostly)	**Creativity (the generative engine)**

Guilford's core distinction: intelligence tests reward convergence on one answer, whereas creativity rests on divergence into many, which is why IQ tests systematically miss it.

8.3 The four scores of divergent thinking: fluency, flexibility, originality, elaboration

Guilford operationalised **divergent** thinking through open-ended tasks, the classic being the **Unusual Uses Task** (name as many uses as you can for a common object such as a brick), and he scored the output on four dimensions that every subsequent test inherits. This quartet is high-yield and worth memorising as a set.

Fluency

The sheer number of appropriate responses generated (how many uses for the brick).

Flexibility

The number of distinct conceptual categories the responses span (using the brick as a weight, a weapon, a building block, and an art object crosses more categories than five uses that are all "as a weight").

Originality

The statistical rarity or unusualness of the responses (an answer few other people give scores higher).

Elaboration
The amount of detail and development added to each idea (how fully the use is worked out).

A related and equally examinable measure is the **Remote Associates Test** (RAT, Mednick 1962), which frames creativity as the ability to link ideas that sit far apart conceptually: given three cue words (widow, bite, monkey) the respondent finds the single word that connects them all (spider). Note that the RAT is convergent in form (one right answer) but taps the associative reach that creativity theorists prize, which is why it survives alongside the divergent tasks.

TRAP The Remote Associates Test is **convergent in form** (one right answer), not a divergent test, even though it is used to probe creativity. Divergent tasks (Unusual Uses, TTCT) fan out to many answers.

8.4 Guilford's structure-of-intellect: where divergent thinking lives

guilford embedded divergent production in a larger and famously over-ambitious map of the mind, the **structure-of-intellect (SOI) model** (1967). It treats every intellectual ability as the crossing of three facets: *operations* (what the mind does, including cognition, memory, evaluation, and the two production types, convergent production and divergent production), *contents* (the material worked on, such as figural, symbolic, semantic, behavioural), and *products* (the form of the result, such as units, classes, relations, systems). Multiplying the facets yielded a large grid of distinct abilities (in its expanded form up to 150). What SOI *fixed* was the placing of creativity firmly inside a theory of intellect rather than treating it as a mysterious spark: divergent production is one operation among several, no more mystical than memory. What it *left debated*, and where it was ultimately rejected, is that the model was too fine-grained and its many hypothesised abilities were not empirically independent, so SOI is remembered chiefly for the enduring convergent-versus-divergent distinction it carried, not for its 150-cell grid.

8.5 Torrance: the tests that made divergent thinking measurable

E. Paul **torrance** translated Guilford's ideas into the field's most widely used instrument, the **Torrance Tests of Creative Thinking (TTCT, 1966, 1974)**. The TTCT comes in verbal and figural forms (the figural form asks the child or adult to complete or build pictures from incomplete figures) and is scored on the Guilford-derived dimensions, principally fluency, flexibility, originality, and elaboration, later refined to emphasise originality and elaboration plus qualities such as resistance to premature closure and abstractness of titles. What Torrance *fixed* was the practical measurement problem: he gave educators and researchers a standardised, normed, scorable creativity test suitable for children, and his longitudinal follow-ups offered some of the first evidence that early divergent-thinking scores relate to later creative achievement. What he *left debated* is the ceiling of that predictive validity (divergent-thinking scores correlate with, but are far from equal to, real creative accomplishment) and the persistent worry that timed tick-box scoring captures only a thin slice of what creativity means.

8.6 Wallas's four-stage creative process

Alongside the ability tradition runs a process tradition, asking not how much creativity a person has but what steps a creative act passes through. The canonical scheme is Graham **Wallas**'s four-

stage model (*The Art of Thought*, 1926), which still frames how the creative process is taught.

Preparation
Conscious, effortful work: defining the problem and saturating oneself in the relevant knowledge and attempted solutions.

Incubation
The problem is set aside and worked on unconsciously; no deliberate effort, often during rest or unrelated activity.

Illumination
The sudden "aha," the insight arriving whole into consciousness (the moment the solution appears).

Verification
Conscious testing, elaboration, and refinement to confirm the insight actually works and to render it usable.

What Wallas *fixed* was the naive view that creation is one instantaneous flash: he showed it is a sequence in which conscious preparation and unconscious incubation both do necessary work before the flash, and verification does the unglamorous work after. What he *left debated* is the mechanism of incubation (is it genuine unconscious processing, mere forgetting of misleading fixed sets, or spreading activation during the pause) and whether the stages are truly discrete or overlapping and recursive. Note the deliberate link to the thinking topic: Wallas's *illumination* is the same Gestalt *insight* ("aha," sudden restructuring) met under problem-solving (cross-ref: Thinking, problem-solving and intelligence, insight).

8.7 Investment and systems theories: creativity as more than a trait

By the 1990s the field had moved from asking "what mental ability is creativity" to "what constellation of factors, inside and outside the person, produces creative work," giving two influential accounts. Robert **Sternberg and Todd Lubart**'s **investment theory** (1991) uses a market metaphor: creative people "buy low and sell high," pursuing ideas that are novel and undervalued (out of favour), developing them, and moving on. It names six convergent resources a creative act requires, namely intellectual abilities, knowledge, thinking styles, personality (tolerance of ambiguity, willingness to take sensible risks), intrinsic motivation, and a supportive environment. Mihaly **Csikszentmihalyi**'s **systems model** (1988, 1996) goes further outward, arguing creativity is not a property of a person at all but of a system with three parts in interaction: the *individual* (who produces a variation), the *domain* (the body of knowledge and symbols, such as mathematics or music, that the individual draws on and changes), and the *field* (the gatekeepers, editors, critics, and experts who decide whether the variation is accepted into the domain). On this view an idea is creative only when the field validates it and the domain absorbs it. What these theories *fixed* was the individualistic narrowness of the ability tradition, showing creativity depends on motivation, personality, and above all social validation, not on divergent thinking alone. What they *leave debated* is measurement: systems and investment accounts are rich but far harder to quantify than a divergent-thinking score.

8.8 Csikszentmihalyi's flow: the subjective state of creative work

Csikszentmihalyi's second major contribution, distinct from the systems model but examinable alongside it, is the concept of **flow** (1975, 1990): the fully absorbed, optimal state of consciousness in which a person is completely immersed in an activity, action and awareness merge, self-consciousness and the sense of time fall away, and the activity becomes intrinsically rewarding (autotelic). Flow arises specifically at the balance point where the *challenge* of the task matches the person's *skill*: too much challenge for the skill breeds anxiety, too little breeds boredom, and only the matched zone produces flow. Flow is the phenomenology of engaged creative (and skilled) activity and connects the creativity literature to positive psychology and to the "engagement" pillar of well-being (cross-ref: Motivation and emotion; positive psychology).

8.9 The threshold hypothesis: how much intelligence creativity needs

The relationship between creativity and intelligence is not "more is always more," and the exam-relevant summary is the **threshold hypothesis** (associated with Guilford and elaborated by later work). It holds that intelligence and creativity are positively correlated up to a point, but only up to a threshold conventionally placed around an **IQ** of **120**: below the threshold, a certain baseline of general intelligence is genuinely necessary for creative achievement (you cannot be creative in a domain you lack the cognitive resources to grasp), so the two rise together. Above the threshold the correlation weakens or disappears: among already-bright people, further increases in IQ do not predict more creativity, which now depends on other factors (divergent thinking, personality, motivation, opportunity). The lesson to carry is that creativity requires *some but not maximal* intelligence: high intelligence is a near-necessary but not sufficient condition, and the most creative individuals are reliably above average in IQ but are not necessarily the very highest scorers. (The precise threshold value is contested and some large modern studies fail to find a clean cut-off, so treat 120 as the classically taught figure rather than a hard constant, flagged under gaps.)

> **COMMON TRAP**
>
> Do not equate creativity with intelligence, and do not treat the threshold hypothesis as saying "the smarter you are, the more creative you are." It says the opposite above the threshold: past roughly IQ 120 the correlation flattens, so the genius-level IQ is neither required nor predictive of creative output. Equally, do not confuse convergent with divergent thinking. Convergent thinking (and the RAT, which is convergent in *form*) narrows to one right answer; divergent thinking (Unusual Uses, TTCT) fans out to many. Intelligence tests measure mostly convergent ability, which is exactly why they miss creativity.

8.10 The creativity-psychopathology question: the "mad genius" debate, stated soberly

The oldest clinical claim about creativity, from Aristotle through the Romantics to Lombroso, is that genius and madness are linked. The modern evidence supports a real but *narrow and non-linear* association, concentrated on the **bipolar spectrum** rather than on severe mental illness in general, and it must be stated carefully to avoid both romanticisation and stigma. The landmark studies are Nancy **Andreasen**'s (1987) controlled interview study of the Iowa Writers' Workshop, which found substantially higher rates of mood disorder (especially bipolar and depressive

spectrum) among eminent writers than controls, and Kay Redfield **Jamison**'s (1989, 1993) work documenting elevated rates of mood disorder and creative productivity tied to mild elevations of mood. The plausible mechanism is that mild hypomania supplies exactly the ingredients divergent thinking needs: increased fluency and speed of thought, expansiveness, reduced need for sleep, heightened energy, confidence, and looser associations, all of which can raise idea generation, provided the mood elevation stays mild.

The sober qualifications are the examinable core, and the DSM-5-TR (2022) states them plainly. First, the relationship is *non-linear*: it is *milder* forms of bipolar disorder, not full severe mania, that associate with greater lifetime creative accomplishment (florid mania and depression are disorganising and disabling, and destroy productive work). Second, higher creativity is found in the *unaffected first-degree relatives* of people with bipolar disorder, which points to a shared genetic or temperamental substrate (a creative "endophenotype") rather than illness itself being the cause. Third, creativity is listed among the *trait-like features* associated with bipolar I (alongside hyperthymic and cyclothymic temperament and reward sensitivity), again framing it as a dispositional correlate, not a product of episodes. The clinically vital and non-obvious point the DSM adds: a patient's attachment to the heightened creativity of hypomania can drive ambivalence about treatment and poor adherence, because they fear that a mood stabiliser will flatten the creative edge (cross-ref: the Social, Learning & Personality Psychology notes bipolar disorder; and note the lithium-and-creativity adherence problem).

HOLD THIS

The mad-genius link is real but narrow and non-linear. It is *milder* bipolar forms, not full mania, that associate with creative accomplishment; higher creativity in unaffected first-degree relatives points to a shared substrate, not illness itself.

CLINICAL ANCHOR

A patient with bipolar II resists lithium, saying it "kills my writing." The evidence lets you answer honestly without either dismissing him or endorsing the romantic myth: the creativity that matters is linked to *mild* hypomanic states and to his underlying temperament, not to full episodes, which are disorganising; unaffected relatives share the creative edge, so it is not the illness "giving" him talent; and untreated mood swings threaten far more of his output than a stabiliser does. Framing treatment as protecting his productive capacity from the disorganising extremes, not confiscating his gift, is the adherence-preserving move the DSM-5-TR flags as the crux.

8.11 Currently accepted account: an interaction of process, person, and system

There is no single grand theory that has won the field the way CHC has won intelligence, but the *currently accepted* synthesis is a componential and interactionist one: creativity is best understood not as one ability but as the interaction of a cognitive process (divergent generation to produce candidate ideas, followed by convergent evaluation to select and refine the good ones), a set of personal resources (adequate but not maximal intelligence past the threshold, relevant domain knowledge, openness to experience, tolerance of ambiguity, sensible risk-taking, and intrinsic motivation), and a social system (the domain that supplies the material and the field that validates

the product, per Csikszentmihalyi). In short, the modern consensus keeps Guilford's divergent-convergent cycle at the cognitive core, wraps it in the investment theory's personal resources, and situates the whole thing in the systems model's social context. The practical upshot for assessment is that no single test captures creativity, and divergent-thinking scores (TTCT) are treated as one indicator among several, not a definitive measure.

8.12 Neural correlate: reduced latent inhibition and network dynamics

The **neural correlate** of creativity has two well-supported strands the exam can ask for by name. The first is **reduced latent inhibition**. Latent inhibition is the normal, adaptive brain process by which stimuli previously experienced as irrelevant are automatically filtered out of conscious attention. Carson, Peterson, and Higgins (2003) showed that *reduced* latent inhibition, a leakier filter that lets nominally irrelevant information into awareness, is associated with higher creative achievement, but specifically in people who *also* have high intelligence and working memory to manage the extra input. This is the mechanistic bridge to psychopathology: the same reduced filtering, without the cognitive resources to harness it, appears in the positive-symptom dimension of psychosis and in schizotypy, so creativity and psychosis-proneness may share a substrate (leaky filtering) whose outcome depends on the intellectual control brought to bear on it. Dopaminergic tone, particularly in the mesolimbic and prefrontal systems, is the leading neurochemical candidate for tuning this filter.

The second strand is **large-scale network dynamics** (Beaty and colleagues 2016 and after). Creative cognition is not localised to a "right brain" but emerges from the flexible cooperation of usually antagonistic networks: the *default-mode network* (medial prefrontal cortex, posterior cingulate, and associated regions), engaged in spontaneous, associative, self-generated idea production, and the *executive control network* (dorsolateral prefrontal and parietal regions), engaged in the goal-directed evaluation, constraint, and refinement of those ideas. The salience network (anterior insula, anterior cingulate) is thought to switch between them. Highly creative people show stronger and more flexible *coupling* between the default-mode (generative) and executive (evaluative) networks, the neural version of the generate-then-select cycle described in 8.11. The old "right-brain equals creative" claim is a myth; creativity is a whole-brain, between-network phenomenon.

8.13 Worked example: the brick, from generation to product

Trace one everyday act through the whole apparatus. Asked for unusual uses of a brick, a person who lists "doorstop, paperweight, weapon, bookend, garden border, art object, water-displacement in a cistern, ground into pigment" is doing *divergent* thinking, and each Guilford score is visible: eight responses (fluency), spanning several conceptual categories from tool to art to material (flexibility), including a rare answer like pigment (originality), and one worked out in detail (elaboration). The generation phase runs on default-mode associative activity with a relatively leaky attentional filter (reduced latent inhibition letting the odd "pigment" idea surface). Then convergent, executive evaluation selects which uses actually work and are worth reporting. Map the same brick onto Wallas: *preparation* is understanding the task, *incubation* is the pause where the pigment idea forms unbidden, *illumination* is its sudden arrival, *verification* is checking

that a ground brick really does make usable pigment. And the systems check: the idea counts as creative only if it is both novel and useful, and, for genuine domain-changing creativity, only once a relevant field accepts it. The brick test is trivial; the machinery it exercises is the whole topic.

MNEMONIC

FFOE for the four divergent scores; "PI-IV" for Wallas

FFOE = **F**luency, **F**lexibility, **O**riginality, **E**laboration (the four Guilford / Torrance divergent-thinking scores). **Wallas** = **PI-IV**: **P**reparation, **I**ncubation, **I**llumination, **V**erification, in that order (the two "I" stages, incubation then illumination, sit in the middle).

GOOD TO REMEMBER

- **Creativity:** novel + useful (add surprising / nonobvious, Simonton 2012 from patent criteria); zero on any one criterion = zero creativity.
- **Guilford (1950 APA address):** founded the field; divergent (fans out, many answers) vs convergent (narrows to one right answer) thinking.
- **Four divergent scores (FFOE):** Fluency (number), Flexibility (categories), Originality (rarity), Elaboration (detail); measured by the Unusual Uses Task.
- **Remote Associates Test (Mednick 1962):** find the word linking three cues (widow/bite/monkey = spider); convergent in form, taps associative reach.
- **Guilford structure-of-intellect (1967):** operations x contents x products grid (up to 150 abilities); divergent production is one operation; rejected as over-fine but carried the convergent/divergent split.
- **Torrance Tests of Creative Thinking (TTCT, 1966/1974):** verbal + figural; scored on Guilford's dimensions; the standard creativity test, usable in children.
- **Wallas four stages (1926, PI-IV):** Preparation, Incubation, Illumination, Verification; illumination = the Gestalt insight / "aha."
- **Investment theory (Sternberg and Lubart 1991):** "buy low, sell high"; six resources = intellect, knowledge, thinking styles, personality, motivation, environment.
- **Systems model (Csikszentmihalyi 1988/1996):** individual x domain x field; the field (gatekeepers) validates, the domain absorbs.
- **Flow (Csikszentmihalyi 1975/1990):** total absorption; challenge matched to skill (too much = anxiety, too little = boredom); autotelic.
- **Threshold hypothesis:** intelligence and creativity correlate only up to about IQ 120; above it, creativity depends on other factors. Some, not maximal, intelligence needed.
- **Mad-genius / bipolar link:** Andreasen (1987, Iowa Writers' Workshop) and Jamison (1993); real but non-linear; *milder* bipolar forms associate with more creative accomplishment; higher creativity in unaffected relatives (shared substrate); a DSM-5-TR trait-like feature; attachment to hypomanic creativity harms treatment adherence.
- **Currently accepted:** creativity = interaction of process (divergent generation + convergent evaluation) + person (resources, above-threshold IQ, openness) + system (domain and field).
- **Neural correlate:** reduced latent inhibition (Carson et al. 2003; leaky filter, creative only if paired with high IQ; shared with psychosis-proneness; dopaminergic); flexible coupling of default-mode network (generation) with executive-control network (evaluation), salience network switching (Beaty et al. 2016). Not "right brain."

9 · Emotional intelligence

Emotional intelligence (EI, popularly EQ) is the capacity to perceive, understand, use, and regulate emotions, in oneself and in others, and to harness that emotional information to guide thinking and action. Salovey and Mayer, who coined the term in its modern scientific form, defined it as "the ability to monitor one's own and others' feelings and emotions, to discriminate among them, and to use this information to guide one's thinking and actions" (Salovey and Mayer 1990). It sits at the junction of intelligence and personality, and the whole topic is a single argument about which of those two it really is: an *ability* you can be tested on like IQ, or a cluster of *traits and dispositions* you can only self-report. **Ability or trait.** Every named model is a different answer, and each fixed a specific gap in the one before it.

For the exam the payload is fourfold: the ordered lineage of models with their authors and the one claim each is remembered for; the ability-versus-trait axis that organises them together with how each is measured (performance test versus self-report); the incremental-validity critique that is the field's central controversy; and the neural correlate, the "social brain" of ventromedial prefrontal cortex, amygdala, and insula. Structure the answer as an evolution, not a list, and end on where alexithymia and the therapeutic alliance make EI clinically real.

9.1 Thorndike: the first seed, "social intelligence"

The starting point. The idea long predates the term. Edward Thorndike (1920) distinguished, alongside abstract (academic) and mechanical intelligence, a **social intelligence**: "the ability to understand and manage men and women, boys and girls, to act wisely in human relations." **What it seeded.** It first proposed that the ability to read and handle people is a real form of intelligence, separate from the logical-verbal ability that IQ tests measure. **What it left debated.** Thorndike named the construct but could not operationalise or measure it, and social intelligence proved almost impossible to separate from general IQ with the tools of the day, so the idea lay largely dormant for decades (Salovey and Mayer 1990).

9.2 Gardner: intrapersonal and interpersonal intelligences within multiple intelligences

Reviving the personal. Howard Gardner (1983), in his theory of **multiple intelligences**, argued that the single general factor of traditional testing was too narrow and proposed several independent intelligences. Two of them are the direct ancestors of EI: *intrapersonal intelligence*, the capacity to access and understand one's own inner emotional life and use it to guide behaviour, and *interpersonal intelligence*, the capacity to read the moods, motives, and intentions of other people. **What it fixed.** It gave Thorndike's neglected social ability a formal place inside a serious theory of intelligence and split it into a self-facing and an other-facing half. **What it left debated.** Gardner's intelligences were broad and hard to measure empirically, and he never welded the two personal intelligences into a single testable emotion-specific construct, which is exactly what the next authors did (Kaplan and Sadock 2024).

9.3 Mayer and Salovey: the four-branch ability model

The scientific core. Peter Salovey and John Mayer (1990) fused Gardner's two personal intelligences into one and named it emotional intelligence, then refined it into the **four-branch**

ability model (Mayer and Salovey 1997), the model to know cold. EI is treated as a genuine cognitive ability, correlated with but distinct from general intelligence, built of four hierarchically arranged branches from lowest (most basic) to highest:

1. Perceiving emotion

The most basic branch: accurately identifying emotion in faces, voices, pictures, music, and in oneself. The entry skill on which the others depend.

2. Using (facilitating) emotion

Harnessing emotion to assist thought: letting mood prioritise attention, and using emotional states to aid reasoning, problem-solving, and creativity (for example, a positive mood widening idea generation).

3. Understanding emotion

Grasping emotional knowledge: how emotions blend, progress, and transition (that contempt mixes anger and disgust, that grief can shade into anger), and reading their causes and vocabulary.

4. Managing (regulating) emotion

The highest branch: regulating emotion in oneself and others to promote growth and reach goals, staying open to feeling while modulating it.

The four branches run lowest to highest: perceive, use, understand, manage. Mnemonic PUUM (see box).

What it fixed. It turned a loose popular idea into a precise, componential, and above all *measurable* ability that meets standard criteria for an intelligence (Mayer, Caruso and Salovey 1999). **What it left debated.** By insisting EI is a pure ability testable by performance, it drew a hard line that a rival tradition, treating EI as personality-like traits, would soon cross (Kaplan and Sadock 2024).

9.4 Goleman: the mixed (competency) model that popularised EI

The bestseller model. Daniel Goleman's 1995 book *Emotional Intelligence: Why It Can Matter More Than IQ* brought the concept to the world and made the striking claim that EI predicts life and career success better than IQ. Goleman built a **mixed model** (also called a competency model), so named because it mixes ability-type emotional skills with personality traits, motives, and social competencies. His framework distils to five domains (later reorganised into competency clusters): *self-awareness*, *self-regulation*, *motivation*, *empathy*, and *social skill* (Goleman 1998). **What it fixed.** It made EI intuitive, teachable, and workplace-relevant, driving a huge applied and training literature. **What it left debated.** By folding in motivation, optimism, and conscientiousness, the mixed model overlaps heavily with established personality traits and risks becoming an "everything but IQ that matters" grab-bag, the core of the incremental-validity critique in 9.7 (Kaplan and Sadock 2024).

9.5 Bar-On: the emotional-social intelligence (ESI) model and the EQ-i

The other mixed model. Reuven Bar-On, who is credited with the abbreviation "EQ," proposed a model of **emotional-social intelligence** (ESI): an array of interrelated emotional and social competencies, skills, and facilitators that determine how effectively we understand and express ourselves, understand and relate to others, and cope with daily demands (Bar-On 2006). His

model is organised into competency areas (intrapersonal, interpersonal, adaptability, stress management, and general mood) and is operationalised by the *Emotional Quotient Inventory (EQ-i)*, the first commercially published, peer-reviewed self-report EI test (Bar-On 1997). **What it fixed.** It gave the trait-and-competency tradition a well-validated, widely used self-report instrument and an explicit link to well-being and adaptation. **What it left debated.** Like Goleman's, it is a mixed model measured by self-report, so it inherits the same overlap-with-personality and self-report-bias problems (Kaplan and Sadock 2024).

9.6 The ability-versus-trait debate and its two measurement families

The organising split. Petrides and Furnham (2001) crystallised the field into two conceptually and psychometrically distinct constructs, distinguished chiefly by *how they are measured*.

FEATURE	ABILITY EI	TRAIT EI
Core claim	EI is a cognitive ability, a form of intelligence	EI is a constellation of emotion-related self-perceptions and dispositions ("trait emotional self-efficacy")
Where it sits	Alongside cognitive abilities	**At the lower levels of the personality hierarchy**
Key proponents	Mayer, Salovey, Caruso	Petrides and Furnham; overlaps Goleman, Bar-On
How measured	**Maximum-performance test with correct answers (MSCEIT)**	**Self-report questionnaire (TEIQue, EQ-i, Goleman inventories)**
Scoring truth-standard	Consensus or expert scoring (there is a "right" answer)	No right answer; measures self-perception
Correlation between them	**Low; empirically they behave as two different constructs**	

Ability EI is tested like IQ (right answers, performance); trait EI is self-reported and lives inside personality. The two correlate only weakly.

The flagship ability measure is the **MSCEIT** (Mayer-Salovey-Caruso Emotional Intelligence Test, V2.0), which scores actual performance on the four branches against consensus or expert norms (Mayer, Salovey, Caruso and Sitarenios 2003). The trait measures (EQ-i, Goleman's inventories, the TEIQue) are self-report and therefore assess belief about one's own emotional competence rather than demonstrated skill. A trait score can be inflated by social desirability or by the very lack of insight it claims to measure, the self-report paradox in emotion research (Kaplan and Sadock 2024).

RULE **Measurement decides the construct.** Ability EI is a performance test with right answers (MSCEIT); trait EI is self-report inside personality (EQ-i, TEIQue). The two correlate only weakly and behave as different constructs.

9.7 The incremental-validity critique

The central controversy. The sharpest scientific challenge to EI is whether it predicts anything *over and above* what we already measure cheaply with IQ and the Big Five personality traits, that is, whether it has **incremental validity**. Critics (notably Locke 2005; and Matthews, Zeidner and Roberts) argue that EI, especially the mixed and trait models, is conceptually overinflated and largely redundant: strip out general intelligence and the Big Five and little unique variance is left, so EI may be old constructs under a fashionable new name. The rebuttal is measurement-specific: performance-based ability EI (MSCEIT) shows the strongest case for genuine incremental prediction of social and clinical outcomes because it is not just relabelled personality, whereas self-report trait EI overlaps most with existing personality scales (Brackett and Mayer 2003). **The verdict for the exam.** EI is a real and useful construct, but its incremental validity is real chiefly when measured as an ability, and Goleman's popular claim that "EI matters more than IQ" is not supported at that strength (Kaplan and Sadock 2024).

HOLD THIS

Salovey and Mayer coined and defined EI; Goleman only popularised it. Ability EI has the strongest case for incremental validity beyond IQ and the Big Five; "EI matters more than IQ" is Goleman's claim, not established fact.

9.8 Neural correlate: the "social brain" of vmPFC, amygdala, and insula

Where EI lives in the brain. The *neural correlate* of emotional intelligence is a core "social brain" network, and the strongest evidence comes from lesion studies: damage to specific nodes selectively degrades EI while sparing general IQ (Hogeveen, Salvi and Grafman 2016). Three structures anchor it. The **ventromedial prefrontal cortex** (vmPFC), including the orbitofrontal cortex, integrates emotion with value and social meaning and regulates the limbic system; its lesions produce the classic dissociation of preserved abstract IQ with collapsed emotional and social decision-making (the Phineas Gage and Damasio vmPFC pattern), impairing the "using" and "managing" branches. The **amygdala** is the hub for perceiving emotional salience, especially detecting fear and threat in faces, the neural basis of the perceiving-emotion branch; amygdala damage impairs recognition of fearful expressions. The **insula** is the cortical seat of *interoception*, the sensing of one's own bodily-emotional state, and is central to empathy and to feeling disgust, grounding self-awareness and the perception of emotion in the body. Together, vmPFC (integration and regulation), amygdala (salience and perception), and insula (interoception and empathy) form the substrate on which the four branches are built (Hogeveen et al. 2016, Kaplan and Sadock 2024).

9.9 Clinical relevance: alexithymia, and EI in the therapeutic alliance

Where it becomes clinical. EI's clinical mirror-image is **alexithymia** (Sifneos 1973), literally "no words for feelings": a difficulty identifying and describing one's own emotions, distinguishing feelings from bodily sensations of arousal, and an externally oriented, concrete cognitive style. Alexithymia is essentially the low-EI end of the perceiving-and-understanding branches made pathological, and it is common in somatoform and functional disorders, substance use, eating disorders, and post-traumatic and personality disorders; it predicts poorer treatment response

and is a target of mentalisation-based and emotion-focused work. On the clinician's side, EI matters for the *therapeutic alliance*: the therapist's ability to accurately perceive a patient's affect, to attune and respond to it, and to regulate their own emotional reactions (countertransference) is EI in action, and higher clinician emotional competence is linked to stronger alliance and better engagement. This is why emotional-competence and empathy training is increasingly built into medical and psychiatric education (Kaplan and Sadock 2024).

9.10 Worked example: the patient who cannot name the feeling

One consultation, read through the models. A man presents with recurrent chest tightness and headaches; every investigation is normal. *Perceiving:* asked how he feels, he reports only the physical sensations and cannot label an emotion, high on somatic complaint, low on the perceiving branch, the signature of alexithymia. *Understanding:* he cannot connect the tightness to the fact that it began the week his father was hospitalised, a failure of the understanding branch to link emotion to cause. *Using and managing:* unable to name or modulate the feeling, he cannot use it to problem-solve and it discharges through the body. *Ability versus trait:* a self-report EI questionnaire might even rate him "fine" because he lacks the insight to report the deficit, exactly why an ability measure like the MSCEIT, or the clinician's own trained perception, catches what self-report misses. *Neural read:* the picture fits weak interoceptive and insular processing feeding a vmPFC that cannot translate bodily signals into labelled, regulable emotion. *The alliance as intervention:* the therapist uses their own EI to name the affect the patient cannot ("this started when your father fell ill, that must have been frightening"), and the therapy itself becomes emotion-labelling training. **Same patient, one somatic complaint, decoded as an emotional-intelligence deficit and treated by borrowing the clinician's EI until his own grows.**

MNEMONIC

Four branches: "PUUM" (Perceive, Use, Understand, Manage)

Read low to high, PUUM climbs the ability model: **P**erceive emotion, **U**se emotion to aid thought, **U**nderstand emotion, **M**anage emotion. Perceiving is the floor, managing is the ceiling.

COMMON TRAP

Do not blur the models. Mayer and Salovey = pure *ability* model (measured by performance, the MSCEIT). Goleman and Bar-On = *mixed* models that fold in personality and motivation (measured by self-report). Petrides = the explicit *trait* EI construct inside personality. A frequent error is crediting Goleman with defining EI: he popularised it, but Salovey and Mayer coined and defined it (1990). Another is claiming "EI predicts success better than IQ" as established fact, it is Goleman's popular claim and the incremental-validity data do not support it at that strength.

GOOD TO REMEMBER

- **Thorndike (1920):** first proposed "social intelligence," the ability to understand and manage people; named it but could not measure it.
- **Gardner (1983):** multiple intelligences; the two EI ancestors are *intrapersonal* (understanding one's own inner life) and *interpersonal* (reading others).
- **Salovey and Mayer (1990):** coined "emotional intelligence" and gave the founding definition; monitor own/others' emotions, discriminate, and use to guide thought and action.
- **Four-branch ability model (Mayer and Salovey 1997):** Perceive, Use (facilitate), Understand, Manage emotion; hierarchical, lowest to highest; EI as a genuine ability.
- **Goleman (1995, 1998):** mixed/competency model; five domains = *self-awareness, self-regulation, motivation, empathy, social skill*; claimed EI can matter more than IQ.
- **Bar-On (1997, 2006):** emotional-social intelligence (ESI); coined "EQ"; operationalised by the self-report EQ-i.
- **Petrides and Furnham (2001):** formalised the *trait EI* construct (trait emotional self-efficacy), sitting in the personality hierarchy.
- **Ability vs trait:** ability EI = performance test with right answers (MSCEIT); trait EI = self-report (EQ-i, TEIQue); the two correlate only weakly.
- **MSCEIT (Mayer-Salovey-Caruso, V2.0, 2003):** the flagship performance measure of the four branches, consensus/expert scored.
- **Incremental-validity critique (Locke 2005; Matthews, Zeidner and Roberts):** does EI predict beyond IQ + Big Five? Case is strongest for ability EI, weakest for self-report/mixed EI.
- **Neural correlate ("social brain"):** ventromedial prefrontal cortex (integration/regulation of value and emotion), amygdala (emotional salience, fear-face perception), insula (interoception, empathy); lesion evidence from Hogeveen, Salvi and Grafman (2016).
- **Alexithymia (Sifneos 1973):** difficulty identifying and describing feelings, externally oriented thinking; the low-EI pole, common in somatoform, substance-use, eating, trauma, and personality disorders.
- **Therapeutic alliance:** clinician EI (accurate affect perception, attunement, countertransference regulation) strengthens alliance; a rationale for empathy/EI training in medical education.

10 · Sensory deprivation and the mind-body problem

This is the philosophy-of-psychiatry topic, and it earns its place in the exam because it is where a clinical phenomenon and a two-thousand-year metaphysical puzzle turn out to be the same question asked twice. **Take away the world and the mind starts to invent one.** That single observation, from the isolation-tank experiments, is the empirical hook; the deeper question it forces is the one Descartes named: what exactly is the relation between the **mind** and the **body** (the brain)? The topic pairs the two deliberately. **Sensory deprivation** shows the mind is not a passive receiver of the world but an active constructor of it, which is exactly why perception is prediction (cross-refer the Perception topic); and the **mind-body problem** is the framework a psychiatrist needs to hold the biological and the psychological together without collapsing one into the other.

For the exam the payload is two halves that meet in the middle. First, sensory deprivation: the classic Hebb/McGill and Lilly experiments, the perceptual and cognitive effects, the hallucinations they produce, and the modern clinical relevance (REST, solitary confinement, the intensive-care unit). Second, the mind-body problem proper: the map of positions from

Cartesian **dualism** to the various **monisms**, the explanatory gap and qualia, and then why it all matters at the bedside: reductionism versus the biopsychosocial model, the brain-disease debate, and free will and responsibility. Ground text is Kaplan and Sadock (2024) for the philosophy-of-mind and sensory-deprivation material, with the New Oxford and Companion for the dualism-in-medicine framing and Engel (1977) for the biopsychosocial answer.

10.1 Sensory deprivation: definition and the classic experiments

Strip out the input and perception destabilises. Sensory deprivation is the drastic and sustained reduction of patterned sensory input across modalities. Humans normally operate in what Hartmann called an "average expectable environment," a certain level and variety of stimulation for which the nervous system is primed; remove it, and the brain, still generating predictions with nothing to correct them against, begins to produce its own content (Kaplan and Sadock 2024). Two lines of experiment defined the field. The **Hebb / McGill studies** (Bexton, Heron and Scott 1954, in Donald Hebb's laboratory at McGill University) paid student volunteers to lie on a bed in a lightproof, soundproof cubicle wearing translucent goggles and cardboard cuffs that abolished patterned touch; most could not tolerate more than two or three days, and they reported deteriorating concentration, disturbed thinking, and vivid visual hallucinations. The **Lilly isolation tank** (John C. Lilly, from 1954) took the reduction further: the subject floated, near-weightless, in a tank of body-temperature salt water in total darkness and silence, removing even gravity and proprioception. Lilly used it to explore altered states and the "higher levels of consciousness" the near-total silencing of input could produce (Psychotherapy Guidebook, Suedfeld). Together they established that the deprivation of stimulation is itself a potent alterer of the mind.

10.2 Perceptual, cognitive and affective effects

A reproducible syndrome, not random noise. The effects of prolonged sensory deprivation form a recognisable cluster that the exam expects enumerated.

Perceptual

Illusions first, then hallucinations, most often visual, progressing from simple flashes and geometric forms to complex, dramatic scenes; also somatic and auditory distortions and disturbances of body image. The three-scientists observation (below) captures the striking individual variability.

Cognitive

Impaired concentration and sustained attention, disorganised and drifting thinking, difficulty with directed thought, distortions of the sense of time, and increased suggestibility.

Affective and behavioural

Rising restlessness, irritability, anxiety and, in some, frank distress and an urge to escape the situation; a smaller group finds it relaxing or absorbing, which is what REST later exploited therapeutically.

Individual variability is the examinable subtlety. Kaplan and Sadock (2024) record the classic demonstration: three scientists floated in sensory-deprivation tanks for long periods; one had a few illusions and no hallucinations, the second had many illusions and a few faint hallucinations, and the third had vivid, dramatic, complex visual and auditory hallucinations. Identical

deprivation, radically different output, which foreshadows the point that what is "released" depends on the perceiver, not just the situation.

10.3 Hallucinations under deprivation: the mechanism (link to perception)

Less input, not more, breeds the hallucination. This is the counter-intuitive fact and the bridge back to the Perception topic. The **perceptual release theory** (Hughlings Jackson; developed by West 1962) holds that a steady stream of sensory input normally suppresses stored perceptual traces, memories and images, from reaching awareness; when input falls (sensory deprivation, blindness, deafness) or arousal-gating fails, those stored images are *released* and experienced as hallucinations located in outer space (Kaplan and Sadock 2024). A complementary framing is the **supersensitivity deprivation hypothesis**: deprived of expected input, the perceptual apparatus over-interprets any faint stimulation as evidence of the needed object. In the modern predictive-processing language of the Perception topic, both say the same thing: when bottom-up sensory evidence is weak, top-down priors dominate and the brain perceives what it expects. This is exactly why the blind develop Charles Bonnet hallucinations, the deaf develop musical hallucinations, and the sensory-deprived subject sees scenes in the dark, and it is the same imbalance, tipped further, that the predictive account gives for psychotic hallucination.

RULE **Less input, not more, breeds the hallucination.** When bottom-up sensory evidence is weak, top-down priors dominate and the brain perceives what it expects, which is why reduced input drives hallucination on the ward.

CLINICAL ANCHOR

The principle generalises to the ward. Any state that *reduces* sensory input or the capacity to process it heightens the risk of hallucination: the intensive-care unit at night, the post-operative patient, the cataract or hearing-impaired elderly patient, and the delirious patient (in whom impaired attention functions as an internal deprivation). It is a practical argument for windows, clocks, spectacles, hearing aids and daylight in delirium prevention.

10.4 REST and clinical relevance: therapy, solitary confinement, the ICU

The same manipulation, three very different valences. Sensory deprivation is neither uniformly harmful nor uniformly benign; its meaning depends on control, duration and consent.

CONTEXT	FORM	EFFECT AND VALENCE
REST (therapeutic)	Restricted Environmental Stimulation Therapy: chamber confinement or flotation-tank immersion, minutes to hours, voluntary and monitored (Suedfeld)	**Deliberately controlled and brief; used for relaxation, smoking cessation and habit change, pain and anxiety; the reframing of deprivation as treatment**
Solitary confinement	Involuntary, prolonged social and sensory isolation in incarceration	**Harmful: the "SHU syndrome," anxiety, perceptual disturbance, hallucination, cognitive impairment and paranoia; a recognised human-rights and forensic-psychiatry concern**
Intensive care unit	Unintended: monotonous, windowless, day-night-blurred environment with immobilisation and impaired attention	**Contributes to ICU delirium; both under-stimulation (monotony) and over-stimulation (alarms, procedures) operate, so the fix is patterned, oriented stimulation, not simply "more" or "less"**

One manipulation, three valences: controlled and consented deprivation heals, imposed and prolonged deprivation harms, and unintended deprivation in the ICU drives delirium.

10.5 The mind-body problem: the question and why it framed medicine

How does the mental relate to the physical? The **mind-body problem** is the question of the relation between mental phenomena (thoughts, feelings, subjective experience, intentions) and physical phenomena (the brain and body). Its modern statement is owed to Rene Descartes (1596 to 1650), whose **substance dualism** split reality into *res cogitans* (thinking, non-extended mind) and *res extensa* (extended, mechanical body), a term the exam attributes to Descartes via Damasio (1994). This is not idle metaphysics for a psychiatrist: the split hardened into the division of illness into "medical" (bodily pathology, treated by physicians) and "psychiatric" (an abnormal mental state, treated by psychiatrists), the very **mind-body dualism** that the New Oxford's "Deconstructing dualism" chapter argues has created obstacles to integrated care (Sharpe and Walker; Companion to Psychiatric Studies). The whole point of studying the positions below is to be able to hold biology and psychology together without falling into that clinically damaging split.

10.6 Dualism: the varieties

Mind and body are, in some sense, two. Dualist positions hold that the mental is not simply identical to the physical. They differ over whether mind is a separate *substance* or only a separate *property*, and over which way causation runs.

Substance dualism (interactionism)

Descartes's view: mind and body are two distinct kinds of substance that causally interact (he proposed, wrongly, at the pineal gland). Mind moves body (I decide, my arm rises) and body affects mind (injury causes pain). The fatal objection is the *interaction problem*: how can a non-physical mind push a physical brain without breaking the conservation of energy?

Epiphenomenalism

Body affects mind but not the reverse: mental states are causally inert by-products of brain activity, like the whistle of a steam engine that plays no part in driving the train. It preserves physics (only the physical causes) but at the price of making consciousness a passenger with no effect, which clashes with the intuition that our reasons cause our actions.

Property dualism

The one substance is physical, but it has two irreducibly different *kinds of property*, physical and mental. Kaplan and Sadock (2024) state this as their working position: the brain and the mind are different *levels of description* of one phenomenon (mechanism versus subjective experience), and because they are different levels they have different properties. It is distinguished sharply from substance dualism: nothing extra exists, but the mental cannot be read off the physical alone.

10.7 Monism: the varieties

There is only one kind of stuff. Monist positions deny a fundamental mind-body split; in psychiatry the relevant monisms are all forms of *physicalism* (everything is physical). They differ over how tightly the mental reduces to the physical.

Identity theory (type physicalism)

Mental states simply *are* brain states: to be in pain *is* to have a particular kind of neural activity (the slogan is "C-fibre firing"). Elegant and thoroughly physical, but criticised for chauvinism about *multiple realisability*: if an octopus or a silicon machine could feel pain with entirely different hardware, pain cannot be identical to one specific human brain state.

Functionalism

The fix for multiple realisability: a mental state is defined not by what it is made of but by its *functional role*, its causal relations to inputs, other states and outputs. Pain is whatever plays the pain-role, in a brain or in principle in silicon. This is the reigning framework in cognitive science, but it is charged with leaving out the felt quality of experience (the "absent qualia" worry).

Emergentism

Mind is a genuinely novel, *emergent* property of sufficiently complex and organised matter, real and causally efficacious yet not predictable from, or reducible to, the properties of the parts. Kaplan and Sadock (2024) note psychological phenomena are "emergent properties of lower-order constituents" (circuits, neurons, genes); consciousness is often described the same way. Emergentism sits between reductive physicalism and property dualism.

10.8 Reductionism: constitutive versus eliminative

Not all reduction is the same, and the difference is clinically loaded. Kaplan and Sadock (2024) draw the line the exam wants. **Constitutive reductionism**, reducing a complex entity to its component parts to *facilitate study*, is uncontroversial and is ordinary science. **Eliminative reductionism** goes further and insists that everything mental will *ultimately be explained away* at the material level, eliminating the need for a psychological level of analysis at all. The text rejects the eliminative move: valuable information is lost when you descend from mental states to neurons, and one may reasonably ask why the reduction should stop at the brain rather than continue to physics. The image they use is Shakespeare: the words on the page are material, but a chemical analysis of the ink will never capture the meaning of the play.

COMMON TRAP

The **treatment-etiology fallacy** (Kaplan and Sadock 2024): the fact that a treatment at one level works does *not* prove the cause lies at that level. An antidepressant helping depression no more proves depression is "a chemical imbalance" than aspirin curing a headache proves the headache was caused by an aspirin deficiency. Cognitive-behavioural therapy is at least as effective as medication for many depressions; both act, neither localises the cause. Do not slide from "responds to a drug" to "is a brain disease."

10.9 The explanatory gap and qualia

The residue no physical account has closed. Even granting full physicalism, a gap remains between the objective description of a brain process and the subjective feel of the experience it produces. This is the **explanatory gap** (Levine 1983) and, in its sharpest form, Chalmers's (1995) *hard problem of consciousness*: why is there *something it is like* to undergo a brain process at all? The felt qualities themselves, the redness of red, the ache of pain, are the **qualia**; Kaplan and Sadock (2024) describe them as subjective secondary qualities interpreted by the mind and attributed to the world, and identify "the subjectivity of experience, the so-called qualia of consciousness" as precisely what separates living consciousness from even the best computers. The philosophical thought-experiments the exam may cite, Nagel's "What is it like to be a bat?" (1974) and Frank Jackson's "Mary the colour scientist" (1982, who knows every physical fact about colour but learns something new on first seeing red), are both arguments that physical facts leave the qualia unexplained. This gap is the honest limit: no current position, dualist or monist, closes it, which is why the field defaults to a pragmatic property-dualist stance rather than a solved theory. (The full theories-of-consciousness sequence, James, Freud, Global Workspace, Integrated Information, is the Consciousness topic; here the gap functions only as the unresolved core of the mind-body problem.)

10.10 Why it matters for psychiatry I: the biopsychosocial model

The clinical answer to the mind-body problem. The discipline's practical resolution is not to pick a metaphysics but to adopt a working model that refuses the dualist split. George Engel's **biopsychosocial model** (Engel 1977) reframed illness as the product of interacting biological, psychological and social levels, a general-systems view in which no single level is privileged as "the real" cause (Tasman 2015). It is the direct clinical descendant of property dualism and emergentism: the levels are all real, none reduces to another, and formulation must move across them. Its virtue is integration and its recognised weakness is looseness (it can become a checklist rather than an explanation), but it remains the field's standard rebuke to both eliminative brain-reductionism and to a psychology that ignores biology. In a viva, "the biopsychosocial model is how psychiatry escapes Cartesian dualism in daily practice" is the line that ties the whole topic together.

HOLD THIS

The mind is a real, emergent, causally potent level of a physical system. Not reducible to its neurons and not a separate ghost; the biopsychosocial model (Engel 1977) is psychiatry's practical, principled escape from Cartesian dualism.

10.11 Why it matters for psychiatry II: the brain-disease debate and free will

Where the metaphysics touches responsibility. Two live controversies show the stakes are not academic. First, the *brain-disease* framing of addiction: Kaplan and Sadock (2024) criticise the neurocentric NIDA model ("addiction is a chronic, relapsing brain disease") precisely as eliminative reductionism, because it leaves the addicted *person*, the agent who retains substantial control and whose choices meditate recovery, in the shadows; the corrective is that neural correlates and voluntariness coexist. Second, *free will and responsibility*: if the mind is nothing but neurons obeying physical law (hard determinism, and the natural reading of epiphenomenalism), the ground for holding people responsible seems to vanish, which matters directly for forensic psychiatry and the insanity defence. Most psychiatrists work with a *compatibilist* stance, that meaningful agency and responsibility are consistent with a physical brain, which is again the property-dualist / biopsychosocial position applied to the will: the person is a real causal level, not an illusion painted over the neurons.

MNEMONIC

"SIP-EF" for the positions: Substance, Interactionism, Property (dualism); Epiphenomenalism between; then the monist Family (Identity, Functionalism, Emergentism)

Read left to right it is a ladder from "most separate" (substance dualism) to "least separate" (identity theory), with property dualism and emergentism as the clinically preferred middle where mind is real but not a separate stuff.

PEARL

The two halves are one argument. Sensory deprivation shows the mind actively constructs experience rather than passively receiving it, which is why removing the world produces hallucination, not blankness. The mind-body problem asks what that constructing mind *is*. The psychiatric answer to both is the same: the mind is a real, emergent, causally potent level of a physical system, not reducible to its neurons and not a separate ghost. Hold that, and you can say why the ICU patient hallucinates, why "chemical imbalance" is a half-truth, and why the biopsychosocial model is not woolly but principled.

GOOD TO REMEMBER

- **Sensory deprivation:** drastic sustained reduction of patterned input; the brain, still predicting, generates its own content.
- **Hebb / McGill studies (Bexton, Heron and Scott 1954):** lightproof-soundproof cubicle, goggles and cuffs; volunteers quit within days; impaired thinking and visual hallucinations. [verify author-year and design details]
- **Lilly isolation tank (John C. Lilly, from 1954):** flotation in body-temperature salt water, total dark and silence; altered states, "higher consciousness." [verify start year]
- **Effects triad:** perceptual (illusions then complex hallucinations, mostly visual), cognitive (impaired attention, disorganised thought, time distortion, suggestibility), affective (restlessness, anxiety, urge to escape; some find it relaxing).
- **Three scientists in tanks (K&S 2024):** one few illusions/no hallucinations, one many illusions/faint hallucinations, one vivid complex hallucinations; individual variability is the point.
- **Perceptual release (Hughlings Jackson; West 1962):** reduced input plus lost gating releases stored images as hallucinations; supersensitivity-deprivation hypothesis is the complement.
- **Clinical relevance:** REST (therapeutic, controlled, Suedfeld); solitary confinement (harmful, "SHU syndrome"); ICU (contributes to delirium; needs patterned oriented stimulation).
- **Mind-body problem:** relation of mental to physical; modern statement from Descartes (1596 to 1650), substance dualism, res cogitans vs res extensa (term via Damasio 1994).
- **Dualism, substance / interactionism (Descartes):** two substances causally interact; fails on the interaction problem (energy conservation).
- **Epiphenomenalism:** brain causes mind, mind causes nothing (the whistle, not the engine); makes consciousness causally inert.
- **Property dualism (K&S 2024's working stance):** one physical substance, two irreducible property-types; brain vs mind = different levels of description.
- **Identity theory (type physicalism):** mental state = brain state ("C-fibre firing"); criticised via multiple realisability.
- **Functionalism:** mental state defined by functional/causal role, not substrate; solves multiple realisability; charged with omitting qualia.
- **Emergentism:** mind a novel, real, non-reducible emergent property of complex organised matter.
- **Reductionism:** constitutive (study by parts, uncontroversial) vs eliminative (explains the mental away; rejected by K&S; the Shakespeare-and-ink image).
- **Treatment-etiology fallacy:** a treatment working at a level does not prove the cause lies there.
- **Explanatory gap (Levine 1983) / hard problem (Chalmers 1995):** why is there something it is like to be conscious; qualia = felt subjective qualities. Nagel's bat (1974); Jackson's Mary (1982).
- **Biopsychosocial model (Engel 1977):** interacting biological, psychological, social levels; psychiatry's practical escape from Cartesian dualism; strength = integration, weakness = looseness.
- **Brain-disease / free-will debate:** eliminative "addiction is a brain disease" critiqued (neural correlates and voluntariness coexist, K&S 2024); most psychiatrists compatibilist on responsibility.

The three depth-psychology schools

11 · Freud and psychoanalysis

The first of the depth schools. Psychoanalysis is both a theory of mind and a treatment. Freud proposed that behaviour is governed by unconscious wishes and conflicts, that early childhood shapes the adult, and that these hidden forces can be reached and modified through a disciplined

verbal method. Every later depth-psychology school (Adler, Jung, Erikson, object relations, self psychology) defines itself by what it kept from Freud and what it rejected, so the exam expects you to hold his two models of mind, the five psychosexual stages with their ages and fixations, the core techniques, and the story of the circle that carried and then splintered the movement.

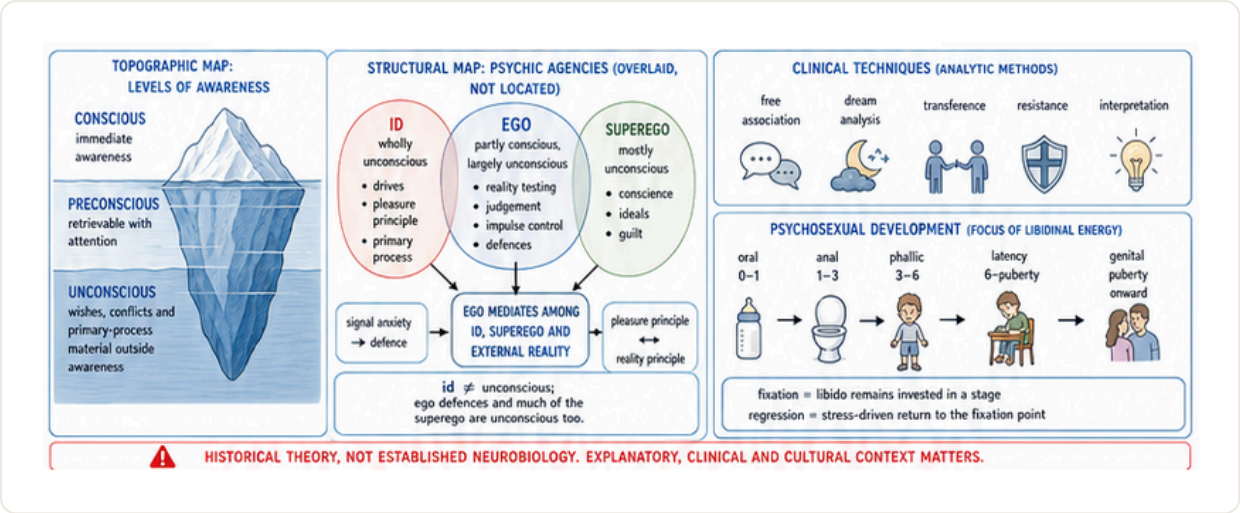


Fig 4.13 Freud's two maps of the mind.

Psychoanalysis rests on three assumptions Freud held throughout (Kaplan & Sadock 2024): *psychological determinism* (no mental event is accidental; symptoms, dreams and slips have meaning), *unconscious mental processes* (much of mind is outside awareness), and *unconscious psychological conflict* (neurosis arises from clashing psychic forces). Note at once: this is a stage-and-concept theory, not one of the general cognitive functions, so it is examined as a system to be enumerated rather than as an evolution toward a currently accepted mechanism.

11.1 The topographic model: three systems of mind

Ucs, Pcs, Cs. Freud's first structural picture (from *The Interpretation of Dreams*, 1900) classified mental contents by their relation to awareness into three systems (Kaplan & Sadock 2024). The **unconscious** (Ucs) holds repressed wishes and drive-representations; it obeys the *pleasure principle* and works by *primary process* thinking (timeless, illogical, tolerating contradiction, using condensation and displacement, seeking immediate discharge). The **preconscious** (Pcs) holds material that is not conscious now but can be summoned; it obeys the *reality principle* and *secondary process* thinking (logical, verbal, tolerating delay). The **conscious** (Cs) is the small surface in immediate awareness. In this model the therapeutic aim was simply to lift repression, making the unconscious wish conscious.

11.2 The structural model: id, ego, superego

The tripartite mind (1923). Freud found the topographic model inadequate because the forces producing resistance and guilt were themselves unconscious, so the ego could not simply equal consciousness. In *The Ego and the Id* (1923) he introduced the **structural model** (the tripartite theory) of three agencies (Kaplan & Sadock 2024). The **id** is wholly unconscious, the primordial reservoir of sexual and aggressive drive energy, ruled by the pleasure principle and primary process. The **ego** is the executive mediator between id, superego and external reality; it is partly conscious but largely unconscious, and it carries out reality testing, judgment, impulse control,

affect regulation and the deployment of defences. The **superego** holds internalised parental and social morals, ideals and prohibitions; it is the seat of conscience and guilt and is again mostly unconscious. Crucially id and Ucs are not synonymous, because ego defences and most of the superego are also unconscious.

TRAP **"Id" and "unconscious" are not the same.** The id is wholly unconscious, but ego defences and most of the superego are unconscious too, so the two models classify by different criteria (awareness versus function).

11.3 Libido, drives and the two principles

The economic idea. Libido is the mental energy of the sexual (life) instincts, a displaceable quantity (cathexis) that presses for discharge. Freud used "sexual" in an extended sense to mean bodily pleasurable, which is why feeding and toilet control count as psychosexual. Mental life is a compromise between the *pleasure principle* (the demand for immediate gratification and tension reduction, native to id and unconscious) and the *reality principle* (the ego's capacity to postpone gratification and adapt to the external world). Maturation is broadly the shift from pleasure-principle to reality-principle governance. Cross-reference the Social, Learning & Personality Psychology notes for the full defence-mechanism catalogue and for the object-relations extension of these ideas.

11.4 The five psychosexual stages

Erogenous zones and conflicts. Freud held that libidinal energy settles successively on a leading body zone, each stage posing a developmental conflict; unresolved conflict leaves a *fixation* that colours adult character (Kaplan & Sadock 2024). Personality is largely set by about age five. The ages below are the standard textbook bands; treat them as approximate rather than sharp cut-offs.

Oral (birth to about 1 year)

Zone: mouth. Pleasure through sucking and biting; the infant is wholly dependent, so trust and dependency are at stake. Central conflict: weaning. Fixation gives oral traits: dependency, passivity or (biting phase) verbal aggression and sarcasm, and habits such as smoking, over-eating and nail-biting.

Anal (about 1 to 3 years)

Zone: bowel and bladder control. Central conflict: toilet training, autonomy versus control. Over-strict or early training yields the *anal-retentive* (orderly, parsimonious, obstinate, obsessional) character; over-lenient training yields the *anal-expulsive* (messy, wasteful, defiant) character. This stage is the classic root of obsessional traits.

Phallic (about 3 to 6 years)

Zone: genitals. The *Oedipus complex* (in boys) is the wish to possess the mother and displace the father, checked by *castration anxiety*; the analogous *Electra complex* (a term from Jung, not Freud) and *penis envy* were proposed for girls. Resolution comes through identification with the same-sex parent, which internalises parental morality and so forms the **superego**. Karen Horney countered penis envy with the concept of *womb envy*.

Latency (about 6 to puberty)

Sexual drives are relatively dormant and repressed; energy is channelled into schooling, skills, hobbies and same-sex peer relations. Ego and superego consolidate. Fixation impairs later social competence and intimacy.

Genital (puberty onward)

Libido re-emerges and, if earlier stages resolved, matures into stable heterosexual object-love with a capacity to work and to care for others. In Freud's scheme the well-resolved adult can love and work.

Fixation and regression. *Fixation* is arrested libido that stays partly invested in an earlier stage; *regression* is a retreat, under stress, to an earlier fixated stage. The two link: the point of fixation determines the point to which one regresses, which is how psychoanalysis tied adult symptom pictures back to specific childhood stages. Karl Abraham later refined the schema, splitting the oral stage into sucking and biting phases and the anal stage into destructive-expulsive (anal-sadistic) and mastering-retaining (anal-erotic) phases.

HOLD THIS

Five stages by body zone: oral, anal, phallic, latency, genital; the superego forms at the Oedipal resolution. Fixation is energy left at a stage; regression is retreat to the fixation point under stress, and the fixation point sets where one regresses to.

11.5 Core techniques of classical analysis

How the method works. Classical psychoanalysis makes the unconscious conflict available for interpretation through a small set of tools (Kaplan & Sadock 2024).

Free association

The *fundamental rule*: the patient reports whatever comes to mind without censoring. Breaks and blocks in the flow mark *resistance*, pointing to where defended material lies.

Dream analysis

Dreams are "the royal road to the unconscious." The remembered *manifest content* is decoded, via the dreamer's associations, to the underlying *latent content* (the disguised wish); the disguising work uses condensation, displacement, symbolisation and secondary revision.

Transference

The patient unconsciously redirects feelings and templates from important early figures onto the analyst. Rather than a nuisance, the *transference neurosis* is the central working material, letting old conflicts be re-lived and interpreted in the room.

Countertransference

The analyst's own emotional reactions to the patient. Freud first saw it as interference; modern analysis treats it as a source of information about what the patient evokes.

The analytic frame

The fixed conditions that make the method possible: the couch with the analyst out of view, high session frequency, a stable time and fee, and the analyst's stance of *neutrality* and *abstinence*. Interpretation and *working through* (repeated interpretation across contexts until insight holds) do the therapeutic work.

11.6 The circle and the Wednesday Society

From a Vienna sitting-room to a movement. In 1902 Freud gathered a handful of physicians for weekly discussion in the **Wednesday** Psychological Society, meeting in his waiting room; early members included Alfred Adler, Wilhelm Stekel, Otto **Rank** (its long-serving secretary) and Hanns **Sachs**, with Paul Federn joining soon after. In 1908 the group was formally reconstituted as the **Vienna psychoanalytic** Society, and the circle widened internationally to Sandor **Ferenczi** in Budapest, Karl **Abraham** in Berlin, **Ernest Jones** in Britain, Max Eitingon, and, most prominently, Carl Jung in Zurich, whom Freud favoured as heir and installed as first president of the International Psychoanalytical Association (1910). To guard doctrinal orthodoxy after the early breaks, Jones proposed a *secret committee* (1912 to 1913) of trusted loyalists, to whom Freud gave engraved Greek intaglio rings.

The defections. The movement fractured over the primacy Freud gave to sexuality and libido. Alfred Adler left in 1911, replacing libido with the striving for superiority and the inferiority complex (individual psychology); Stekel departed the same period (1912) over orthodoxy; Carl Jung broke in 1913, recasting libido as a general psychic energy and adding the collective unconscious and archetypes (analytical psychology); and Otto Rank drifted away in the mid-1920s after emphasising the birth trauma. These splits are examined the Social, Learning & Personality Psychology notes and in the Adler and Jung topics as the birth of the rival depth schools.

PEARL

Two models, one mind: the topographic model classifies mental contents by *awareness* (Ucs, Pcs, Cs), the structural model by *function* (id, ego, superego). They coexist rather than the second erasing the first. The ego and superego straddle both, which is exactly why "unconscious" and "id" are not the same thing.

COMMON TRAP

The *Electra complex* and *penis envy* are frequently miscredited to Freud in full. Freud described the girl's phallic conflict and penis envy; the term "Electra complex" was coined by Jung. Also do not confuse *fixation* (energy stuck at a stage) with *regression* (retreat to an earlier stage under stress).

CLINICAL ANCHOR

Psychosexual character types still cue clinical pattern recognition: anal-retentive traits (orderliness, parsimony, obstinacy) map onto the obsessional character, and oral fixation onto dependency and substance-seeking. These are heuristics, not diagnoses; the fixation ages themselves are not empirically validated, so cite them as Freudian theory.

MNEMONIC

Old (Oral) Age (Anal) Pensioners (Phallic) Love (Latency) Grapes (Genital)

Reads the five stages in order. For the ego's job, remember it serves "three masters": the id, the superego, and external reality.

GOOD TO REMEMBER

- **Topographic model (1900):** unconscious (pleasure principle, primary process), preconscious, conscious (reality principle, secondary process).
- **Structural model (1923, *The Ego and the Id*):** id (drives, pleasure principle), ego (mediator, reality testing), superego (conscience, formed at Oedipal resolution).
- **Oral:** birth to about 1 year, zone mouth, conflict weaning; fixation gives dependency, smoking, over-eating.
- **Anal:** about 1 to 3 years, zone bowel/bladder, conflict toilet training; fixation gives retentive (obsessional) or expulsive character.
- **Phallic:** about 3 to 6 years, zone genitals, Oedipus/Electra complex, castration anxiety and penis envy; superego forms here.
- **Latency:** about 6 to puberty, drives dormant, social and skill development.
- **Genital:** puberty onward, mature object-love, capacity to love and work.
- **Fixation vs regression:** fixation = energy left at a stage; regression = retreat to the fixation point under stress.
- **Techniques:** free association (fundamental rule), dream analysis (manifest to latent), transference, countertransference, the analytic frame (couch, neutrality, abstinence, working through).
- **Wednesday Psychological Society:** founded 1902 in Freud's waiting room.
- **Vienna Psychoanalytic Society:** renamed 1908; International Psychoanalytical Association founded 1910 (Jung first president).
- **Circle members:** Adler, Stekel, Rank, Sachs, Federn, then Ferenczi, Abraham, Ernest Jones, Eitingon, Jung.
- **Secret committee (1912 to 1913):** Jones's loyalist inner ring, marked by Freud's engraved rings.
- **Defections over primacy of sexuality/libido:** Adler 1911 (individual psychology), Stekel 1912, Jung 1913 (analytical psychology), Rank mid-1920s (birth trauma).

12 · Adler and individual psychology

Adler is the **second primary school** of the psychodynamic tradition and, for the exam, the cleanest contrast case to Freud: where Freud made the unconscious sexual drive the engine of the mind, Adler made a conscious, forward-pulling **striving** the engine, and made the person's embeddedness in a social world the measure of health. His system is called **individual psychology**, a name that is routinely misread. It does not mean a psychology of the isolated individual; it comes from the Latin *individuum*, meaning **indivisible,** and asserts that the person is a single unified whole (holism) that cannot be split into warring drives and agencies the way Freud split the psyche. Adler (1870 to 1937), an Austrian general physician, was one of the original members of Freud's Vienna circle from 1902, rose to president of the Vienna Psychoanalytic Society, and in 1911 broke away, the first of the inner circle to leave, because he rejected the primacy of the libido and the sexual origin of neurosis (Kaplan & Sadock 2024).

The examinable core is a small chain of concepts that hang together: an **inferiority feeling** is universal, it drives a **striving for superiority** (better read as striving for competence or perfection), that striving is organised by a self-chosen goal (fictional finalism) into a consistent **style of life**, and the whole enterprise is healthy only insofar as it is turned outward toward others as **social interest**. Learn the chain and you can place any Adlerian term. Because this topic names a theorist, dated events, and a set of hard classifications (inferiority versus superiority complex, birth-order positions, safeguarding tendencies), it closes with a good-to-remember box that enumerates them (Kaplan & Sadock 2024; The Psychotherapy Guidebook 1976).

12.1 Individual psychology: the person as an indivisible, goal-directed whole

Holism plus teleology is the frame. Adler's two founding commitments are that the person is a *unit*, not a collection of drives divided against themselves, and that behaviour is *future-directed*. He called the second principle **dynamism**: in every individual the psyche moves toward a goal, and once the goal is set the whole psychic apparatus, memories, dreams, perceptions, shapes itself to attain it. This is a **teleological** account (explanation by final cause, the goal ahead) and it is the sharpest break from Freud's causal, backward-looking model in which the past determines the present. For Adler the person is not pushed from behind by instinct but pulled from in front by a chosen aim, and because the goal is chosen it can be changed, which is what makes therapy possible (Kaplan & Sadock 2024).

RULE **Adler is teleological, Freud causal.** Freud is pushed from behind by buried sexual conflict; Adler is pulled from in front by a chosen goal, and "individual" means indivisible whole (holism), not the isolated individual.

12.2 Organ inferiority: the biological seed

Adler's earliest idea, and the root of the whole system. Before the psychology came the medicine. In his *Study of Organ Inferiority* (Adler 1907), a constitutionally weak or defective organ (poor eyesight, weak lungs, poor eye-hand coordination) was shown to provoke **compensation**: the organism, or the person, works to overcome the deficit, sometimes overshooting into **overcompensation** and turning the weak point into a strength. The classic illustration is the stammerer who becomes an orator. Adler then generalised this bodily principle into a psychological law: the felt weakness drives the striving that builds the personality. Organ inferiority is thus the concrete biological seed from which the broader *inferiority feeling* grows (Kaplan & Sadock 2024).

12.3 The inferiority feeling and the striving for superiority: the great upward drive

This is the master motive of the whole theory. Every child begins life small, weak, and dependent among larger, more capable adults, so a **feeling of inferiority** is universal and normal, not pathological. The response to it is the single dynamic force Adler placed at the centre of personality: the **striving for superiority**, better translated as striving for significance, competence, mastery, or perfection, the "great upward drive" from a felt minus toward a felt plus. Adler was explicit that this is the one master motive to which all traits and drives are subordinated: standing before the unknown, each person strives to become more perfect and

complete. Note the exam point that Adler *himself* shifted the emphasis over his career, from raw compensation for weakness toward a positive striving for self-realisation, so "superiority" here means self-perfection, not domination over others (The Psychotherapy Guidebook 1976; Kaplan & Sadock 2024).

12.4 Inferiority complex versus superiority complex: the two pathological outcomes

Distinguish the normal feeling from the pathological complex. The universal inferiority *feeling* is the engine of healthy growth. It becomes pathological when the person cannot move from the felt minus to a felt plus and instead becomes stuck. The two failures are mirror images and are a favourite discriminate.

Inferiority complex

An exaggerated, entrenched sense of inadequacy in which the normal inferiority feeling is not overcome but overwhelms the person, producing discouragement, avoidance, and a retreat from life's tasks. The term entered ordinary language; Adler coined it.

Superiority complex

A defensive overcompensation: the person masks deep inferiority behind a facade of arrogance, boastfulness, vanity, or a drive to dominate. It is not the opposite of the inferiority complex but its concealment, the same wound covered by bluster.

> **COMMON TRAP**
>
> Do not equate the *inferiority feeling* (universal, normal, motivating) with the *inferiority complex* (pathological, entrenched, disabling). The feeling drives healthy striving; the complex is striving that has failed and calcified. And the superiority complex is not the healthy striving for superiority: it is a mask *over* inferiority, so a boastful, domineering patient is showing you a hidden inferiority complex, not confidence.

12.5 Fictional finalism: the guiding self-ideal

The goal that organises everything is an invented one. Adler borrowed from the philosopher Hans Vaihinger the idea that people live by useful fictions, "as if" propositions that are not literally true but guide action. The person's central fiction is a **guiding self-ideal** or **final goal**, an imagined picture of the self as complete, significant, and secure, toward which all behaviour is aimed. This is **fictional finalism** (also called the guiding fiction): the final goal is subjective and largely out of awareness, yet it is the true cause of the person's movements. Two people with the same objective circumstances live utterly differently because they aim at different fictional goals. This is the mechanism that makes Adler teleological in practice: understand the patient's fictional final goal and the apparently disparate pieces of the life snap into a single pattern (Kaplan & Sadock 2024; The Psychotherapy Guidebook 1976).

12.6 Style of life: the unique, early-set signature of striving

The consistent pattern by which a person pursues the final goal. The **style of life** (lifestyle) is the individual's characteristic, unified way of striving toward significance, the personal method of solving the three great tasks of life, work, friendship (society), and love (sexuality). It forms early, by roughly age four to five, out of the child's constitution, family atmosphere, and creative

interpretation of its situation, and then runs as a single theme through everything the person perceives and does; it is, in effect, the person's perceptual style. Crucially the style of life is not simply stamped in by heredity or environment. Adler insisted on the **creative self** (creative power): the child actively, creatively interprets and responds to its circumstances, so two children in the same family build different lifestyles. If you grasp a patient's style of life, their behaviour stops looking random and starts making sense (The Psychotherapy Guidebook 1976).

12.7 Social interest (Gemeinschaftsgefuhl): the index of mental health

This is the single most examinable Adlerian concept. Social interest renders Adler's German *Gemeinschaftsgefuhl*, literally community feeling: an innate but developable capacity to feel with and for others, to identify with the human community, and to contribute to the common good rather than pursue private superiority. For Adler this is the *criterion of mental health*. The healthy person turns the upward striving outward, into socially useful contribution; the neurotic and the criminal turn it inward, striving for a personal superiority on the "useless side of life" at others' expense. Adler summarised the whole diagnosis in one line: the more social interest a person has, the fewer feelings of inferiority they carry, and the aim of therapy is to increase the patient's sense of belonging and contribution. Distinguishing neurosis from psychosis in his system also runs on this axis: the neurotic *retains* social interest but is blocked from life goals by symptoms, whereas the psychotic *loses* social interest and retreats into a private world (Kaplan & Sadock 2024; The Psychotherapy Guidebook 1976).

> **PEARL**
>
> If one word survives from Adler into the exam, it is *social interest* (Gemeinschaftsgefuhl) as the yardstick of mental health. Freud measures health by the capacity to love and to work; Adler measures it by the capacity to contribute to the community. A patient whose striving is all private ambition with no social feeling is, in Adler's terms, unwell however successful they look.

12.8 Birth order and the family constellation

Adler's most popularly known and most testable classification. Adler argued that a child's *psychological* position in the **family constellation**, not the birth date as such, shapes the lifestyle, because each position offers a different situation to interpret. He is credited as the first theorist to make birth order a serious variable in personality.

POSITION	ADLER'S CHARACTERISTIC SITUATION	TYPICAL TENDENCY
First-born (oldest)	**"Dethroned" by the arrival of a sibling, having once been the sole focus**	Tends toward conservatism, order, and authority; may become achievement-oriented or, if the loss is felt as trauma, insecure
Second / middle	Grows up with a "pacemaker" ahead to overtake, never had the parents alone	**Ambitious, competitive, often better adjusted; may become the social activist, open to change**
Youngest	Never displaced, surrounded by older models, often pampered	Can be highly driven to surpass all others, or dependent and spoiled if over-indulged
Only child	Never shares the parents; adult world is the reference	**Precocious with adults but may struggle when not the centre; risk of pampering**

Adler's birth-order positions and their characteristic situations: it is the child's interpreted *psychological* position in the family constellation, not the ordinal number, that shapes lifestyle (Kaplan & Sadock 2024).

12.9 Safeguarding tendencies and the masculine protest

Two named defensive concepts examiners like to surface. When the fictional goal of superiority is threatened, the person protects self-esteem rather than face reality, and Adler called these manoeuvres **safeguarding tendencies**, his forward-looking, self-esteem-protecting counterpart to Freud's defence mechanisms. They include *excuses* (the neurotic symptom offered as an alibi, "I would succeed, but for this"), *aggression* (depreciating others, accusation, self-accusation to secure superiority), and *distance-seeking* (moving backward, standing still, hesitating, or constructing obstacles so as never to risk the test). The **masculine protest** is his term for the overstriving, in either sex, to escape a felt "feminine", that is weak, inferior, submissive, position toward an idealised "masculine", strong, dominant one; Adler used it to reframe as a social-power struggle what Freud had explained sexually (for example penis envy), locating the drive in the culture's overvaluing of masculinity rather than in anatomy (Kaplan & Sadock 2024).

12.10 The 1911 break from Freud

Know why he left, not just that he left. Adler joined Freud's discussion circle in 1902 and became president of the Vienna Psychoanalytic Society, but he never accepted the pillars of Freud's system: the primacy of the libido, the sexual origin of neurosis, and the determining power of infantile sexual wishes. Where Freud looked backward to buried sexual conflict, Adler looked forward to a chosen goal; where Freud saw a psyche split into id, ego, and superego, Adler saw an indivisible whole; where Freud made drive central, Adler made social embeddedness central. The disagreement was irreconcilable, and in 1911 Adler resigned, taking a group of followers with him and founding individual psychology, the first major secession from psychoanalysis (Jung's followed in 1914) (Kaplan & Sadock 2024; The Psychotherapy Guidebook 1976).

12.11 Theory of psychopathology: the mistaken style of life

Neurosis is a discouraged, socially useless lifestyle, not repressed sex. For Adler, emotional disorder springs from a **mistaken style of life** built on false ideas about the self and the world and on goals of private superiority that lead away from social usefulness. The pampered child, for instance, grows up expecting others to serve them, avoids responsibility, blames others for failures, and yet feels chronically insecure because their whole worth depends on being served. When such a lifestyle meets a real challenge it cannot solve, symptoms appear, and the symptoms have a *purpose*: they protect self-esteem and provide an excuse ("I could have, but for this illness") while letting the person sidestep the task they fear. Pathology is thus discouragement plus deficient social interest, and it is correctable by insight and re-education because the goal that organises it was chosen (Kaplan & Sadock 2024).

HOLD THIS

Social interest (Gemeinschaftsgefuhl) is Adler's yardstick of mental health. The neurotic retains it but is blocked by symptoms; the psychotic loses it and retreats into a private world.

12.12 Therapy and legacy: encouragement, early recollections, and the line into CBT

Adlerian technique is brief, active, collaborative, and re-educative. The therapist works with the patient as an equal to uncover the style of life and its mistaken goals, then *re-orients* the patient toward socially useful living. The signature tools are **encouragement** (the therapeutic antidote to discouragement, building the patient's confidence to attempt life's tasks), **early recollections** (the earliest memories, read not as historical fact but as a projective clue to the present lifestyle, since what is remembered is selected to fit the current goal), analysis of **birth order and dreams** (dreams as an expression of present-day concerns and problem-solving, not disguised infantile wishes), and **task-setting** (assigning concrete, graded real-world tasks). Adler anticipated much of what came later: his focus on mistaken beliefs and faulty perceptions of self and world prefigured **cognitive therapy** (Beck and Ellis both acknowledged the debt); his stress on the person's inherent worth, agency, and phenomenology fed the **humanistic** tradition (Maslow, Rogers); and his attention to the family constellation and the person shaping their own interpersonal world seeded **family-systems** thinking. His techniques of *reframing* and *paradoxical intention* are now standard across schools (Kaplan & Sadock 2024).

CLINICAL ANCHOR

A high-achieving professional presents with paralysing procrastination on the one project that would confirm their talent. Freud might hunt an unconscious conflict; Adler asks what the delay *achieves*. The unfinished work is a safeguarding tendency: while the project is incomplete the fictional self-ideal of "the great talent" is never put to the test and cannot fail. Adlerian therapy names the mistaken goal (superiority without risk), reframes the procrastination as protection of a fragile self-estimate, and sets a graded real task to rebuild courage and turn striving back toward useful contribution.

INDIA

Birth-order and family-constellation reasoning translates readily to the large, multi-generational Indian joint family, where the eldest son's "dethronement" and burden of expectation, or the youngest's pampering, are lived realities rather than abstractions. Adler's *social interest* also maps onto collectivist framings of the self as embedded in family and community, which can make his community-feeling yardstick of health intuitive in the Indian setting; the caution is not to read culturally normative interdependence as pathological dependency.

MNEMONIC

I Saw For Sure Some Big Sisters Mock

Adler's eight examinable concepts in order: **I**nferiority feeling, **S**uperiority striving, **F**ictional finalism, **S**tyle of life, **S**ocial interest, **B**irth order, **S**afeguarding tendencies, **M**asculine protest. Run the sentence and you have recalled the spine of individual psychology.

GOOD TO REMEMBER

- **Alfred Adler (1870 to 1937):** Austrian physician; founder of *individual psychology* ("individual" = indivisible whole, holism).
- **Circle and break:** joined Freud's Vienna circle 1902, became president of the Vienna Psychoanalytic Society, resigned 1911 (first major secession) over the primacy of libido and the sexual origin of neurosis.
- **Organ inferiority (1907):** a weak organ provokes compensation / overcompensation; the biological seed of the theory.
- **Inferiority feeling:** universal and normal (the small child among adults); the engine of healthy striving.
- **Striving for superiority:** the single master motive; the "great upward drive" from felt minus to plus; means self-perfection / competence, not domination.
- **Inferiority complex:** entrenched, disabling sense of inadequacy (term coined by Adler).
- **Superiority complex:** arrogant overcompensation masking a hidden inferiority.
- **Fictional finalism (guiding fiction):** a subjective, mostly unconscious final self-ideal that pulls all behaviour (borrowed from Vaihinger's "as if").
- **Style of life:** the unified, unique pattern of striving; set by about age four to five; shaped by the *creative self*, not just heredity/environment.
- **Three life tasks:** work, friendship (society), and love (sexuality).
- **Social interest (Gemeinschaftsgefuhl):** community feeling; the *index / criterion of mental health*; neurosis retains it, psychosis loses it.
- **Birth order / family constellation:** psychological position shapes lifestyle, first-born "dethroned"; second/middle competitive; youngest driven or pampered; only child precocious but risk of pampering.
- **Safeguarding tendencies:** self-esteem-protecting manoeuvres (excuses, aggression, distance-seeking); Adler's forward-looking analogue of defence mechanisms.
- **Masculine protest:** overstriving to escape a felt "weak/feminine" position; his social-power reframing of Freud's sexual account.
- **Therapy tools:** encouragement, early recollections, dream and birth-order analysis, task-setting, reframing, paradoxical intention; brief, active, egalitarian, re-educative.
- **Legacy:** anticipated cognitive therapy (Beck, Ellis), humanistic psychology (Maslow, Rogers), and family-systems thinking.

13 · Jung and analytical psychology

Jung is the **third primary school** of the psychodynamic tradition and, for the exam, the school that pushed the unconscious deepest and widest: Freud made it a personal repository of repressed sexual wishes, Adler barely used it, but Jung split it into a *personal* layer and a *collective* layer inherited by the whole species. His system is called **analytical psychology** (to distinguish it from Freud's psychoanalysis and Adler's individual psychology). Carl Gustav Jung (1875 to 1961), a Swiss psychiatrist who worked under Bleuler at the Burgholzli, was Freud's chosen heir and the first president of the International Psychoanalytic Association, then broke away in 1913 over the nature of libido, and founded the school that developed the concepts of the **collective unconscious**, the **archetypes**, and the two personality attitudes **introversion** and **extraversion** (Kaplan & Sadock 2024).

The examinable spine is a layered map of the psyche plus a typology. The map runs ego at the surface, then the personal unconscious holding the **complexes**, then the collective unconscious holding the archetypes (persona, **shadow**, anima/animus, the Self, the wise old man, the great mother). The typology crosses two attitudes with four functions and is the direct ancestor of the MBTI. The goal of the whole enterprise is **individuation**. Because this topic names a theorist, a dated break, a fixed set of psychic structures, the named archetypes, and hard classifications of attitude and function, it closes with a good-to-remember box that enumerates every one (Kaplan & Sadock 2024; Companion to Psychiatric Studies).

13.1 The word-association test: Jung's empirical root and the birth of the "complex"

Start where the exam rarely does, with the data. Jung's earliest and most rigorously empirical work at the Burgholzli was the **word-association test**: a standard list of stimulus words is read aloud and the patient responds with the first word that comes to mind, while the examiner times the reaction. Jung noticed that certain words provoked disturbances, a delayed reaction time, an unusual or absent response, repetition of the stimulus, or bodily signs measured by the galvanic skin response. He inferred that these disturbances clustered around emotionally charged themes, and he named such a cluster a **complex**: a group of unconscious ideas bound together by a common emotional tone (Kaplan & Sadock 2024). This is the origin of the everyday word "complex," and it is worth stressing that Jung's central construct was born from a laboratory reaction-time procedure, not from the couch. It was this work on complexes, and its relevance to the meaning of psychotic symptoms, that first drew Freud and Jung together.

13.2 The structure of the psyche: ego, personal unconscious, collective unconscious

Learn the three-layer model as a nested map. Jung replaced Freud's id-ego-superego apparatus with a layered psyche. At the surface sits the **ego**, the centre of conscious life and the bridge to external reality (in Jungian terms the ego is itself a complex). Below it lies the **personal unconscious**, the equivalent of Freud's unconscious, a repository of an individual's own repressed or forgotten memories, and the home of the complexes. Deeper still, and this is Jung's radical addition, lies the **collective unconscious** (also called the objective psyche): a shared, inherited stratum that is not personal at all but is the residue of humankind's evolutionary and ancestral past, "much as human DNA is an aggregate of the past" (Kaplan & Sadock 2024). The

collective unconscious houses the instincts, the potential for creativity, and the archetypes. Note the exam-critical boundary: complexes live in the personal unconscious, archetypes live in the collective unconscious.

RULE **Complexes sit in the personal unconscious, archetypes in the collective.** The archetype is the inherited mould; the complex is the personal cast filled in by lived experience.

13.3 Complexes and archetypes: how the two connect

An archetype is the inherited mould; a complex is what gets cast in it. A **complex** is a group of unconscious ideas around an emotionally toned experience, endowed with psychic energy from its affective charge; the more intense the complex, the greater its pull on imagery, emotion, and action, and a dormant complex can be stimulated by an external cue (a father complex fired by an older friend, or by music that evokes father memories) and then rise to dominate consciousness (Kaplan & Sadock 2024). Crucially, complexes are built around **archetypes**: genetically determined, universal, inherited predispositions to perceive and act in typically human ways (nurturance, aggression). The archetype supplies the inborn template; lived experience fleshes it out into a personal complex. Jung's own illustration is the *earth mother*: every infant is born with a dim, universal model of an all-nurturing caretaker (the mother archetype), and the individual's actual mother complex emerges as that template meets real mothering. Archetypes surface in dreams, myths, and fantasies as **primordial images** (the many-breasted animal as unlimited nurturance, the mandala as wholeness) that recur across cultures without transmission (Companion to Psychiatric Studies; Wolberg 1988).

13.4 The named archetypes: persona, shadow, anima/animus, the Self

These four (plus the great mother and wise old man) are the ones examiners want by name. Several universal archetypes attend the ego and structure the personality.

Persona

The public personality, the social mask that mediates between the ego and the outer world; the face one shows to others. Named after the mask of the classical actor. Over-identification with the persona (being only one's role) is a recognised pathology.

Shadow

The reverse image of the persona: the sum of traits unacceptable to the persona, whether negative or, importantly, positive. A brave persona has a fearful shadow. The shadow's archetype is the enemy or feared intruder, and its unacknowledged contents are the material most readily projected onto others.

Anima / animus

The contrasexual archetype. The *anima* is the residue of all experience of woman in a man's psychic heritage; the *animus* is the residue of all experience of man in a woman's. It connects the ego to the inner world and is projected onto partners in intimate relationships.

The Self

The archetype of wholeness and the innate ordering principle of the whole psyche, the unconscious centre that directs psychic life and gives rise to the ego. Not to be confused with the ego: the Self is the totality, the ego only the conscious fragment. Often symbolised by the mandala.

Two further named archetypes carry the personified wisdom and nurturance of the collective unconscious: the **wise old man** (the archetype of meaning, spirit, and guidance, appearing as the sage, teacher, or magician) and the **great mother** (the archetype of nurturance and of creation-and-destruction, the earth mother above) (Kaplan & Sadock 2024).

COMMON TRAP

Do not conflate the *ego* with the *Self*. In Jung the ego is only the centre of consciousness, a small part; the Self is the archetype of the whole psyche, conscious and unconscious together, and is the goal that individuation moves toward. Inflation of the ego with the Self's power (mistaking the part for the whole) is, for Jung, a route to grandiosity; being cut off from the Self yields alienation and depression. Likewise the *persona* is the outward mask and the *shadow* is the disowned inner opposite; they are complementary, not the same axis as ego and Self.

13.5 The two attitudes and four functions: Jung's typology behind the MBTI

This is the most widely known part of Jung and the highest-yield to memorise cleanly. Jung's **psychological types** (from *Psychological Types*, 1921) combine two *attitudes* of energy orientation with four *functions* of psychological activity. The two attitudes are **extraversion** (energy oriented outward, to others and the world of objects) and **introversion** (energy oriented inward, to the subject's own inner world); Jung himself described his type as an introverted intuitive. The four functions split into two pairs. The two *rational* (judging) functions are **thinking** (evaluating by logic) and **feeling** (evaluating by values and relationship, not by logic, so "feeling" here means valuing, not emotion). The two *irrational* (perceiving) functions are **sensation** (grasping a situation by assembling its concrete details, seeing the trees first) and **intuition** (grasping the whole first, seeing the forest). Everyone has all functions but a superior, most-developed one and an inferior, least-developed one (Kaplan & Sadock 2024). The **Myers-Briggs Type Indicator (MBTI)** operationalised Jung's attitudes and functions into a self-report instrument and is the most popular, most widely known descendant of his theory, though it is used detached from its Jungian roots and lacks strong psychometric standing.

POLARITY	POLE A	POLE B	WHAT IT CONCERNS
Attitude	Extraversion (energy outward)	Introversion (energy inward)	**Direction of psychic energy / object relatedness**
Rational (judging) function	Thinking (logic)	Feeling (values)	**How information is evaluated and judged**
Irrational (perceiving) function	Sensation (details, "trees")	Intuition (whole, "forest")	**How information is perceived / taken in**

Jung's typology: one attitude axis and two function axes (thinking/feeling are rational, sensation/intuition irrational); crossing them yields the eight function-attitude types operationalised by the MBTI (Kaplan & Sadock 2024).

13.6 Individuation and the transcendent function: the goal of the psyche

Individuation is Jung's word for the lifelong drive toward wholeness. Where Freud's endpoint was the resolution of infantile conflict, Jung's is **individuation**: the process by which a person becomes a whole, unique individual by integrating the unconscious (especially the shadow and

the anima/animus) into conscious life, so that the ego comes into a working relationship with the Self. Jung placed this squarely in the *second half of life*: in youth the ego builds itself and adapts to the world, but at midlife the task turns inward, toward meaning, and toward the parts of the personality left undeveloped (the inferior functions, the disowned shadow). The **transcendent function** is the mechanism of integration: it is the psychic function that unites conscious and unconscious contents, typically through a symbol that holds both opposites, so that the tension between them is resolved at a higher level rather than by one side suppressing the other (Kaplan & Sadock 2024; Companion to Psychiatric Studies). Individuation is thus not becoming self-centred; it paradoxically yields broader, more mature relationships and greater creativity.

HOLD THIS

Three Jung survivors: the collective unconscious and archetypes (unique to him), introversion/extraversion plus four functions (the root of the MBTI), and individuation as the goal. Individuation is a task of the second half of life.

13.7 Synchronicity and the compensatory unconscious

Two smaller Jungian concepts worth a line each. **Synchronicity** is Jung's term for a meaningful coincidence of an inner state and an outer event that are connected by *meaning* rather than by cause, an "acausal connecting principle." It sits at the mystical edge of his system and is one of the concepts that separates Jungian thought from mainstream scientific psychology. Second, Jung held that the psyche is self-balancing: his **law of compensation** states that for any one-sided or overly intense conscious attitude, the unconscious produces a compensating counterweight, which is why he read a dream by asking what conscious attitude it compensated for (a neglected person dreams of a huge, many-breasted mother) (Kaplan & Sadock 2024).

13.8 The 1913 break from Freud: libido as general psychic energy

Know the specific point of rupture, not just the fact of it. Jung was Freud's designated successor, but the friendship ended around 1913 over the *nature of libido*. Freud insisted libido was fundamentally *sexual* energy; Jung redefined it as a general, undifferentiated **psychic energy** or "life urge," of which sexuality was only one expression (Companion to Psychiatric Studies). From this single disagreement the rest of the split followed: Jung rejected the Oedipus complex as a universal developmental stage, minimised the causal weight of infantile sexuality, and replaced Freud's backward-looking, causal model with a teleological one in which the psyche is also pulled forward by the drive toward individuation and meaning. He further parted from Freud on the unconscious itself, adding the collective layer Freud never accepted. Jung's own turbulent period of self-analysis from 1913 to about 1918, during which he experienced quasi-psychotic imagery and used it as a spur to introspection, produced the raw material of much of his theory (Kaplan & Sadock 2024).

13.9 Therapeutic legacy: analytical psychotherapy, active imagination, dream amplification

Jungian technique is active, symbol-centred, and pitched at meaning. **Analytical psychotherapy** abandons the couch and the authoritarian analyst for a face-to-face (vis-a-vis) partnership, keeps the relationship positive and avoids fostering a transference neurosis, and

tailors technique to type (the introvert given elaborate interpretations, the extravert helped to pragmatic adjustment) (Wolberg 1988). Its signature methods are: **active imagination** (the patient deliberately enters and dialogues with unconscious images in a waking, semi-directed reverie, giving the unconscious a voice); **dream amplification** (elaborating a dream image by connecting it to parallel mythological, religious, and cultural motifs to draw out its archetypal meaning, rather than reducing it to a disguised infantile wish); and the use of drawings, paintings, mandalas, and the sand tray to externalise unconscious contents. Dreams are read as reflecting present strivings and future direction, not only the buried past. Beyond the clinic, Jung's reach is unusually wide: he seeded the MBTI, the word "complex," concepts of introversion and extraversion that entered ordinary language and later trait psychology, and a deep influence on the study of myth, religion, art, and spirituality (Wolberg 1988; Kaplan & Sadock 2024).

CLINICAL ANCHOR

A successful surgeon in his early fifties, secure in career and family, presents with a flat, purposeless depression and recurrent dreams of a locked room he cannot enter. Nothing in his life has "gone wrong." A Jungian reading treats this as a midlife individuation crisis: the ego-project of the first half of life is complete, and the Self is pressing for the neglected, unlived parts of the personality (the inferior functions, the shadow). The locked room is amplified as an image of the closed-off inner world; therapy uses dream work and active imagination to open a dialogue with it, aiming not to remove a symptom but to integrate what has been left out. This is precisely the "Who is the real me?" presentation Jungian analysis is considered well suited to (Kaplan & Sadock 2024).

PEARL

If three things survive from Jung into the exam, they are: (1) the *collective unconscious* with its *archetypes* as the one idea unique to him; (2) *introversion / extraversion* and the four functions as the root of the MBTI; and (3) *individuation* as the goal. Anchor the map with one boundary rule: complexes sit in the *personal* unconscious, archetypes in the *collective* unconscious.

INDIA

Jung engaged directly with Indian thought: the *mandala* he took as the central symbol of the Self is drawn from Hindu and Buddhist iconography, and his notion of individuation toward wholeness has been read alongside concepts of Self-realisation in Indian philosophy. For the Indian trainee this makes several Jungian symbols intuitively familiar; the exam caution is to keep the technical Jungian meanings (mandala = archetype of the Self and of psychic order) distinct from their devotional or ritual meanings.

MNEMONIC

PSA-S = Persona, Shadow, Anima/animus, Self

The four core archetypes in the order they are usually met in analysis (outermost mask to innermost centre): **P**ersona (the mask), **S**hadow (the disowned opposite), **A**nima/animus (the contrasexual bridge to the inner world), **S**elf (the archetype of wholeness at the centre). Add the two personified figures, the wise old man (meaning) and the great mother (nurturance), and you have the named archetype set.

GOOD TO REMEMBER

- **Carl Gustav Jung (1875 to 1961):** Swiss psychiatrist; worked under Bleuler at the Burgholzli; founder of *analytical psychology*.
- **Break from Freud (c. 1913):** over libido, Freud held it sexual, Jung held it a general psychic energy or "life urge"; Jung also rejected the universal Oedipus complex and added the collective unconscious.
- **Word-association test:** Jung's empirical root; origin of the term *complex* (a cluster of emotionally toned unconscious ideas, detected by disturbed reaction times).
- **Structure of the psyche:** ego (surface, centre of consciousness) → personal unconscious (holds the complexes) → collective unconscious / objective psyche (holds the archetypes).
- **Boundary rule:** complexes = personal unconscious; archetypes = collective unconscious.
- **Archetype vs complex:** archetype = inherited universal template (mould); complex = the personal cast filled in by lived experience.
- **Persona:** the social mask mediating ego and world.
- **Shadow:** the disowned reverse of the persona (positive or negative); readily projected.
- **Anima / animus:** the contrasexual archetype (anima = the feminine in a man; animus = the masculine in a woman).
- **Self:** the archetype of wholeness and the ordering centre of the whole psyche (symbol: mandala); not the same as the ego.
- **Wise old man / great mother:** personified archetypes of meaning/guidance and of nurturance.
- **Two attitudes:** extraversion (energy outward) and introversion (energy inward).
- **Four functions:** rational (judging) = thinking (logic) and feeling (values); irrational (perceiving) = sensation (details, "trees") and intuition (whole, "forest").
- **MBTI:** Myers-Briggs Type Indicator; the popular self-report descendant of Jung's attitudes and functions (used detached from Jungian theory, weak psychometrics).
- **Individuation:** the goal, integration of the unconscious into a whole, unique self; a task of the second half of life.
- **Transcendent function:** the psychic function that unites conscious and unconscious via a symbol holding both opposites.
- **Synchronicity:** meaningful (acausal) coincidence of inner state and outer event.
- **Law of compensation:** the unconscious counterbalances a one-sided conscious attitude (basis of Jung's dream reading).
- **Therapy:** analytical psychotherapy (face-to-face, active, type-tailored); active imagination; dream amplification; drawings, mandalas, sand tray. Dreams read for present and future, not only the past.
- **Key works:** *Psychological Types* (1921), *Two Essays on Analytical Psychology*, *The Archetypes and the Collective Unconscious*.

Developmental psychology

14 · Erikson psychosocial stages

The theory that took development off the couch and across the whole lifespan. Erik Erikson (1902 to 1994) is the ego psychologist every psychiatry exam expects you to command in full, because his eight-stage schema is the reference frame for adolescent identity work, midlife crisis, and the psychology of ageing, and because it is the cleanest illustration of how psychoanalysis was extended beyond the drives. Where Freud's psychosexual stages ended at the genital stage and fell back on themselves after adolescence, Erikson's **psychosocial** stages continued through youth, middle age, and old age, describing the maturing ego's relations with an ever-widening social world rather than a biological unfolding of erogenous zones (Kaplan & Sadock 2024).

For the exam hold four things: the eight stages in order with their ages, the crisis and the **virtue** that each resolves into, the **epigenetic principle** that binds the sequence together, and Marcia's four identity statuses as the empirical operationalisation of stage five. Erikson is best remembered as the man who coined the phrase **identity crisis**, drawing it explicitly from his own alienated, wandering adolescence (Kaplan & Sadock 2024).

14.1 Who Erikson was, and what he fixed

From Freud's drives to the ego's adaptation. Erikson was trained in Vienna by Anna Freud, absorbed her ego psychology (her 1936 treatise on the defence mechanisms), and carried it into a developmental theory of growth rather than pathology (Kaplan & Sadock 2024). His three landmark works map onto his own model: *Childhood and Society* (1950) laid out the life cycle; *Young Man Luther* analysed an adolescent identity crisis resolved in early adulthood; *Gandhi's Truth* demonstrated generativity at midlife. What he fixed from classical psychoanalysis was its two blind spots: it stopped at adolescence, and it read development as a biological unfolding of libido. Erikson kept the psychosexual scaffolding but recast each stage as a **psychosocial** crisis anchored in family, society, and history, and he pushed the sequence all the way to death. What he left debated was the empirical status of the stages themselves, which is exactly the gap Marcia later filled (see 14.6).

14.2 The epigenetic principle

The organising rule of the whole theory. Erikson borrowed the **epigenetic principle** from embryology: just as an organism in utero develops according to a predetermined ground plan in which each part has its time of special ascendancy, psychosocial growth proceeds in a fixed sequence of phases (Kaplan & Sadock 2024). Three consequences follow, and each is examinable. First, the elements of every stage are present from birth and merely differentiate over time. Second, each stage has its own period of quiescence and its own critical ascendancy, and depends on the proper resolution of the stages before it. Third, work on any stage is never finished; an old conflict can be reactivated by a later life event, which is why an adult can be thrown back into a trust or an identity crisis. The stages are not water-tight boxes but points along a continuum, and

the later four can be read as recombinations of the earlier ones (intimacy, for instance, fuses trust and autonomy).

14.3 Crisis, virtue, and the syntonic-dystonic balance

Each stage is a turning point, not a catastrophe. Erikson was precise that **crisis** means a turning point of heightened vulnerability and heightened potential, not a threat of disaster (Kaplan & Sadock 2024). Every stage pits a positive **syntonic** tendency against a negative **dystonic** one, and healthy resolution is not the total victory of the positive pole but a favourable ratio in which the syntonic quality predominates while a measure of the dystonic is retained. From that balance emerges a **virtue** or "basic strength", which Erikson defined as an inherent strength, the way one speaks of the virtue of a medicine. A useful refinement to quote: overshooting the positive pole produces a **maladaptation** (for example, sensory maldjustment, an over-trusting naivety), while collapse to the negative pole produces a **malignancy** (for example, withdrawal, entrenched mistrust). Both represent failed resolution of the crisis.

TRAP A crisis is a turning point of heightened vulnerability and potential, **not a catastrophe**. Healthy resolution is a favourable syntonic-over-dystonic ratio, not total victory of the positive pole.

14.4 The eight stages in order

The spine of the topic, learn it cold. The ages below follow Kaplan & Sadock (2024); note that the commonly taught bands (for example, trust to about 1 year, industry 6 to 12) are the same stages under rounder ages, and either set is acceptable in an answer so long as the sequence and virtues are exact. Stage five is the pivot of adolescent psychiatry; stages seven and eight are the ones examiners use to test the lifespan extension.

1. Trust versus mistrust (birth to about 18 months; virtue: hope)

The infant learns from consistent, responsive caregiving whether the world is dependable. The Freudian correlate is the oral stage. Failure yields basic mistrust; the malignancy is withdrawal.

2. Autonomy versus shame and doubt (about 18 months to 3 years; virtue: will)

Toilet training and mobility let the toddler exercise self-control and choice. The Freudian correlate is the anal stage. Over-control by caregivers breeds shame and self-doubt; the virtue is willpower.

3. Initiative versus guilt (about 3 to 5 years; virtue: purpose)

The child plans, initiates, and asserts through play and questions. The Freudian correlate is the phallic-oedipal stage. Excessive prohibition breeds guilt; the virtue is purpose.

4. Industry versus inferiority (about 6 to 12 years; virtue: competence)

School-age children build skills, compare themselves to peers, and derive self-esteem from accomplishment. The Freudian correlate is latency. Repeated failure or invidious comparison breeds inferiority; the virtue is competence.

5. Identity versus role confusion (adolescence, about 12 to 18 years; virtue: fidelity)

The adolescent integrates childhood identifications into a coherent, continuous sense of self and vocation. This is the identity crisis; the psychosocial moratorium is its healthy exploratory phase. Failure yields role (or identity) confusion; the virtue is fidelity, the capacity to sustain loyalties despite contradictions.

6. Intimacy versus isolation (young adulthood, about 20s to 40; virtue: love)
Having secured an identity, the young adult can fuse it with another's in genuine intimacy without fear of ego loss. Failure yields isolation and superficial relationships; the virtue is love.

7. Generativity versus stagnation (middle adulthood, about 40 to 65; virtue: care)
The adult invests in guiding the next generation through parenthood, mentorship, and productive work. Failure yields stagnation and self-absorption; the virtue is care.

8. Ego integrity versus despair (old age, about 65 to death; virtue: wisdom)
The elder reviews the life lived and either accepts it as meaningful and inevitable (integrity) or is overwhelmed by regret and the shortness of remaining time (despair). The virtue is wisdom, a detached yet active concern with life in the face of death.

14.5 Freud beside Erikson: the psychosexual-to-psychosocial extension

Same childhood scaffold, then Erikson keeps going. The single most common comparison question asks how Erikson relates to Freud (Tasman 2015). The two theories run in parallel through childhood, then Freud's stops and Erikson's continues for three more stages across the whole adult life.

AGE BAND	FREUD (PSYCHOSEXUAL)	ERIKSON (PSYCHOSOCIAL)	VIRTUE
0 to ~1.5 y	Oral	Trust vs mistrust	**Hope**
~1.5 to 3 y	Anal	Autonomy vs shame and doubt	**Will**
~3 to 5 y	Phallic (oedipal)	Initiative vs guilt	**Purpose**
~6 to 12 y	Latency	Industry vs inferiority	**Competence**
Adolescence	Genital	Identity vs role confusion	**Fidelity**
Young adulthood	**(Freud stops here)**	Intimacy vs isolation	**Love**
Middle adulthood	**(no Freudian stage)**	Generativity vs stagnation	**Care**
Old age	**(no Freudian stage)**	Ego integrity vs despair	**Wisdom**

The discriminator: Freud's map ends at the genital stage in adolescence, whereas Erikson adds three adult stages (intimacy, generativity, integrity), which is precisely his lifespan extension of psychoanalysis.

14.6 Marcia's four identity statuses: the empirical extension

The evidence base examiners want attached to stage five. James Marcia (1966) operationalised Erikson's identity-versus-role-confusion crisis into a testable paradigm, crossing two dimensions: **exploration** (the presence or absence of a crisis, an active period of trying out alternatives) and **commitment** (whether the person has settled on values, vocation, and beliefs). The two-by-two grid yields four **identity statuses**, and this cross-tabulation is the single most examinable diagram in the topic.

STATUS	EXPLORATION (CRISIS)	COMMITMENT	CHARACTER
Identity achievement	**Yes (explored)**	**Yes (committed)**	Confident, self-directed; the mature resolution
Moratorium	**Yes (in active crisis)**	**No (not yet committed)**	Anxious but open, actively searching
Foreclosure	**No (no crisis)**	**Yes (committed)**	Conformist; commitments taken wholesale from parents or authority without questioning
Identity diffusion	**No**	**No**	Aimless, detached, no direction; the least adaptive status

Foreclosure is the classic trap: commitment without exploration. Diffusion is neither; achievement is both; moratorium is the healthy exploratory phase Erikson himself lived through.

The clinical and cultural nuance to add. Diffusion carries the highest risk for internalising and externalising problems and for suicidality, whereas achievement predicts higher subsequent intimacy, generativity, and integrity (longitudinal data). Marcia noted that in some cultural and gender contexts foreclosure can be socially adaptive, so the statuses are not a simple ranking from bad to good.

HOLD THIS

Erikson psychosocialised Freud and ran him across the whole lifespan; Marcia then made stage five empirical. The four statuses cross exploration (crisis) with commitment: achievement (both), moratorium (crisis only), foreclosure (commitment only), diffusion (neither).

14.7 Worked clinical example

Reading a case through the schema. A 19-year-old who abruptly abandons the engineering course his parents chose, drops his social group, and describes feeling "there is no real me under all this" is presenting a stage-five failure: an unresolved **identity versus role** crisis. In Marcia's terms he has moved out of *foreclosure* (a borrowed, unexamined commitment) into *moratorium* (active exploration without a new commitment). The developmentally correct clinical stance is not to rush him to a decision but to protect the psychosocial moratorium, because premature foreclosure would only re-create the problem. If, decades later, the same man at 68 sits in your clinic consumed by regret that he "wasted his life" and terrified of dying, you are looking at stage eight, despair rather than **integrity**, and the therapeutic task is a supported life review toward acceptance and wisdom. The same theory frames both encounters, which is exactly why Erikson endures in clinical psychiatry.

COMMON TRAP

Do not swap the virtues between stages: initiative gives *purpose* (not competence) and industry gives *competence* (not purpose); intimacy gives *love* and generativity gives *care*. And do not confuse Marcia's *moratorium* status (active exploration, no commitment) with *foreclosure* (commitment without exploration): foreclosure is the one that looks settled but has skipped the crisis.

PEARL

The one-line integration for an examiner: Erikson psychosocialised Freud and extended him across the whole lifespan under the epigenetic principle, and Marcia then made the adolescent identity stage empirical by crossing exploration with commitment. Name that arc (Freud to Erikson to Marcia) and you have framed the entire topic.

MNEMONIC

Virtues: "Hope Will Push Children Fully Loving Caring Wisely"

Stage virtues in order: **H**ope, **Wi**ll, **P**urpose, **C**ompetence, **F**idelity, **L**ove, **C**are, **Wi**sdom. For the statuses, remember the crisis-by-commitment grid: achievement (both), moratorium (crisis only), foreclosure (commitment only), diffusion (neither).

GOOD TO REMEMBER

- **Stage 1, trust vs mistrust:** birth to about 18 months; virtue *hope*; Freudian oral stage.
- **Stage 2, autonomy vs shame and doubt:** about 18 months to 3 years; virtue *will*; Freudian anal stage.
- **Stage 3, initiative vs guilt:** about 3 to 5 years; virtue *purpose*; Freudian phallic-oedipal stage.
- **Stage 4, industry vs inferiority:** about 6 to 12 years; virtue *competence*; Freudian latency.
- **Stage 5, identity vs role confusion:** adolescence (about 12 to 18 years); virtue *fidelity*; the identity crisis and psychosocial moratorium.
- **Stage 6, intimacy vs isolation:** young adulthood; virtue *love*.
- **Stage 7, generativity vs stagnation:** middle adulthood (about 40 to 65); virtue *care*.
- **Stage 8, ego integrity vs despair:** old age (about 65 to death); virtue *wisdom*.
- **Epigenetic principle:** fixed, predetermined sequence; each stage present from birth, ascendant in turn, dependent on prior resolution.
- **Crisis:** a turning point of heightened vulnerability and potential, not a catastrophe (Erikson).
- **Virtue / basic strength:** the ego strength emerging from a favourable syntonic-over-dystonic ratio.
- **Maladaptation vs malignancy:** too much positive pole (maladaptation) vs collapse to the negative pole (malignancy); both are failed resolution.
- **Marcia (1966) statuses:** achievement (crisis + commitment), moratorium (crisis, no commitment), foreclosure (commitment, no crisis), diffusion (neither).
- **Extension of Freud:** Erikson made the stages psychosocial and added three adult stages past the genital stage (intimacy, generativity, integrity).
- **Key works:** *Childhood and Society* (1950), *Young Man Luther*, *Gandhi's Truth*.

15 · Piaget cognitive development, Vygotsky and theory of mind

The map of how thinking is built. Jean Piaget (1896 to 1980) gave psychiatry its dominant account of how the child's mind is constructed, stage by qualitatively distinct stage, from reflex to abstract reason. The exam wants three things held together and often contrasted: Piaget's **constructivist** stage theory (the mechanisms, the four periods with their ages and signature tasks, and the standard critiques), Lev Vygotsky's rival **sociocultural** theory (learning as socially mediated, the zone of proximal development, scaffolding), and the **theory of mind** tradition that grew out of the egocentrism question and reset the age at which a child grasps that others hold false beliefs.

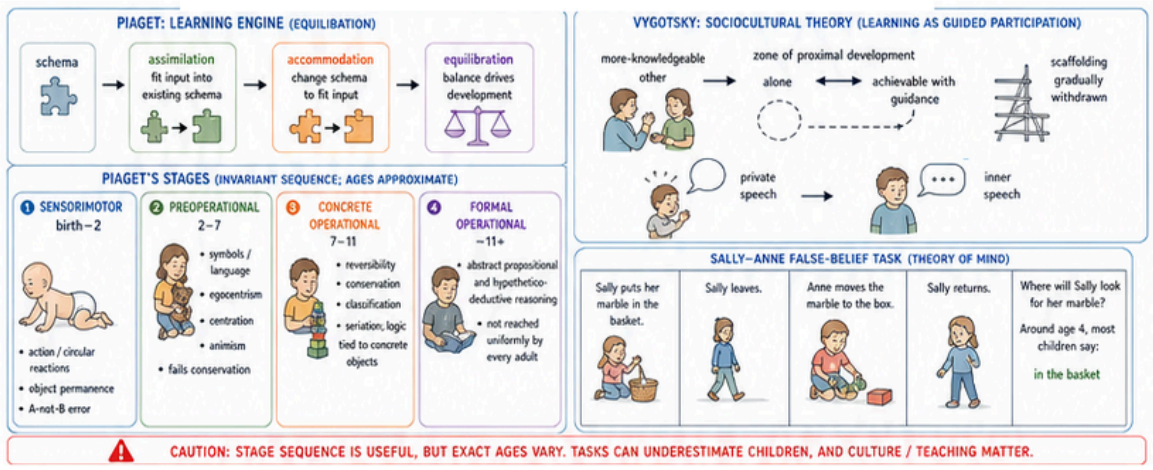


Fig 4.14 Cognitive development: from action to abstract thought.

Piaget held that the child's mental life is *qualitatively* different from the adult's, not merely a smaller version of it (Companion to Psychiatric Studies). The child is an active builder, an epistemologist: by acting on the world the child constructs internal structures, and those structures, not the environment itself, govern how the child thinks (Kaplan & Sadock 2024). This is a stage-and-concept theory, so it is examined as a system to enumerate rather than as an evolution toward a single currently accepted mechanism; treat the ages below as the standard textbook bands, not sharp cut-offs.

15.1 The building blocks: schema, assimilation, accommodation, equilibration

Functional invariants. A **schema** (scheme) is a unit of cognition: the organised structure of an action, generalised by repetition to analogous situations, from the infant's grasping reflex to the adolescent's logical operation (Kaplan & Sadock 2024). Schemata change through two complementary processes that operate at every level of development. In **assimilation**, the child incorporates new input into an existing schema: a child who meets a dachshund for the first time assimilates it into the schema "dog" (Tasman 2015). In **accommodation**, a novel stimulus that will not fit forces the schema to expand or reorganise: the schema "all four-legged animals are dogs" must be altered when the child meets a cat. **Equilibration** is the self-regulating drive that balances assimilation against accommodation; Piaget called it "compensation for an external disturbance," the internal factor that structures developing intelligence and pushes it toward

wider adaptation. Biological maturation, learning and social interaction feed into development and crystallise through equilibration.

TRAP In **assimilation** the input is bent to fit the schema (a dachshund fits "dog"); in **accommodation** the schema is bent to fit the input (the schema changes when a cat will not fit "dog"). Assimilation keeps the schema, accommodation changes it.

15.2 Sensorimotor stage (birth to about 2 years): object permanence

Knowing through action. In the **sensorimotor** period the child constructs schemata purely through perception and bodily movement, with no symbols or representational thought yet (Kaplan & Sadock 2024). Piaget divided it into six substages, tracked through the infant's growing repertoire of *circular reactions*, repeated actions that reproduce an interesting result: *primary* circular reactions centre on the infant's own body (repeating a chance motor act), *secondary* circular reactions act on external objects (shaking a rattle to reproduce a sound), and *tertiary* circular reactions in stage 5 explore variation deliberately (using a stick to move a distant object), the hallmark of active experimentation and discovery. The crowning achievement is **object permanence**, the knowledge that objects exist independently of the child's perception of them; Piaget called it the first victory of conservation and the foundation of all future knowledge. Early on, a toy dropped out of sight simply ceases to exist; by around 12 months the child searches for a hidden object. The classic error is the *A-not-B error* of stage 4: after an object is repeatedly hidden and found at point A, the infant keeps searching at A even after watching it hidden at point B.

15.3 Preoperational stage (about 2 to 7 years): symbols without logic

Representation arrives, operations do not. The **preoperational** subperiod opens with the *semiotic (symbolic) function*, the ability to let a signifier stand for something absent (Kaplan & Sadock 2024). Piaget flagged it by five behaviours emerging in the second year: deferred imitation, symbolic (pretend) play, drawing, mental imagery and language. Thought is now representational but not yet logical, limited by several features:

Egocentrism

The child cannot separate its own viewpoint from another's and assumes others share its perceptions and tastes; a toddler covers its own eyes and says "now you can't see me." Demonstrated by the *three-mountains task*, where the child fails to report how the scene looks from a doll's position.

Centration

Narrow focusing on one salient dimension of a situation while ignoring others; the child judges a quart of milk poured into two smaller containers as "less" because it attends only to the containers' smaller size (Tasman 2015).

Animism

Attributing life, feelings and intentions to inanimate objects (the sun "wants" to shine).

Lack of conservation

The child does not grasp that a quantity stays invariant across a change in appearance; poured into a tall thin glass, the same liquid is judged to be "more."

15.4 Concrete operational stage (about 7 to 11 years): logic on the concrete

Reversibility unlocks conservation. The **concrete operational** child can now perform mental *operations*, which are interiorised actions that are *reversible* and organised into a system (Kaplan & Sadock 2024). Reversibility, the ability to mentally undo a transformation (pour the liquid back), is what lets the child achieve **conservation**: the certainty that quantity, mass, number, weight or volume stays invariant despite a perceptual change. Piaget noted a fixed order within the stage, a *horizontal decalage*: conservation of number and quantity around 7, of weight around 9 to 10, and of volume only around 11 to 12. Two further operations appear: *classification* and *class inclusion* (holding a superordinate class in mind while perceiving subordinate ones, so the child grasps that there are more "pets" than "dogs"), and *seriation* (ordering rods by length, which underlies dimensional thinking). Thought is logical but tied to concrete, present objects; the child still struggles with the purely abstract or hypothetical.

~7 y	~9 to 10 y	~11 to 12 y
CONSERVE NUMBER/QUANTITY	CONSERVE WEIGHT	CONSERVE VOLUME

15.5 Formal operational stage (about 11 years onward): hypothetico-deductive reasoning

The possible over the real. In the **formal operational** stage, the relationship between the real and the possible reverses: for the adolescent the possible has priority and the actual is treated as one instance of what could be (Kaplan & Sadock 2024). Three features follow. Thought becomes *hypothetico-deductive*, moving from a general hypothesis to its testable consequences, mirroring scientific reasoning. It becomes *propositional*, operating on abstract statements freed from concrete referents, so transitive inferences (A less than B, B less than C, therefore A less than C) can be made without demonstration. And it can *isolate variables and systematically examine all combinations*, holding other factors constant to test each cause in turn. Piaget noted a fresh burst of *adolescent egocentrism* at this transition, in which the adolescent unrealistically assumes others are as preoccupied with them as they are, feeding social anxiety and idealism.

15.6 Critiques of Piaget

Right sequence, wrong timetable and boundaries. The developmental sequence Piaget described is robustly supported and rarely reverses, but three lines of criticism are exam-standard (Companion to Psychiatric Studies; Kaplan & Sadock 2024). First, he *underestimated infants and young children*: Gibson and Walk's visual-cliff work showed depth perception by 6 months, and Margaret Donaldson's redesigned conservation task, in which "naughty teddy" rather than a deliberate adult moves the counters, let far more 4 to 6 year olds conserve, arguing that Piaget's tasks misled children rather than measuring pure incompetence. Second, *ages vary and the stages are too broad*; specific training accelerates conservation, and many adolescents and adults fail formal-operations tasks, so the timetable is not fixed. Third, there is *cultural bias*: cross-cultural work shows tasks are mastered at different ages across cultures, and the supremacy of formal over concrete operations is culturally relative. Piaget also relied heavily on the child's verbal justification, confounding logical competence with verbal skill, and gave little weight to social intelligence or to knowledge acquired by social transmission, the very gap Vygotsky fills.

15.7 Vygotsky: the sociocultural alternative

Learning is social first, individual second. Lev Vygotsky's sociocultural theory treats cognitive development as a fundamentally **social** process, not the solitary journey of discovery Piaget emphasised (Tasman 2015). Learning is driven and mediated by interaction with a *more-knowledgeable other* (parent, teacher, more capable peer), and culture shapes which skills are learned, so development varies across cultures; children internalise the "tools of intellectual adaptation" their culture supplies. Its core constructs:

Zone of proximal development (ZPD)

The gap between what a learner can do independently (actual developmental level) and what they can achieve with guidance (level of potential development). Instruction is most effective, and cognitive growth maximised, when pitched into this zone.

Scaffolding

The graduated, temporary support a more-knowledgeable other gives within the ZPD (modelling, visual aids, worked examples, one-to-one feedback), progressively withdrawn as the learner becomes able to perform the task alone. (The term is Wood, Bruner and Ross's, applied to Vygotsky's framework.)

More-knowledgeable other (MKO)

Anyone with greater mastery of the task, most often a parent, teacher or peer, who guides the learner across the ZPD.

Private speech

Self-directed audible speech (typically from about age 3) that regulates the child's own behaviour and problem-solving; for Vygotsky it is a transitional stage between social external speech and silent inner speech (from about age 7), and thought and language, initially separate, merge around this age. Contrast Piaget, who read the same self-talk as immature egocentric speech that simply fades.

15.8 Piaget versus Vygotsky

DIMENSION	PIAGET	VYGOTSKY
Engine of development	**Individual construction: the lone child acting on the world**	**Social mediation: guided interaction, then internalisation**
Role of culture	Universal, culture-general stages	Central; development varies across cultures
Role of language	A product of thought; egocentric speech is immature	The root of learning; private speech regulates and builds thought
Learning and development	Development leads; readiness gates learning	Learning leads development within the ZPD
Adult / other	Peers spur cognitive conflict; direct teaching can constrain	The MKO actively scaffolds new competence

Two constructivisms: Piaget builds the mind from the inside out, Vygotsky from the social world in.

15.9 Theory of mind and the false-belief task

Knowing that others can be wrong. **Theory of mind** is the ability to attribute mental states (beliefs, desires, intentions) to oneself and others and to use them to predict behaviour, and to grasp that beliefs can be true or false and that different people can hold different beliefs (Companion to Psychiatric Studies). It is tested with the **false-belief** task, which Wimmer and Perner introduced in 1983 (the "Maxi" task, in which a child must predict where a character will look for chocolate that was moved in his absence). Simon Baron-Cohen, Alan Leslie and Uta Frith adapted it into the *Sally-Anne task* (1985): Sally places a marble in a basket and leaves; Anne moves it to a box; the watching child is asked where Sally will look on returning. Children of about 3 and under answer "the box," the marble's true location, failing to separate their own knowledge from Sally's; from about *4 years* children answer "the basket," correctly tracking Sally's false belief. This resets Piaget's egocentrism finding: the shift out of egocentrism on a belief task happens nearer 4 than the 7 years Piaget implied for perspective-taking. Its clinical weight is in autism: Baron-Cohen, Leslie and Frith found children with autism selectively failed the Sally-Anne task despite adequate mental age, giving rise to the influential *mindblindness* account of autism as a specific theory-of-mind deficit, with theory-of-mind impairment later also implicated in schizophrenia (Frith).

HOLD THIS

False belief emerges about age 4, resetting Piaget's egocentrism. Object permanence is sensorimotor; conservation is concrete-operational; the Sally-Anne autism study is Baron-Cohen, Leslie and Frith (1985), the paradigm Wimmer and Perner (1983).

CLINICAL ANCHOR

Theory-of-mind testing sits directly in the autism assessment. A child with intact general ability who selectively fails false-belief tasks fits the mindblindness profile; theory-of-mind deficits also feature in the social cognition literature on schizophrenia. Piagetian stage is a useful frame for pitching psychoeducation: a concrete-operational child reasons about present, tangible facts, so explanations of illness or medication should be concrete rather than abstract until formal operations are in place.

COMMON TRAP

Do not confuse the ages: object permanence in the *sensorimotor* stage, conservation in the *concrete operational* stage. Do not credit "scaffolding" to Vygotsky as a term (it is Wood, Bruner and Ross; the underlying ZPD is Vygotsky's). And the false-belief milestone is about *4 years*, not the 7 years Piaget gave for perspective-taking; the Sally-Anne autism study is Baron-Cohen, Leslie and Frith 1985, while the false-belief paradigm itself is Wimmer and Perner 1983.

MNEMONIC

Some People Can Fly = Sensorimotor, Preoperational, Concrete, Formal

Reads Piaget's four periods in order. Anchor one signature to each: Sensorimotor to object permanence, Preoperational to egocentrism (no conservation), Concrete to conservation, Formal to hypothetico-deductive abstraction.

GOOD TO REMEMBER

- **Schema:** unit of cognition; changed by assimilation (fit new input to old schema) and accommodation (alter schema to fit new input), balanced by equilibration.
- **Sensorimotor:** birth to about 2 years; action-based, circular reactions (primary, secondary, tertiary); achieves object permanence; A-not-B error.
- **Preoperational:** about 2 to 7 years; symbolic/semiotic function; egocentrism (three-mountains task), centration, animism, no conservation.
- **Concrete operational:** about 7 to 11 years; reversibility gives conservation, plus classification, class inclusion and seriation; logic tied to the concrete.
- **Formal operational:** about 11 years onward; abstract hypothetico-deductive and propositional thought, isolating variables; adolescent egocentrism.
- **Conservation order (decalage):** number/quantity about 7, weight about 9 to 10, volume about 11 to 12.
- **Piaget critiques:** underestimated infants (Donaldson's naughty-teddy task; Gibson and Walk visual cliff), ages vary and stages too broad, cultural bias.
- **Vygotsky (sociocultural):** zone of proximal development, scaffolding, more-knowledgeable other, private speech; learning is socially mediated and culture-dependent.
- **Piaget vs Vygotsky:** individual construction vs social mediation; Piaget development leads learning, Vygotsky learning leads development.
- **Theory of mind:** attributing mental states and grasping false belief; emerges about 4 years.
- **False-belief task:** Wimmer and Perner 1983 (Maxi); Sally-Anne = Baron-Cohen, Leslie and Frith 1985, relevant to autism (mindblindness).

16 · Kohlberg moral development

Where it sits. Lawrence **Kohlberg** (1958, 1969, 1984) took Piaget's two-phase account of moral judgment (the young child's **moral realism**, in which rules are fixed and sacred and wrongness equals the size of the damage, giving way to the older child's **moral relativism** or autonomy, in which rules are negotiable agreements and intention counts) and built it into a full **six-stage, three-level** theory of moral *reasoning*. Piaget wrote *The Moral Judgment of the Child* but did not develop the area further; Kohlberg's extension is, in Kaplan and Sadock's phrasing, "the first and perhaps best-known attempt to extend Piaget theory" (Kaplan & Sadock 2024).

For the exam this is the single most examinable moral-development theory: know the three level names, the six stage names, that it is elicited by the **Heinz dilemma**, that it is the *reasoning and not the answer* that fixes the stage, that progression is invariant and forward-only but that most people never reach the top, and that it draws two famous critiques, Gilligan's ethic-of-care/gender-bias critique and the cross-cultural critique. The stages presuppose Piagetian

cognitive stages: conventional reasoning needs concrete operations, principled reasoning needs formal operations (Kaplan & Sadock 2024).

16.1 The method: moral dilemmas and the Moral Judgment Interview

What Kohlberg measured. He adopted Piaget's storytelling technique but standardised it into the **Moral Judgment Interview** (MJI): each participant was read a set of ten hypothetical dilemmas, each engineered to pit one ethical norm against another (property versus life, law versus compassion, loyalty versus honesty), and then probed with follow-up questions asking *why* a course of action was right or wrong. The original sample was 72 Chicago boys aged 10 to 16 years, of whom 58 were followed at roughly three-yearly intervals for 20 years (Kohlberg 1984). Kohlberg was deliberately indifferent to the participant's final choice: development pertained to the *form* of the thinking, not the content of the solution (Kaplan & Sadock 2024).

16.2 The Heinz dilemma

The stimulus. Heinz's wife is dying of a cancer that a new drug might cure. The chemist who discovered it charges ten times its cost, far more than Heinz can raise even with help. The chemist refuses to sell cheaper or to accept later payment, so Heinz breaks in and steals the drug. *Should Heinz have stolen it, and why?* The genius of the design is that "yes" and "no" answers appear at every level, so it is only the **justification** that reveals the stage: fear of jail (preconventional), a good husband's duty (conventional), or the relative worth of life over property (postconventional). This is the load-bearing exam point, the same answer can be stage 1 or stage 6 depending on the reason.

RULE **It is the reasoning, not the answer, that fixes the stage.** Two people who both say Heinz should steal can be a stage apart; two who disagree on the verdict can share a stage.

16.3 Level I: Preconventional morality (moral authority is external)

The child accepts an outside code. Typically the mode until about age 9, and grounded in the anticipated consequence of the act to oneself. There is no internal sense of right and wrong yet; "right" is what avoids punishment or brings reward (Kaplan & Sadock 2024).

Stage 1 : Punishment and obedience orientation

Rules are fixed and absolute; an act is "bad" purely because it is punished. Intent is ignored. Heinz should not steal because he could be jailed. The defining test of "right" becomes being able to get away with it.

Stage 2 : Instrumental exchange (naive hedonism, self-interest)

The child recognises that different people have different interests and acts to serve personal need. Reciprocity is transactional, "an eye for an eye," "you scratch my back," "what's in it for me." Heinz may steal if the wife's survival serves him, not from any principle.

16.4 Level II: Conventional morality (moral authority is internalised but unquestioned)

The standards of the group become one's own. Prevalent from adolescence; the person internalises the moral standards of valued adults and the norms of the group, and reasons to maintain relationships and social order. Authority is taken on board but not interrogated (Kaplan & Sadock 2024).

Stage 3 : Good-boy / good-girl, interpersonal conformity

Morality is being seen as good by others: trust, loyalty, living up to what a nice person in one's role would do. Heinz should steal because a devoted husband is *expected* to do everything to save his wife; the motive is approval and the maintenance of the relationship.

Stage 4 : Law-and-order, authority and social-order maintenance

The frame widens from the immediate circle to society as a whole. One obeys laws, respects authority and does one's duty because the social system depends on it. Heinz should not steal because upholding the law prevents the chaos that would follow if everyone broke it.

16.5 Level III: Postconventional morality (moral authority is self-chosen principle)

Principles come to outrank both the group and the law. Reached, if at all, in late adolescence or early adulthood, and only by a minority: Kohlberg held that roughly 10 to 15 percent of people ever reason predominantly at this level, because it demands the abstract, formal-operational thought needed to weigh competing rights (Kohlberg 1984).

Stage 5 : Social contract and individual rights

Laws are seen as social agreements serving the greatest good, but as fallible and revisable when they conflict with fundamental rights. Heinz should steal because the preservation of life is a more basic value than the chemist's property right; the law here works against a legitimate individual interest.

Stage 6 : Universal ethical principles

Reasoning rests on self-chosen, universal principles of justice, equality and the dignity of human life that apply to everyone and override any law. The person will act on them, and accept punishment, even against the whole of society (non-violent civil disobedience is the paradigm). Kohlberg himself doubted that many people ever reach stage 6 and in later work questioned whether it could be reliably identified.

16.6 The structure of the sequence: invariant, forward-only, not universal in attainment

How the stages behave. The levels form an invariant sequence; a person passes through them in fixed order and each new stage replaces the reasoning of the one before, so stages cannot be skipped and there is no regression (Kaplan & Sadock 2024). Progress is driven by cognitive **disequilibrium**, the discomfort of meeting a viewpoint one's current reasoning cannot handle, and by improving perspective-taking. Crucially, Kohlberg did *not* claim that all or even most people reach the highest levels: attainment is capped by cognitive development and by exposure, and the top level is rare. Colby and Kohlberg's (1983) longitudinal re-analysis of the original cohort, tested repeatedly over more than two decades, supported the fixed-order claim.

16.7 Scoring: how a stage is assigned

The 50 percent rule. Responses across the ten dilemmas are coded and a person is formally classified at a stage only if they reason at that stage 50 percent or more of the time, so the stage represents their dominant, preferred mode rather than a single answer. The standardised scoring manual (Colby & Kohlberg 1983) defined explicit stage criteria and sharply improved inter-rater reliability, addressing an early complaint that scoring was subjective.

72	50%	10 to 15%
CHICAGO BOYS, ORIGINAL SAMPLE	REASONING TO BE SCORED AT A STAGE	EVER REACH POSTCONVENTIONAL

16.8 Gilligan's critique: an ethic of care versus an ethic of justice

The gender-bias objection. Kohlberg's original sample was entirely male, and his data suggested men more often progressed past stage 4, which read as though women were morally deficient (typically "stuck" at stage 3). His research associate Carol **Gilligan** (1977, 1982, *In a Different Voice*) argued the theory was androcentric: it defined morality narrowly as abstract justice and so mis-scored a genuinely different, equally mature **ethic of care** centred on relationships, responsibility and context, more common in women. In the Heinz dilemma a care voice attends to consequences for the marriage (if Heinz is jailed his wife loses him) rather than ranking abstract rights. Gilligan's charge is that women reason from care and connection, men from justice and fairness, and that Kohlberg mistook difference for deficiency (Kaplan & Sadock 2024).

COMMON TRAP

Do not present Gilligan's critique as the settled last word. Kaplan and Sadock note that *subsequent empirical research showed women score as high as, or higher than, men* on Kohlberg's stages, so the original claim of a female deficit did not hold up, which paradoxically weakens the premise Gilligan was attacking while leaving her positive point (that care is a legitimate moral orientation) intact. The examinable nuance: state the care-versus-justice distinction AND the finding that the sex difference in stage scores was not replicated.

16.9 The other criticisms: content, verbal skill, ecological validity and culture

Beyond gender. Kaplan and Sadock (2024) list several further objections. First, the moral *subject* was criticised as detached from moral *content*, and individual differences in reasoning stage did not correlate strongly or consistently with actual moral *behaviour* (reasoning and conduct diverge). Second, the method may have confounded verbal skill and general intelligence with moral reasoning, since higher stages simply require more articulate justification. Third, the dilemmas are artificial and hypothetical and so lack ecological validity (Rosen 1980); ten-to-sixteen-year-old boys had never been married or faced anything like Heinz's plight. The **cross-cultural critique.** Kohlberg's work was criticised as culturally biased toward the Western middle-class male: postconventional, individual-rights reasoning reflects an individualist liberal ethic, and members of collectivist and traditional societies who reason from communal duty, family honour or religious law are systematically scored lower, which many regard as an artefact of the instrument rather than genuinely lower morality (Kaplan & Sadock 2024).

HOLD THIS

Progression is invariant and forward-only, but attainment is not universal. Conventional reasoning needs concrete operations, principled reasoning needs formal operations; the theory is justice-centred and Western, which Gilligan and the cross-cultural critics attacked.

INDIA

The cross-cultural critique matters directly in the Indian setting. In collectivist, family-centred and duty-oriented moral cultures, an appeal to *dharma*, filial obligation or the maintenance of family and social order (which Kohlberg codes as conventional, stage 4) is often the most mature and considered response available, yet the MJI grades individual-rights reasoning as superior. Shweder and colleagues' Indian work on the "big three" ethics (autonomy, community, divinity) is the classic demonstration that Kohlberg's justice-and-rights scheme captures only the autonomy ethic and undervalues community and divinity moralities. Read Kohlberg's hierarchy as culture-bound, not as a universal ranking of moral worth.

16.10 Clinical and exam relevance

CLINICAL ANCHOR

Moral-reasoning frameworks surface in child and adolescent psychiatry (assessing conduct disorder and callous-unemotional traits, where the question is whether reasoning is delayed versus behaviourally uncoupled from reasoning), in forensic and personality-disorder assessment, and in medical ethics teaching. Beck's cognitive therapy of antisocial personality disorder explicitly draws on Kohlberg's model, framing treatment as helping the patient move from egocentric, preconventional cost-benefit reasoning toward more perspective-taking, mutual-benefit reasoning (Beck, Freeman & Davis). In Young's schema therapy, the Self-Sacrifice schema is located as a higher moral level than Subjugation precisely by reference to Kohlberg's stages, one surrenders one's needs from an inner standard rather than from external coercion.

MNEMONIC

"Pre-Con-Post" outer to inner · stages 1 to 6 = "Please Stop Getting Little Stupid Points"

Levels move from an **outside** code (Preconventional) to the **group's** code (Conventional) to a **self-chosen** code (Postconventional). For the six stages: **P**unishment, **S**elf-interest, **G**ood-boy, **L**aw-and-order, **S**ocial-contract, **P**rinciples. Pair each level with its Piagetian floor: conventional needs concrete operations, principled needs formal operations.

LEVEL	STAGE	RIGHT IS DEFINED BY	HEINZ JUSTIFICATION
I Preconventional (to ~age 9)	1 Punishment / obedience	Avoiding punishment; rules absolute	**Don't steal, he'll be jailed**
	2 Instrumental exchange	Self-interest, transactional reciprocity	**Steal if the wife is useful to him**
II Conventional (adolescence on)	3 Good-boy / conformity	Approval, being a good person in one's role	**Steal, a good husband would**
	4 Law-and-order	Duty, obeying law, social order	**Don't steal, uphold the law**
III Postconventional (10 to 15% only)	5 Social contract	Laws as revisable agreements; rights	**Steal, life outranks property**
	6 Universal principles	Self-chosen universal justice, dignity	**Steal, sanctity of life is absolute**

Kohlberg's three levels and six stages, with the same dilemma scored differently at each stage: the reasoning, not the verdict, fixes the level.

PEARL

The one line that answers most viva questions: *"It is the reasoning, not the answer, that determines the stage."* Two people who both say Heinz should steal can be a stage apart; two who disagree on the verdict can share a stage. Add the two headline caveats, progression is invariant but attainment is not universal (only 10 to 15 percent reach postconventional), and the theory is justice-centred and culturally Western, which is exactly what Gilligan and the cross-cultural critics attacked.

GOOD TO REMEMBER

- **Theorist:** Lawrence Kohlberg (1958 onward); built on Piaget's moral realism to relativism shift.
- **Elicited by:** the Heinz dilemma, scored via the Moral Judgment Interview (10 dilemmas).
- **Original sample:** 72 Chicago boys aged 10 to 16; 58 followed for 20 years (Kohlberg 1984).
- **Level I Preconventional (to ~age 9):** Stage 1 punishment-and-obedience; Stage 2 instrumental exchange / self-interest.
- **Level II Conventional (adolescence onward):** Stage 3 good-boy interpersonal conformity; Stage 4 law-and-order / social-order maintenance.
- **Level III Postconventional (only 10 to 15% reach it):** Stage 5 social contract and individual rights; Stage 6 universal ethical principles.
- **Core rule:** the reasoning, not the answer, fixes the stage; sequence invariant and forward-only; attainment not universal.
- **Cognitive floor:** conventional needs concrete operations, principled needs formal operations (Piagetian dependency).
- **Scoring rule:** classified at a stage if reasoning at it 50% or more of the time; standardised by Colby & Kohlberg (1983).
- **Gilligan critique:** androcentric, justice-biased; proposed an ethic of care (relationships, context) versus ethic of justice; note women later scored as high as or higher than men.
- **Cross-cultural critique:** Western, individualist, middle-class male bias; undervalues collectivist duty and divinity moralities (Shweder).
- **Related models:** Loevinger (ego), Fowler (faith/spiritual) as parallel adult stage theories of maturation.

17 · Attachment theory: Bowlby, Ainsworth and Harlow

The bond that builds the self. Attachment theory is the developmental account of the child's first tie to a caregiver, and it is examined as a linked chain of three names. Harry Harlow's rhesus-monkey experiments overturned the old view that the infant loves the mother because she feeds it; John Bowlby recast attachment as an evolved **behavioural system** serving survival, with the caregiver as a **secure base**; and Mary Ainsworth turned Bowlby's theory into a measurable laboratory procedure, the **Strange Situation**, that yields the attachment classifications the exam most often asks for. Hold the sequence: Harlow the empirical challenge, Bowlby the theory, Ainsworth the measurement, with the disorganised type and reactive attachment disorder as the later additions.

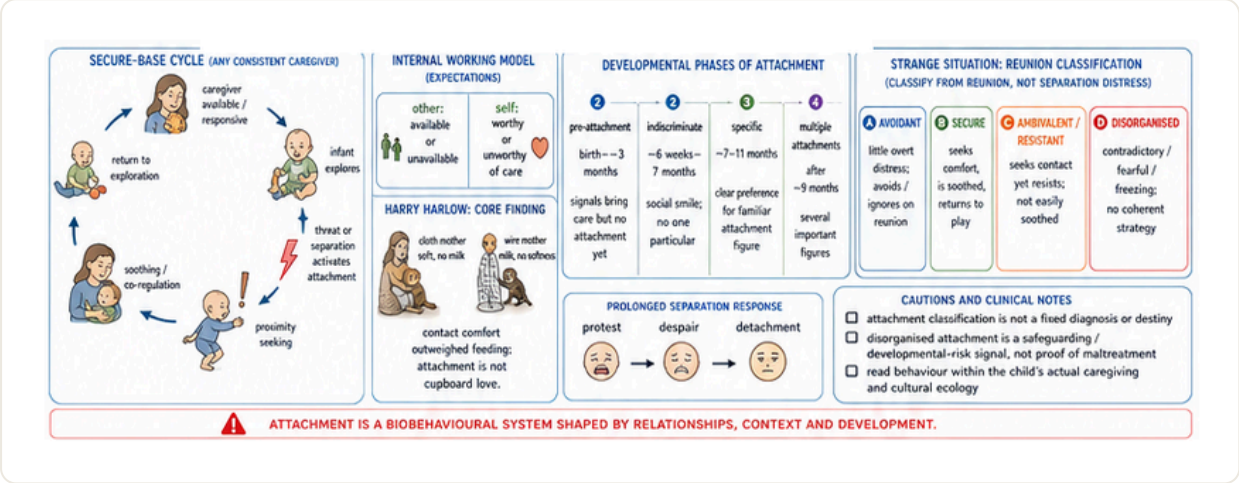


Fig 4.15 Attachment: secure base, working model and reunion.

The topic matters clinically because attachment is a major developmental-psychopathology construct: insecure and especially disorganised attachment in infancy is a replicated risk marker for later disorder, adult attachment style shapes the therapeutic relationship, and reactive attachment disorder is the diagnosable clinical extreme cross-referenced in Paper III child psychiatry (Kaplan & Sadock 2024). This is a stage-and-concept theory, so it is examined as a system to enumerate rather than as an evolution toward a single mechanism; treat the ages and percentages below as the standard textbook figures.

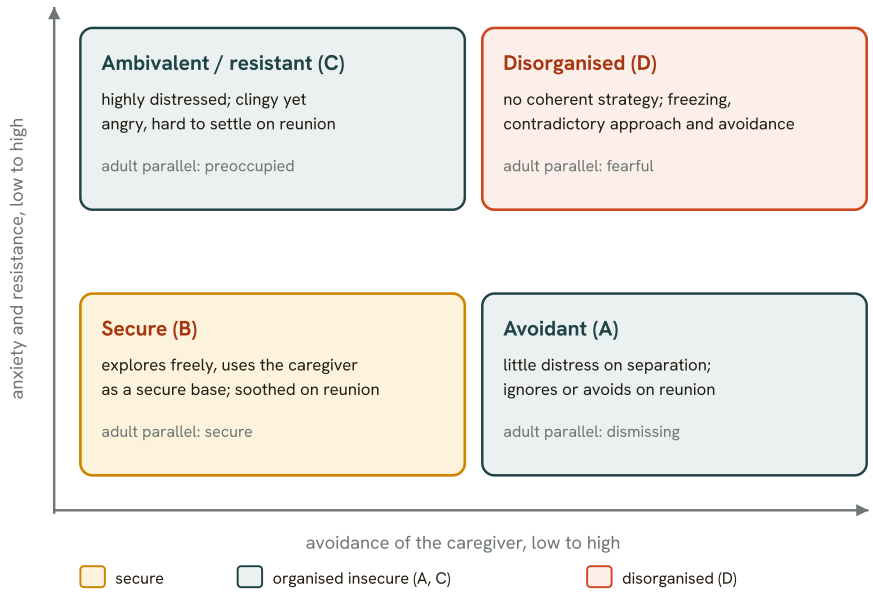


Fig 4.16 Ainsworth's strange-situation classification, read on two axes: how much the infant avoids the caregiver, and how much anxiety and resistance it shows. Secure infants (B) use the caregiver as a secure base and are soothed on reunion; avoidant infants (A) show little overt distress and turn away; ambivalent-resistant infants (C) are highly distressed and cannot be settled. Disorganised attachment (D, Main and Solomon) is the collapse of any coherent strategy and carries the greatest developmental-psychopathology risk. The adult-attachment parallels are noted in each cell.

17.1 Harlow: contact comfort overturns cupboard love

The wire mother and the cloth mother. Before Harlow, both psychoanalysis and learning theory held a **drive-reduction** (or "cupboard-love") view: the infant bonds to the mother because she reduces the primary hunger drive, so love is a secondary, learned reward for feeding (Kaplan & Sadock 2024). Harry Harlow tested this in the 1950s by rearing newborn rhesus monkeys with two surrogate "mothers," one a bare wire cylinder fitted with a feeding bottle, the other wire covered in soft terry cloth but giving no food (Harlow 1958). The prediction of cupboard love was that the infant would prefer whichever surrogate fed it. Instead, the infant monkeys spent almost all their time clinging to the cloth mother and went to the wire mother only to feed, then returned to the cloth; when frightened by a novel stimulus they fled to the cloth mother for comfort and used her as a base from which to venture out. The bond formed with the source of **contact comfort**, not the source of food. Harlow's later isolation experiments showed that monkeys reared without a real mother developed profound and lasting social, sexual and emotional deficits, evidence for a sensitive period in social development and against the idea that feeding is what matters.

PEARL

Harlow's single most exam-quoted conclusion: attachment is built on comfort and responsiveness, not on feeding. His work gave Bowlby the empirical footing to reject the psychoanalytic secondary-drive theory of the bond, and it prefigured the modern idea, carried into Emotionally Focused Therapy, that soothing physical contact directly regulates the threatened brain.

17.2 Bowlby: attachment as an evolved behavioural system

A control system for keeping the infant safe. John Bowlby (1907 to 1990), drawing on ethology, reframed attachment as a biologically evolved **behavioural system** whose set-goal is proximity to the caregiver and whose survival function is protection from predators and danger (Bowlby 1969). Attachment behaviours (crying, clinging, following, smiling, calling) are activated by fear, separation or fatigue and terminated by contact with the attachment figure. Two of Bowlby's terms recur in the exam. The **secure base** is the caregiver used as a base from which the child explores and to which it retreats when alarmed, so that attachment and exploration are reciprocally balanced. **Monotropy** is Bowlby's claim that the infant has an innate bias to form one principal, hierarchically superior attachment (usually but not necessarily the mother), which is qualitatively distinct from its bonds to other figures. Bowlby deliberately wrote "attachment figure" rather than "mother," acknowledging that fathers, grandparents and other caregivers can serve as attachment figures; the field's later focus on mothers reflected sampling convenience more than theory (Cassidy et al. 2013).

17.3 Bowlby: the internal working model

A cognitive template of self and other. The **internal working model** (IWM) is Bowlby's mechanism for how early experience persists: from repeated interactions the child builds a mental representation of whether the attachment figure is reliably available and responsive, and a complementary model of the self as worthy or unworthy of care (Bowlby 1969; Kaplan & Sadock 2024). These paired models operate largely outside awareness, guide expectations in later relationships, and are the theorised route by which infant attachment security predicts adult relational functioning. The IWM is the conceptual bridge from Ainsworth's infant classifications to the adult attachment literature and to the intergenerational transmission of attachment: a parent's own working model, captured on the Adult Attachment Interview, tends to predict the classification their infant will show in the Strange Situation.

17.4 Phases of attachment development

From indiscriminate signalling to a focused bond. Attachment is not present at birth but assembles over the first year through a described sequence of phases; the widely taught four-phase version comes from Schaffer and Emerson's longitudinal study of 60 infants (Schaffer & Emerson 1964), and maps closely onto Bowlby's own phase model.

Pre-attachment (birth to about 3 months)

No specific attachment; innate signals such as crying and smiling draw any caregiver near and are not yet directed at a particular person.

Indiscriminate attachment (about 6 weeks to 7 months)

The infant distinguishes familiar from unfamiliar people and responds more positively to primary caregivers but still accepts comfort from others.

Discriminate (specific) attachment (about 7 to 11 months)

A focused bond to one figure emerges; the infant now shows *separation protest* when parted from that figure and *stranger anxiety*, both appearing around 7 to 9 months.

Multiple attachments (after about 9 months)

Additional bonds form with other consistent caregivers (second parent, siblings, grandparents).

17.5 Maternal deprivation and separation: protest, despair, detachment

The sequence of a young child losing the caregiver. Bowlby's early work on prolonged separation described a predictable three-phase response in a young child removed from the attachment figure, for example on hospital or institutional admission (Kaplan & Sadock 2024). In **protest** the child cries, searches and refuses comfort, actively trying to recover the caregiver. In **despair** the child becomes quiet, withdrawn, hopeless and inactive, appearing to mourn. In **detachment** the child superficially recovers, engaging with surroundings and even the returning parent with apparent indifference, having defensively deactivated the attachment. Bowlby's **maternal deprivation hypothesis** linked disrupted early care to later disturbance, echoing René Spitz's earlier account of *anaclitic depression* in institutionalised infants deprived of a mothering figure (Spitz 1946). The strong "critical-period" reading of the hypothesis was later softened: outcome depends on the quality and reversibility of care, and later good caregiving can partly repair early deprivation.

17.6 Ainsworth: the Strange Situation procedure

A laboratory microcosm of attachment. Mary Ainsworth operationalised Bowlby's theory in the **Strange Situation**, a standardised observational procedure for infants of roughly 12 to 18 months (Ainsworth et al. 1978). It comprises eight brief episodes (about three minutes each) staged in an unfamiliar toy-filled room, using structured separations from and reunions with the caregiver plus the entry of a stranger, deliberately escalating mild stress to activate the attachment system. Observers rate four behavioural dimensions: *proximity and contact seeking*, *contact maintaining*, *avoidance* of proximity and contact, and *resistance* to contact and comfort, together with separation anxiety, stranger anxiety and, most diagnostically, the child's behaviour on *reunion*. The classification rests principally on the reunion episodes, not on how much the child cries at separation.

RULE **Read the type from reunion, not separation.** Both secure (B) and ambivalent (C) infants are highly distressed at separation, so separation distress alone never classifies.

17.7 The attachment classifications

Three original patterns plus a fourth. Ainsworth's analysis yielded three patterns, one secure and two insecure; Mary Main and Judith Solomon later added a fourth, **disorganised**, for infants who did not fit the original coding (Main & Solomon 1986).

TYPE	LABEL	EXPLORATION / SEPARATION	REUNION BEHAVIOUR (THE DISCRIMINATOR)	TYPICAL CAREGIVING
B	Secure	Explores freely using caregiver as a base; distressed at separation	**Actively seeks and is readily comforted by caregiver, then returns to play**	Sensitive, consistently responsive

TYPE	LABEL	EXPLORATION / SEPARATION	REUNION BEHAVIOUR (THE DISCRIMINATOR)	TYPICAL CAREGIVING
A	Insecure-avoidant	Explores with little reference to caregiver; little or no distress at separation	**Avoids or ignores caregiver on return; treats stranger and caregiver similarly**	Rejecting, dismissing of needs
C	Insecure-ambivalent / resistant	Clingy, explores little; intensely distressed at separation	**Seeks contact yet resists it, may arch away or push the caregiver away; not settled**	Inconsistent, unpredictable
D	Disorganised	No coherent strategy for managing distress	**Contradictory, odd or fearful acts on reunion: freezing, dazed expression, approaching then backing away**	Frightening / frightened; abuse or neglect

The reunion column is what separates the four types; separation distress alone does not, since both secure and ambivalent infants are distressed.

Distribution. In Ainsworth's original middle-class US sample the classic split was roughly secure 70 percent, avoidant 15 percent, ambivalent 15 percent, before the disorganised category existed (Ainsworth et al. 1978). A large modern meta-analysis of 285 studies and over 20,000 infant-caregiver pairs gives a global distribution of secure 51.6 percent, avoidant 14.7 percent, resistant 10.2 percent and disorganised 23.5 percent (Madigan et al. 2023). The A, B, C patterns are described as **organised** strategies (each a coherent, if insecure, way of managing an available or unavailable caregiver), whereas D reflects a breakdown of strategy.

51.6%	14.7%	10.2%	23.5%
SECURE (B)	AVOIDANT (A)	RESISTANT (C)	DISORGANISED (D)

COMMON TRAP

Do not equate crying at separation with insecurity: a securely attached infant is typically distressed when the caregiver leaves and comforted on return, whereas the avoidant infant shows little separation distress. The classification is read from *reunion*, not separation. Keep the letters and their labels aligned: A is avoidant, B is secure, C is ambivalent/resistant, D is disorganised. And attribute the fourth category correctly: the original three are Ainsworth's, the disorganised type is Main and Solomon.

17.8 Adult attachment, intergenerational transmission and psychopathology risk

The IWM carried forward and across generations. The infant patterns have adult counterparts assessed on the Adult Attachment Interview (autonomous corresponding to secure, dismissing to

avoidant, preoccupied to ambivalent, and unresolved/disorganised to disorganised), and a parent's classification statistically predicts their infant's, the phenomenon of **intergenerational transmission** of attachment; the imperfect link between parental state of mind and observed caregiving is the well-known "transmission gap" (Cassidy et al. 2013). Clinically, **disorganised** attachment is the pattern of greatest concern: it is over-represented in maltreated infants and is a robust early risk marker in developmental psychopathology, prospectively associated with later externalising problems, dissociation and personality pathology (Tasman 2015). Attachment concepts also underpin mentalization-based treatment, which locates the capacity to understand mental states within the security of early attachment relationships (Bateman & Fonagy).

HOLD THIS

Harlow theory, Bowlby framework, Ainsworth measure; disorganised (D) carries the greatest psychopathology risk. Harlow showed contact comfort beats feeding; the disorganised type (Main & Solomon) is over-represented in maltreated infants and is a safeguarding cue.

17.9 Reactive attachment disorder: the clinical extreme

When a selective attachment fails to form. **Reactive attachment disorder** (RAD) is the diagnosable disorder at the far end of the attachment spectrum, cross-referenced in Paper III (Kaplan & Sadock 2024). In DSM-5-TR and ICD-11 it requires a developmental age of at least **9 months** (the level at which selective attachment first becomes possible), onset before age 5, and a documented history of grossly insufficient care: social neglect, repeated changes of caregiver that prevent stable bonds, or rearing in settings with high child-to-caregiver ratios. The child shows an *emotionally withdrawn, inhibited* pattern: minimal seeking of or response to comfort when distressed, blunted positive emotion, and unexplained irritability, sadness or fearfulness. Autism spectrum disorder must be excluded. Its former "disinhibited" subtype is now the separate **disinhibited social engagement disorder** (DSED), marked by indiscriminate over-familiarity and reduced stranger wariness, and increasingly regarded as distinct from attachment as such. The evidence base is the English and Romanian Adoptees study and the Bucharest Early Intervention Project, which showed RAD signs recede within weeks of adequate care, whereas DSED can persist; neuroimaging in RAD has found reduced visual cortex volume and altered thalamic and white-matter measures (Kaplan & Sadock 2024).

CLINICAL ANCHOR

Attachment thinking is used at the bedside well beyond the RAD diagnosis. A child's attachment status frames how it will use a hospital admission or a new caregiver, and Bowlby's protest to despair to detachment sequence still describes the young inpatient separated from a parent. Adult attachment style shapes the therapeutic alliance: a dismissing patient may minimise distress and disengage, a preoccupied patient may over-seek reassurance, and an unresolved/disorganised state of mind flags trauma to be handled carefully. Disorganised attachment in an infant is a safeguarding cue, since it clusters with maltreatment.

INDIA

The Strange Situation was normed on Western nuclear families, and its coding of "avoidance" and independent exploration can misread culturally valued behaviour; in multiple-caregiver and joint-family settings common in India, distributions and the very meaning of a single monotropic figure may differ. Read a child's attachment behaviour against its actual caregiving ecology rather than against the original US base rates.

MNEMONIC

"A Avoids, B is Best, C Clings, D is Disordered"

Maps the four Strange-Situation letters to their signature: A avoidant (avoids the caregiver on reunion), B secure (the best-adjusted, comforted on reunion), C ambivalent/resistant (clings yet resists), D disorganised (no coherent strategy, odd or fearful reunion).

GOOD TO REMEMBER

- **Harlow (1958):** rhesus monkeys; cloth (contact-comfort) mother preferred over wire (feeding) mother, disproving cupboard-love / drive-reduction.
- **Bowlby (1907 to 1990):** attachment as an evolved behavioural system; secure base, monotropy, internal working model.
- **Internal working model:** mental template of caregiver-availability and of self-worth; route to adult and intergenerational transmission.
- **Separation response:** protest to despair to detachment (Bowlby); anaclitic depression (Spitz 1946).
- **Phases of attachment:** pre-attachment (0 to 3 mo), indiscriminate (6 wk to 7 mo), discriminate/specific (7 to 11 mo, separation protest and stranger anxiety), multiple (after ~9 mo).
- **Ainsworth (1978):** Strange Situation, infants ~12 to 18 months, 8 episodes; classification read from reunion.
- **Type B, Secure (~70% original):** distressed at separation, readily comforted on reunion; sensitive caregiving.
- **Type A, Insecure-avoidant (~15%):** little separation distress, avoids caregiver on reunion; rejecting caregiving.
- **Type C, Insecure-ambivalent/resistant (~15%):** intense distress, seeks yet resists contact; inconsistent caregiving.
- **Type D, Disorganised (Main & Solomon 1986):** contradictory/fearful reunion behaviour; frightening caregiving, maltreatment; highest psychopathology risk.
- **Modern distribution (Madigan et al. 2023):** secure 51.6%, avoidant 14.7%, resistant 10.2%, disorganised 23.5%.
- **Reactive attachment disorder:** developmental age ≥9 months, onset before age 5, pathogenic care; withdrawn/inhibited; ASD excluded. DSED is the separate disinhibited disorder. Evidence: ERA study, Bucharest Early Intervention Project.

18 · Temperament: Thomas and Chess

The idea that a child arrives with a behavioural signature, and the environment either fits it or fights it. **Temperament** refers to the constitutionally based, early-appearing, moderately heritable and relatively stable individual differences in how a person reacts to the world and regulates that reaction. It is the raw behavioural material on which later personality is built. For

the psychiatry exam this topic is owned by two child psychiatrists, Stella Chess and Alexander Thomas, whose New York Longitudinal Study (NYLS, begun in the 1950s) gave the field its enduring vocabulary: nine temperament dimensions, three temperamental constellations, and the concept of goodness of fit (Kaplan & Sadock 2024).

Hold four things for the exam and you command the topic: the nine **dimensions** Chess and Thomas rated; the three **types** (easy, difficult, slow-to-warm-up) with their approximate proportions; **goodness of fit** as the actual predictor of outcome (not the temperament alone); and the later models that refined the picture, Kagan's behavioural inhibition, Rothbart's reactivity and self-regulation, and Cloninger's psychobiological model that bridges temperament to personality. The etymology is worth a line: temperament comes from the Latin *temperare*, "to mix", the same idea that ran through Galen's four humoral temperaments and survives today in talk of neurotransmitter balance (Kaplan & Sadock 2024).

18.1 What temperament is, and how it differs from character and personality

Three words that are not synonyms. Examiners like the distinction because textbooks warn it is habitually blurred (Kaplan & Sadock 2024). **Temperament** is the biologically given, early-emerging, heritable substrate of reactivity and self-regulation, observable in infancy and stable across years. **Character** is the acquired layer: the self-concepts, goals, and values that develop through learning and experience and mature into adulthood (in Cloninger's model, self-directedness, cooperativeness, and self-transcendence). **Personality** is the integrated whole, temperament plus character, further shaped by culture, cognition, and life experience. Most theorists treat temperament as one of the foundations of personality, with the boundary between them genuinely obscure, "somewhat akin to pinpointing exactly when someone is an adult" (Kaplan & Sadock 2024). A useful shorthand: temperament is the *how* of behaviour (style and intensity), character is the *what for* (goals and values), personality is the sum.

18.2 The New York Longitudinal Study and the nine dimensions

Where the nine came from. During the 1950s, against a climate in which both psychoanalysis and behaviourism attributed almost everything to nurture, Chess and Thomas interviewed parents and observed children over many years and proposed that infants show measurable, heritable behavioural styles from the start (Kaplan & Sadock 2024). Rating behaviour, not underlying motive, they extracted **nine dimensions**. Each is a continuum, and the profile across all nine defines the child.

1. Activity level

The proportion of active to inactive periods; the child's overall motor tempo and vigour.

2. Rhythmicity (regularity)

The predictability of biological functions: sleep, hunger, and bowel habit falling into a regular schedule or not.

3. Approach or withdrawal

The nature of the first response to a new stimulus, person, food, or place: does the child move toward it or pull back?

4. Adaptability

How readily the initial response is modified in the desired direction once the novelty is no longer new; ease of settling into change.

5. Intensity of reaction

The energy level of a response, positive or negative, irrespective of its quality or direction.

6. Threshold of responsiveness

The strength of stimulation needed to evoke a discernible response (sensory threshold to light, sound, touch, and social cues).

7. Quality of mood

The balance of pleasant, joyful, friendly behaviour against unpleasant, crying, unfriendly behaviour.

8. Distractibility

The degree to which extraneous stimuli divert the child from ongoing behaviour.

9. Attention span and persistence

How long an activity is pursued (span) and whether it is continued despite obstacles or interruption (persistence); treated as one paired dimension.

18.3 The three constellations: easy, difficult, slow-to-warm-up

The person-centred layer that made the study famous. Beyond the nine variables, Chess and Thomas noticed that certain dimensions cluster into recognisable constellations, and named three types (a fourth group could not be classified). The proportions below are the NYLS figures and are examinable (Kaplan & Sadock 2024). Note that later writers, uneasy with judgemental labels for infants, renamed the types (flexible, feisty, cautious), and either set is acceptable.

TYPE (ALTERNATIVE NAME)	APPROX. PROPORTION	DEFINING TEMPERAMENTAL PROFILE
Easy child (flexible)	~40%	Regular rhythmicity, positive approach to novelty, high adaptability, mild-to-moderate intensity, predominantly positive mood; settles into routines quickly.
Difficult child (feisty)	~10%	Irregular rhythmicity, withdrawal from the new, poor (slow) adaptability, high intensity of reaction, predominantly negative mood; the low-threshold, intense, hard-to-soothe child.
Slow-to-warm-up child (cautious)	~15%	Initial withdrawal and slow adaptability like the difficult child, but with low activity and low-intensity reactions; warms up gradually if allowed repeated low-pressure exposure.
Undifferentiated / unclassified	~35%	A mix of characteristics not fitting any single type; positive on some dimensions, negative on others.

The discriminator between the two withdrawing types: the difficult child reacts with high intensity and negative mood, whereas the slow-to-warm-up child withdraws quietly, with low activity and low intensity; time and gentle re-exposure win the slow-to-warm child over.

Why the difficult child matters clinically. Chess and Thomas were emphatic that no type is pathology per se, but in the longitudinal follow-up it was the difficult children, roughly 10% of the sample, who most often went on to poorer adjustment and greater psychiatric disturbance (Kaplan & Sadock 2024). The precise cluster they defined as difficult was low rhythmicity, low response threshold, low adaptability, and high response intensity.

~40%	~10%	~15%
EASY	DIFFICULT (HIGHEST RISK)	SLOW-TO-WARM-UP

18.4 Goodness of fit: the real predictor of outcome

The single most important concept in the topic. Chess and Thomas' deepest contribution was to insist that temperament does not determine outcome by itself. **Goodness of fit** is the match between the child's temperament and the demands, expectations, and capacities of the environment, above all the caregivers (Kaplan & Sadock 2024). A good fit, in which environmental demands are consonant with the child's style, promotes healthy development; a poor fit, in which demands clash with the child's temperament, breeds stress, conflict, and later disturbance. The corollary is that no trait is intrinsically good or bad: a fearful, withdrawing temperament may be adaptive in a genuinely dangerous setting and maladaptive in a safe, predictable one. Outcome depends less on the child's temperament than on how the environment

responds to it, which is exactly why this construct anchors modern parent-guidance and early-intervention work.

RULE **Goodness of fit, not temperament, predicts outcome.** No type is pathology; a difficult child is only at higher risk, and that risk is realised or averted by the match between the child's style and the environment's demands.

CLINICAL ANCHOR

A "difficult" infant (irregular, intense, slow-adapting) placed with a calm, flexible, patient parent who paces transitions gently can develop well; the same infant with an anxious or rigid parent who reads intensity as defiance and escalates is set up for a coercive cycle and later behaviour problems. Rettew and colleagues showed this empirically: high child novelty-seeking predicted attention problems only when paired with a high-novelty-seeking mother, not with a low-novelty-seeking one. The lesson for the clinic is to treat the dyad, not the child alone, and to reframe temperament for parents as a style to be worked with rather than misbehaviour to be disciplined out.

18.5 Kagan's behavioural inhibition

The most heavily researched single temperamental trait. Jerome Kagan and colleagues at Harvard defined **behavioural inhibition** (BI) as the tendency of a subgroup of young children, roughly 10% to 15% of the population, to respond to novel people and situations consistently with reticence, restraint, and fear (Kaplan & Sadock 2024). Its opposite, behavioural disinhibition, is the sociable, approach-dominant response to novelty. Unlike most dimensions, BI has been studied largely as a near-categorical trait a child does or does not show. It matters because toddlers with BI carry an elevated risk of later anxiety disorders, above all social anxiety disorder. Its neural signature is durable: adults who were behaviourally inhibited at age 2 show heightened amygdala activation to novel faces on fMRI decades later, even when they report no current anxiety, evidence that the physiology of a temperamental trait can persist beneath a behaviourally regulated surface.

18.6 Rothbart's reactivity and self-regulation

The definition most textbooks now adopt. Mary Rothbart reframed temperament as "constitutionally based individual differences in **reactivity** and **self-regulation**", where reactivity is the excitability of emotional, motor, and attentional systems and self-regulation is the capacity (chiefly **effortful control**) to modulate that reactivity (Kaplan & Sadock 2024). Her structure resolves into three broad higher-order factors that recur across modern taxonomies: **surgency/extraversion** (approach, activity, positive emotion), **negative affectivity** (fear, anger, discomfort, sadness), and **effortful control** (attentional focusing and inhibitory control). What Rothbart fixed from Chess and Thomas was the addition of a genuine regulatory dimension, effortful control, which lets temperament account for how a child governs reactivity, not merely how strongly it reacts.

18.7 Cloninger: the bridge from temperament to personality

Where temperament research meets personality-disorder theory. C. Robert Cloninger's psychobiological model is the standard bridge, and it is the model that formally separates the two words this topic keeps distinguishing (Companion to Psychiatric Studies; Kaplan & Sadock 2024). His Temperament and Character Inventory (TCI) posits four heritable **temperament** dimensions, each tied to a neurotransmitter system, and three **character** dimensions that mature with experience.

Temperament (heritable, early, neurotransmitter-linked)

Novelty seeking (dopaminergic, approach to novelty), **harm avoidance** (serotonergic, behavioural inhibition to punishment), **reward dependence** (noradrenergic, sensitivity to social reward), and **persistence** (perseverance despite frustration).

Character (experiential, maturing)

Self-directedness (being responsible and goal-directed), **cooperativeness** (tolerance and helpfulness toward others), and **self-transcendence** (identification with something beyond the self).

The clinical payoff examiners want: low self-directedness and low cooperativeness (the character dimensions) are the core marker that a personality disorder is present, while the temperament profile shapes *which* disorder, for example high novelty seeking with low harm avoidance and low reward dependence maps to the antisocial/adventurous profile (Kaplan & Sadock 2024). This is how a childhood temperament construct connects to adult personality pathology.

> HOLD THIS
> **Temperament is the heritable early substrate (the how), character the acquired goals and values (the what for), personality the sum.** In Cloninger, low self-directedness and low cooperativeness are the core marker that a personality disorder is present.

18.8 Neurobiology of temperament

The "usual suspects" of psychiatry reappear here. Temperament is 20% to 60% heritable across twin and adoption studies, with additive polygenic effects and substantial nonshared-environmental contribution (Kaplan & Sadock 2024). The **neural correlates** map cleanly onto the three higher-order dimensions. Negative affectivity, harm avoidance, and behavioural inhibition centre on the **amygdala** and its circuitry (reduced amygdala-anterior-cingulate connectivity tracks higher harm avoidance; amygdalar hyperreactivity underlies BI), with serotonergic dorsal-raphe projections and HPA-axis dysregulation. Approach, novelty seeking, and extraversion run on **dopaminergic** mesolimbic and nigrostriatal pathways. Reward dependence and social affiliation involve **noradrenergic** locus-coeruleus output, median-raphe serotonin, and **oxytocin** at reward centres. Effortful control and persistence are mediated by **anterior/prefrontal cortex** and the **anterior cingulate** modulating subcortical drive. An EEG signature is examinable: left frontal activation tracks approach and positive emotion, right frontal activation tracks withdrawal and negative emotion.

COMMON TRAP

Do not say a "difficult" temperament causes psychopathology. Chess and Thomas explicitly denied that any type is pathology; the difficult child is only at higher *risk*, and that risk is realised or averted by goodness of fit. Equally, do not conflate temperament with personality on the exam, temperament is the heritable early substrate, personality is temperament plus acquired character. And do not confuse Kagan's behavioural inhibition (a near-categorical trait predicting social anxiety) with Chess and Thomas' slow-to-warm-up type; they overlap in withdrawal but are separate constructs from separate research programmes.

PEARL

The three big modern taxonomies converge: Rothbart's negative affectivity, Cloninger's harm avoidance, and the personality trait neuroticism describe the same amygdala-linked withdrawal dimension; Rothbart's surgency, Cloninger's novelty seeking, and extraversion describe the same dopamine-linked approach dimension; Rothbart's effortful control, Cloninger's persistence, and conscientiousness describe the same prefrontal regulatory dimension. If you can state these three axes, you can answer almost any temperament comparison question.

MNEMONIC

A RAAI TMDP

Read the nine dimensions in this order: **A**ctivity level, **R**hythmicity, **A**pproach-withdrawal, **A**daptability, **I**ntensity of reaction, **T**hreshold of responsiveness, **M**ood, **D**istractibility, **P**ersistence (attention span). For the three types, the fit is on a sliding scale: the child who fits Easily, the one who is Difficult, and the one who is Slow to warm.

GOOD TO REMEMBER

- **Chess and Thomas, New York Longitudinal Study (1950s):** the origin of the nine dimensions, three types, and goodness of fit.
- **Nine dimensions:** activity level, rhythmicity, approach-withdrawal, adaptability, intensity of reaction, threshold of responsiveness, quality of mood, distractibility, attention span and persistence.
- **Easy child (~40%):** regular, approaching, adaptable, positive mood; also called flexible.
- **Difficult child (~10%):** irregular rhythmicity, withdrawing, poorly adaptable, intense, negative mood; highest risk of later disturbance; also called feisty.
- **Slow-to-warm-up child (~15%):** initial withdrawal and slow adaptation but low activity and low intensity; warms with gentle re-exposure; also called cautious.
- **Undifferentiated (~35%):** mixed profile, unclassifiable.
- **Goodness of fit:** match between child temperament and environmental demand is the actual predictor of outcome, not temperament alone.
- **Kagan, behavioural inhibition:** ~10% to 15% of children, fearful/reticent to novelty, near-categorical, predicts social anxiety disorder; persistent amygdala signature on fMRI.
- **Rothbart:** temperament as reactivity and self-regulation; three factors, surgency/extraversion, negative affectivity, effortful control.
- **Cloninger TCI:** four temperament dimensions (novelty seeking, harm avoidance, reward dependence, persistence) plus three character dimensions (self-directedness, cooperativeness, self-transcendence); low self-directedness and cooperativeness mark personality disorder.
- **Temperament vs character vs personality:** temperament is the heritable early substrate (the how); character is the acquired goals and values (the what for); personality is the integrated whole.
- **Heritability of temperament:** about 20% to 60% across twin and adoption studies.

19 · Mahler separation-individuation

The psychological birth of the human infant, mapped month by month. Margaret Mahler (1897 to 1985), a Hungarian-born analyst working in New York, did for the first three years of life what Erikson did for the whole lifespan: she took direct, systematic observation of infants and their mothers and built from it a stage theory of how a self is born out of fusion (Kaplan & Sadock 2024). Her **separation-individuation** theory is the developmental spine of psychodynamic child psychiatry, and it is the theory examiners reach for whenever they want to test the developmental roots of borderline personality organisation. The title of her 1975 book with Fred Pine and Anni Bergman, *The Psychological Birth of the Human Infant*, is itself the thesis: biological birth and psychological birth are separate events, and the second one takes about three years.

For the exam hold four things: the two normal precursor phases (**autism** and **symbiosis**), the four subphases of separation-individuation in order with their ages, the two conceptual poles the whole process moves between (**separation**, the emergence from fusion, and **individuation**, the growth of an autonomous self), and the endpoint, **emotional object constancy**. Then attach the one clinical hypothesis every examiner wants: the rapprochement-failure account of borderline pathology (Masterson & Rinsley 1975). Mahler is a developmental map only; the fuller object-relations school that grew alongside her (Klein, Winnicott, Fairbairn) is **the Social, Learning & Personality Psychology notes** material and is signposted below, not taught here.

19.1 Who Mahler was, and what her method fixed

From reconstructed fantasy to observed behaviour. Before Mahler, most analytic accounts of infancy were reconstructions, inferred backwards from adult patients or from the analysis of older children. Mahler's contribution was methodological as much as theoretical: she and her collaborators watched mother-infant pairs directly, over time, in a naturalistic playroom setting, and derived the phases from what infants actually did (Kaplan & Sadock 2024). What this fixed was the empirical thinness of earlier drive-based accounts of the first year. What she kept from psychoanalysis was its central question, how the mind comes to distinguish self from other; what she left debated was whether her earliest phases (normal autism above all) survive scrutiny against modern infant research, which shows newborns to be far more socially oriented from birth than a phase of "objectless" autism would allow. Hold that critique for 19.8; it is the standard higher-order examiner follow-up.

19.2 Normal autistic phase (birth to about 1 month)

The closed system. In the **normal autistic phase** the newborn is described as being in a state of absolute primary narcissism, without awareness of a mothering agent, functioning as though within a closed psychological system (Kaplan & Sadock 2024). Needs are met but not yet attributed to anything outside the self; the infant does not know that the satisfaction comes from a caregiver. Mahler suggested a normal degree of autism here may be protective, buffering the immature nervous system against a flood of stimuli. This is the phase most challenged by later research, and Mahler herself, late in her career, questioned whether it should be retained; keep that caveat ready.

19.3 Normal symbiotic phase (about 1 to 5 months)

The dual unity within one common boundary. In the **normal symbiotic phase** the infant develops a dim awareness that need satisfaction comes from outside the self, and behaves as though it and the mother were "an omnipotent system, a dual unity within one common boundary" (Kaplan & Sadock 2024). Self and object are not yet distinguished; the boundary between them differentiates only momentarily, in states of **affect hunger**, and dissolves again once the need is gratified. This fused, need-satisfying matrix is the ground from which the true psychological birth will emerge. The word **symbiosis** is Mahler's, and it is the term examiners test: it names a subjective fusion, not a biological one.

19.4 Subphase 1, differentiation or hatching (about 5 to 9 months)

Breaking out of the symbiotic shell. Separation-individuation proper begins with **differentiation**, which Mahler called **hatching**: the infant gradually emerges from the symbiotic orbit and begins to sense the body-self as distinct from the mother (Kaplan & Sadock 2024). Attention turns outward, from an internal preoccupation to active curiosity about the surroundings and about the caregiver as a separate entity. The behavioural markers are the classic ones of this age: increased alertness, scanning, and comparative examination of the mother against strangers. Stranger reactions and the beginnings of exploration belong here. The two threads of the process are already visible and should be named separately: *separation* (emerging

from fusion) and *individuation* (the growth of the infant's own capacities), which advance in parallel but are not the same thing.

19.5 Subphase 2, practising (about 9 to 16 months)

The love affair with the world. The **practising** subphase is powered by upright locomotion: crawling, then walking, let the toddler physically leave the mother's orbit and return to it (Kaplan & Sadock 2024). Mahler split it into an early phase (the infant moves away by crawling but keeps visually "checking back") and a practising period proper (free upright walking). Two concepts are examinable here. The first is **emotional refuelling**: the toddler ventures out, and returns to physical contact with the mother to be recharged before venturing again, using her as a **home base**. The second is the elated, seemingly grandiose mood of this period, the toddler "intoxicated with their own faculties", relatively impervious to knocks and frustrations, which Mahler's colleague Greenacre called the toddler's "love affair with the world". Separation anxiety is at its lowest ebb here, which is exactly why the next subphase lands so hard.

19.6 Subphase 3, rapprochement (about 16 to 24 months): the crisis

The single most examinable moment in the whole theory. By the middle of the second year the toddler's growing cognitive and language ability delivers an unwelcome discovery: it is small, separate, and dependent after all. This is the **rapprochement** subphase, and its defining feature is the **rapprochement crisis** (Kaplan & Sadock 2024). The elated omnipotence of practising collapses into an acute awareness of separateness, and the child oscillates: it wants autonomy and it wants the mother, and it cannot have both without contradiction.

The behavioural signature. The child alternates between clinging to the mother (shadowing) and darting away from her (darting-off), and between demanding help and angrily refusing it. Mahler named this vacillation **ambitendency**. It generates the classic tantrums and neediness of the period, and it places a specific demand on the mother: she must remain emotionally available and tolerant of the child's ambivalence, surviving its aggression without retaliating or withdrawing. Optimal maternal availability here lets the child integrate the loving and the frustrating images of the mother into one whole. Failure of that maternal function is the hinge of the borderline hypothesis in 19.8.

RULE **Rapprochement is the crisis of the whole theory.** Practising omnipotence collapses into an awareness of separateness, and the toddler oscillates (ambitendency: shadowing and darting-off), needing the mother to survive its aggression without withdrawing.

19.7 Subphase 4, consolidation and emotional object constancy (about 24 to 36 months)

Carrying the mother inside. The last subphase is the **consolidation of individuality** and the attainment of **emotional object constancy** (Kaplan & Sadock 2024). Two achievements define it. First, a stable, integrated sense of self (individuality consolidated). Second, and the term to get exactly right, **emotional object constancy**: the capacity to hold a stable, unified internal representation of the mother as both good and frustrating, so that her image can be sustained and can comfort the child even in her absence and even when she is frustrating the child. This is distinct from Piaget's *object permanence*, which is merely knowing that a physical object continues

to exist when out of sight; a discriminator examiners love. With object constancy the child can tolerate longer separations, accept symbolic substitutes, and finally hold together love and hate for the same person. This is the true endpoint of psychological birth.

PHASE / SUBPHASE	AGE (MONTHS)	CORE TASK OR STATE	SIGNATURE MARKER
Normal autism	0 to 1	Closed system, primary narcissism	**No awareness of a mothering agent**
Normal symbiosis	1 to 5	Dual unity, one common boundary	**Fusion; boundary appears only in affect hunger**
Differentiation (hatching)	5 to 9	Body-self felt as distinct	**Hatching; outward attention, stranger reactions**
Practising	9 to 16	Locomotor exploration from a home base	**Emotional refuelling; elated "love affair with the world"**
Rapprochement	16 to 24	Awareness of separateness and dependence	**Rapprochement crisis; ambitendency, shadowing and darting**
Consolidation / object constancy	24 to 36	Stable self plus internalised whole mother	**Emotional object constancy**

The whole arc at a glance: two normal precursor phases, then four subphases of separation-individuation, ending at emotional object constancy by about the third birthday. The discriminator column carries the term most likely to be asked for each row.

19.8 The rapprochement-failure hypothesis of borderline pathology

Why Mahler is on a psychiatry syllabus at all. The clinical payoff of the theory is a developmental account of **borderline personality organisation**. Masterson and Rinsley (1975), building directly on Mahler, proposed that borderline pathology is a fixation at, or failure of, the rapprochement subphase (Bateman & Fonagy 2004). Their model runs as follows. The mother of the pre-borderline child (in their formulation, herself often borderline) rewards clinging, regressive dependence and withdraws her emotional supply, her **libidinal availability**, precisely when the child moves toward autonomy. The child is left with a lasting equation: separation and individuation bring abandonment. Because the loving and the frustrating images of the mother are never integrated, the person's inner world stays organised by **splitting** into all-good and all-bad object representations, and emotional object constancy is never securely reached (Kaplan & Sadock 2024).

What this explains, and its limits. The adult correlates fall out neatly: the terror of abandonment, the unstable and intense relationships that swing between idealisation and devaluation, the identity disturbance, and the abandonment depression Masterson placed at the centre of the disorder. This is a high-yield exam line, but state it as a hypothesis, not fact: it is a retrospective, reconstructive model, and contemporary aetiology of borderline personality disorder is multifactorial (temperament, trauma, invalidating environments, and gene-

environment interaction), with the developmental account one contributing strand rather than the whole story.

HOLD THIS

Failed rapprochement is the developmental template for borderline splitting (Masterson & Rinsley). The loving and frustrating images never integrate, so emotional object constancy is never reached and the inner world stays split into all-good and all-bad. State it as a hypothesis.

CLINICAL ANCHOR

An adult patient who cannot be alone, who idealises then abruptly devalues the same person, and who experiences any move toward independence in therapy as an abandonment, can be formulated in Mahlerian terms as arrested at rapprochement: love and hate for the object were never integrated, so object constancy fails and the inner world stays split. In the transference this shows as the therapist being all-good one week and all-bad the next. Naming that mechanism (splitting from failed rapprochement) is the developmental half of a borderline formulation; the treatment half belongs to the the Social, Learning & Personality Psychology notes object-relations therapies.

19.9 Boundary line: where Mahler ends and object-relations theory begins

Know the fence so you place each name on the right side of it. Mahler gives the developmental cartography, the observed sequence from fusion to a self. The wider **object-relations** school gives the theory of how internal images of self and other are built, split, repaired, and used, and that school is taught in full on **the Social, Learning & Personality Psychology notes**. Three names sit on the far side of that fence and should be signposted, not developed here.

Melanie Klein (the Social, Learning & Personality Psychology notes)

The paranoid-schizoid position and the depressive position; part-objects (good and bad breast), projective identification, and the origin of the object-relations view. The Kleinian "positions" are the structural counterpart to Mahler's developmental subphases.

Donald Winnicott (the Social, Learning & Personality Psychology notes)

The good-enough mother, the holding environment, the transitional object and transitional space. Winnicott's "there is no such thing as a baby, only a nursing couple" is the object-relations echo of Mahler's symbiosis.

Ronald Fairbairn (the Social, Learning & Personality Psychology notes)

The most thoroughgoing object-relations theorist: libido is object-seeking rather than pleasure-seeking, and the ego is split (central, libidinal, and anti-libidinal or internal saboteur) through frustrating early relationships.

The one link to carry across the fence: Mahler's *emotional object constancy* and Klein's *depressive position* describe the same maturational achievement from two vantage points, the integration of a whole object that is both loved and hated. Everything else about Klein, Winnicott and Fairbairn waits for the Social, Learning & Personality Psychology notes.

COMMON TRAP

Do not conflate Mahler's *emotional object constancy* with Piaget's *object permanence*. Object permanence (roughly 8 to 12 months) is the cognitive knowledge that a thing still exists when hidden; emotional object constancy (by about 36 months) is the affective capacity to hold a stable, integrated internal image of a specific person as both good and bad, and to be soothed by it in their absence. They are different constructs, different theorists, and different ages. A second trap: *symbiosis* in Mahler is a subjective psychological fusion, not the biological symbiosis of two organisms.

PEARL

The one-line integration for an examiner: Mahler mapped the psychological birth of the infant across two normal phases and four subphases, ending at emotional object constancy, and the failure of the rapprochement subphase (Masterson & Rinsley) is the developmental template for borderline splitting. Name that arc (symbiosis to rapprochement crisis to object constancy, and its borderline failure) and you have the whole topic.

MNEMONIC

Subphases: "Dear Practising Reaches Consolidation"

Differentiation (hatching, 5 to 9m), **P**ractising (9 to 16m), **R**approchement (16 to 24m), **C**onsolidation and object constancy (24 to 36m). Prefix the two normal precursors with "**A**utism, **S**ymbiosis" and the full order is A, S, then D, P, R, C.

GOOD TO REMEMBER

- **Margaret Mahler (1897 to 1985):** separation-individuation theory; book with Pine and Bergman, *The Psychological Birth of the Human Infant* (1975).
- **Normal autistic phase:** birth to about 1 month; closed system, primary narcissism, no awareness of a mothering agent.
- **Normal symbiotic phase:** about 1 to 5 months; dual unity within one common boundary; boundary appears only in affect hunger.
- **Differentiation (hatching):** about 5 to 9 months; body-self felt as distinct; outward attention, stranger reactions.
- **Practising:** about 9 to 16 months; locomotor exploration, home base, emotional refuelling, elated "love affair with the world".
- **Rapprochement:** about 16 to 24 months; rapprochement crisis; ambitendency, shadowing and darting-off; separation anxiety peaks.
- **Consolidation / emotional object constancy:** about 24 to 36 months; stable self plus integrated whole-object image of the mother.
- **Separation vs individuation:** separation = emergence from fusion; individuation = growth of the autonomous self; parallel but distinct threads.
- **Emotional object constancy vs object permanence:** affective (stable inner image of a person, by ~36m, Mahler) vs cognitive (a thing persists when hidden, ~8 to 12m, Piaget).
- **Rapprochement-failure hypothesis:** Masterson & Rinsley (1975); mother withdraws libidinal availability at moves toward autonomy; fixation at rapprochement, persistent splitting, failed object constancy; developmental template for borderline organisation (a hypothesis, not settled fact).
- **the Social, Learning & Personality Psychology notes boundary (object-relations school):** Klein (paranoid-schizoid and depressive positions), Winnicott (good-enough mother, holding, transitional object), Fairbairn (object-seeking libido, ego splitting) are taught on the Social, Learning & Personality Psychology notes, not here.

20 · Language and motor developmental milestones

The developmental yardstick. A **milestone** is a functional skill that a typically developing child acquires at a roughly predictable age, and the milestones are conventionally tracked along four parallel **streams**: gross motor, fine motor (adaptive), language, and personal-social (adaptive-social). The exam wants two things from this topic. First, the milestone ages themselves, because a psychiatrist reads them backwards: a delayed or lost milestone is the earliest sign of intellectual developmental disorder, autism, cerebral palsy or a regressive condition, and the developmental history is a fixed part of every child psychiatric assessment (Kaplan & Sadock 2024). Second, the competing theories of how one milestone in particular, spoken language, is acquired, because the Skinner-to-Chomsky argument is a set-piece and Chomsky's language acquisition device is the single most asked-about idea in this area.

Handle the two halves differently. The milestone ages are learned as a table to be enumerated, with a small set of high-yield anchor ages committed to memory. The language-acquisition theories, by contrast, follow the standard evolution-of-theories flow: Skinner's learning account, what Chomsky's nativism fixed, then the interactionist synthesis that is currently accepted, followed by the neural correlate and a worked example. Treat the ages below as the standard

textbook figures (K&S / Gesell schedule); normal children vary, and a lag of a month or two around any single milestone is not itself pathological.

20.1 The four streams and why they are read together

One age, four windows. Development is assessed across four streams because a child can be typical in one and delayed in another, and the *pattern* of delay is diagnostic. **Gross motor** covers posture and large-muscle control (head control, sitting, standing, walking). **Fine motor** or adaptive covers hand skills and eye-hand coordination (reaching, grasp, the pincer grip, tower-building, copying shapes). **Language** covers both reception and expression (cooing, babbling, first words, phrases). **Personal-social** covers interaction and self-care (social smile, stranger anxiety, feeding self, dressing). An *isolated* motor delay points to a neuromuscular or cerebral-palsy picture; an isolated language delay points to hearing loss or developmental language disorder; a *global* delay across all four streams is the developmental signature of intellectual developmental disorder, and a delay concentrated in language plus social-reciprocity flags autism spectrum disorder (Kaplan & Sadock 2024).

TRAP Do not read one milestone in isolation; it is the **pattern of delay** that is diagnostic. Isolated motor delay points to cerebral palsy, isolated language delay to hearing loss, global delay to intellectual developmental disorder, language-plus-social delay to autism.

20.2 Gross-motor milestones

Cephalocaudal progression: head, trunk, legs. Motor control descends the body, so head control precedes sitting, which precedes standing and walking. The high-yield ages are head control (steady head-holding, lifting the head to 90 degrees prone) by about 3 months; rolling over and sitting with support by about 5 months; sitting steadily without support with a straight back by about 6 to 8 months; pulling to stand and cruising around furniture by about 10 months; and walking well without support by about 14 to 15 months (Kaplan & Sadock 2024). By 2 years the child runs and climbs stairs; by 3 years climbs stairs with alternating feet and rides a tricycle.

20.3 Fine-motor (adaptive) milestones

From whole-hand rake to precise pincer. Grasp matures from a crude palmar rake toward the **pincer grasp**, the opposition of thumb and index finger that lets the infant pick up a small pellet, which appears at about 9 to 10 months and is a classic exam item because it marks a qualitative advance in hand control (Kaplan & Sadock 2024). Construction and copying then follow a fixed order used clinically to estimate developmental age: a tower of 3 to 4 cubes by about 18 months, a tower of 6 to 7 cubes and copying a horizontal line by 2 years, then copying a circle at 3 years, a cross at 4 years, a square at 5 years, a triangle at 6 years and a diamond at 7 years. The copy-a-shape sequence (circle 3, cross 4, square 5, triangle 6, diamond 7) is a favourite because the ages step up by one year.

20.4 Language milestones

Sound before words, words before sentences. Expressive language runs through a conserved sequence: vocalising apart from crying and laughing aloud by about 3 months; saying "mama, dada" and other repeated syllables non-specifically by about 9 months; the **first words** used

meaningfully at around 12 months; roughly 10 words including the child's name by 18 months; and combining two different words into simple phrases between 18 and 24 months (Kaplan & Sadock 2024). By 3 years the child uses plurals and has a fair vocabulary; by 5 years names the primary colours accurately and defines simple words. Reception runs slightly ahead of expression throughout: a 10-month-old understands "where is mama?" before it can say much itself.

20.5 Personal-social milestones

The social calendar. The **social smile**, the first smile given in response to a human face rather than reflexively, appears at about 6 to 8 weeks and is the earliest social milestone routinely asked about (Kaplan & Sadock 2024). The infant recognises the mother by about 3 months and smiles at its mirror image by about 6 months. **Stranger anxiety**, wariness or distress at an unfamiliar face, emerges at about 8 months (the range 7 to 9 months is quoted), signalling that the infant now discriminates the primary caregiver from others; separation anxiety appears in the same window. Self-care then advances: feeding self with a spoon by about 18 months, dressing with help by 3 years, and dressing without supervision by 5 years.

PEARL

Stranger anxiety at about 8 months is not a problem, it is a milestone: it means the infant has formed a specific, discriminated attachment and can tell its caregiver from a stranger. Its *absence* at the expected age is the concern. The same 8-month window is why reactive attachment disorder requires a developmental age of at least 9 months, the point at which a selective attachment (and therefore its failure) first becomes possible.

20.6 The milestone table (verified ages)

The four streams side by side. The following consolidates the high-yield ages across streams for rapid recall (Gesell schedule as reproduced in Kaplan & Sadock 2024).

AGE	GROSS MOTOR	FINE MOTOR / ADAPTIVE	LANGUAGE	PERSONAL-SOCIAL
6 to 8 weeks	Lifts head momentarily prone	**Regards / follows a face**	Vocalises, coos	Social smile
3 months	Head control (holds head, 90 degrees prone)	**Follows object past midline**	Laughs aloud	Recognises mother
6 months	Sits with support; rolls over	**Palmar (raking) grasp; reaches**	Babbles	Smiles at mirror image
8 months	Sits steadily without support	**Transfers object hand to hand**	Non-specific "mama, dada"	Stranger anxiety
9 to 10 months	Pulls to stand; cruises furniture	**Pincer grasp (thumb-index)**	Understands "where is mama?"	Responds to social play
12 months	Stands alone; may take first steps	**Neat pincer; releases object**	First words (meaningful)	Waves bye-bye

AGE	GROSS MOTOR	FINE MOTOR / ADAPTIVE	LANGUAGE	PERSONAL-SOCIAL
14 to 15 months	Walks well without support	**Tower of 2 cubes; scribbles**	Jargon; few words	Points to indicate wants
18 months	Runs stiffly; walks up stairs, hand held	**Tower of 3 to 4 cubes**	About 10 words	Feeds self with spoon
2 years	Runs well; climbs stairs	**Tower of 6 to 7 cubes; copies line**	Two-word phrases; simple sentences	Wears simple garments
3 years	Stairs with alternating feet; tricycle	**Copies a circle; tower of 9 to 10**	Plurals; fair vocabulary	Dresses/undresses with help

Anchor ages to memorise: social smile 6 to 8 wk, head control 3 mo, sits without support 6 mo, stranger anxiety 8 mo, pincer 9 to 10 mo, first words ~12 mo, walks 14 to 15 mo, two-word phrases 18 to 24 mo.

6 to 8 wk	8 mo	9 to 10 mo	~12 mo
SOCIAL SMILE	STRANGER ANXIETY	PINCER GRASP	FIRST WORDS

COMMON TRAP

Do not conflate the walking figure quoted in different books. One common figure gives independent walking at 14 to 15 months as the age most children walk *well*; many texts quote the wider normal range of 12 to 15 months, and the red-flag cut-off for referral is failure to walk by 18 months. State the figure with its book, and use the red flag, not the median, to decide whether a child is delayed. Likewise "first words at 12 months" is the median; the delay threshold is no single words by *2 years*.

20.7 Red-flag delays

When variation becomes concern. A single milestone reached a little late is usually normal; a red flag is a delay large enough to warrant assessment, or any *loss* of a skill already gained (regression), which is always abnormal (Kaplan & Sadock 2024). The standard motor and social red flags are: no head control by 4 months, not sitting unsupported by 9 months, not walking by 18 months, and no social smile by 3 months. The language red flags are the most examinable and come straight from ICD-11: the *absence of single words by 2 years* of age and the *failure to generate simple two-word phrases by 3 years*, especially when persistent or with a family history of language problems, are the thresholds that separate a late talker (who usually catches up) from developmental language disorder (World Health Organization ICD-11 2019). Loss of previously acquired language or social skills, at any age, warrants urgent evaluation for autism spectrum disorder or a neurodegenerative or epileptic process.

20.8 Stages of language: cooing, babbling, holophrastic, telegraphic

The universal sequence. Before the theories, fix the stages, because every account has to explain this sequence and all typically developing infants pass through it in the same order (Tasman 2015). **Cooing**, the production of vowel-like sounds, begins at about 2 months. **Babbling** proper

follows as consonants are added at about 4 to 6 months, becoming *canonical (reduplicated) babbling* with repeated consonant-vowel syllables such as "da-da-da" by about 7 months. The **holophrastic** or one-word stage begins around 12 months, when a single word ("milk") is used to carry the force of a whole utterance. The **telegraphic** or two-word stage begins at about 18 to 24 months, when the child combines two content words ("more milk", "daddy go") while omitting grammatical function words, like a telegram. The child then acquires roughly 5 to 9 new words a day through the preschool years, reaching about 5,000 words by kindergarten (Tasman 2015).

20.9 Skinner: the learning (operant) account

Language as verbal behaviour shaped by reinforcement. The first systematic theory was B. F. Skinner's, set out in *Verbal Behavior* (Skinner 1957). On this behaviourist account, language is learned like any other operant: the infant emits sounds, the caregiver *reinforces* approximations to real words with attention, praise and getting what is named, and through selective reinforcement, shaping and imitation the child's output is gradually moulded toward the adult language (Tasman 2015). There is no special language faculty; the same principles of operant conditioning (reinforcement, extinction, stimulus control) that Skinner used to explain all behaviour explain speech. *What it got right:* environmental input clearly matters, since children learn the specific language they are exposed to, vocabulary tracks the amount of speech directed at the child, and reinforcement does influence output. *What it left unexplained:* the sheer speed of acquisition, the fact that children produce grammatical forms and novel sentences they have never heard and could not have been reinforced for, and their regular *over-generalisation* errors ("goed", "foots") which are the opposite of what imitation predicts.

20.10 Chomsky: nativism and the language acquisition device

An innate grammar organ. Noam Chomsky's 1959 review of Skinner's book is the standard turning point (Chomsky 1959). Chomsky argued that language cannot be learned by reinforcement alone because of the **poverty of the stimulus**: the speech a child actually hears is finite, error-filled and degenerate, yet from it every normal child rapidly extracts an infinite generative grammar and masters most of the basic rules by about age 4 (Tasman 2015). To bridge this gap Chomsky proposed an innate, biologically given **language acquisition device** (LAD): humans are born with a domain-specific facility for acquiring language (Chomsky 1975). Its content is a **universal grammar**, a set of structural principles common to all human languages, so that the environment only has to *set the parameters* for the particular language, not teach grammar from scratch. This is the **nativist** or innateness hypothesis: at least some linguistic knowledge exists in humans at birth (Chomsky 1986; Tasman 2015). *What it fixed:* it explained the speed, the creativity (novel grammatical sentences), the universality of the stage sequence, and the ease with which children handle grammatical transformations. *What it left debated:* the strong version treats environmental input as almost irrelevant, which sits badly with the robust evidence that responsive, socially contingent talk accelerates acquisition, and the LAD itself is a postulated faculty rather than a localised structure.

COMMON TRAP

Keep the labels straight. The *LAD* is the hypothesised innate device or faculty; *universal grammar* is its content, the shared structural principles; *nativism / innateness hypothesis* is the broader position that some grammar is inborn; and *poverty of the stimulus* is the argument *for* nativism, not a synonym for it. Skinner is the learning theorist Chomsky was refuting, not a nativist. And Chomsky 1959 is the review of Skinner; the LAD is elaborated in the later works (1975, 1986).

20.11 The interactionist / social-pragmatic view (currently accepted)

Innate capacity plus social input. The **currently accepted** position is neither pure Skinner nor pure Chomsky but an **interactionist** synthesis (Tasman 2015). Interactionist theorists accept Chomsky's evidence for an innate, biologically prepared capacity for language, but hold that this capacity is realised only through environmental and, crucially, *social* input: language emerges from the interaction of the child's endowment with responsive communication tuned to the child's level. The *social-pragmatic* strand (drawing on Bruner's "language acquisition support system" and on Vygotsky) stresses that language is acquired in the service of shared social goals, scaffolded by joint attention and contingent caregiver talk; the classic experimental support is that socially contingent feedback to an infant's babble accelerates phonological learning (Goldstein & Schwade 2008). This resolves the Skinner-Chomsky opposition: the nativists were right that experience alone is insufficient and a prepared capacity is needed, and the learning and social theorists were right that input, especially interactive input, is what switches that capacity on and shapes it to the ambient language.

HOLD THIS

Language = an innate capacity switched on by social input (interactionist synthesis). Skinner (reinforcement) could not explain over-generalisation ("goed"); Chomsky's LAD and universal grammar could; the currently accepted view keeps both.

20.12 Neural correlate and a critical period

Where language lives, and when the window is open. The **neural correlate** of language is a left-hemisphere-dominant perisylvian network: *Broca's area* in the left inferior frontal gyrus for speech production and syntax, *Wernicke's area* in the left posterior superior temporal gyrus for comprehension, and the *arcuate fasciculus* connecting them (Kaplan & Sadock 2024). Consistent with the nativist claim of a biological substrate, a seed language-processing network is already detectable in the temporal cortex of newborns just a few days old, an experience-independent "attractor" template on which the mature network is built through exposure (Kaplan & Sadock 2024). Language acquisition is subject to a **critical period**: the capacity to acquire a first language effortlessly, and to attain native accent in a second, declines from childhood and closes around puberty, which is why very early deprivation of language input has lasting effects while later good input can only partly compensate.

20.13 Worked example

The over-regularisation error, read by each theory. A 3-year-old who has correctly said "went" for months suddenly starts saying "goed". Skinner's account struggles here: the child was never

reinforced for, and never heard, "goed", so imitation and reinforcement cannot have produced it. The nativist reads it as decisive evidence for an internal rule system: the child has extracted the productive past-tense rule "add -ed" from universal grammar's parameter-setting and is over-applying it to an irregular verb, generating a form it could not have copied. The interactionist adds that the child will drift back to "went" as continued interactive exposure supplies the correct irregular form and the caregiver's contingent recasts ("yes, he went") tune the rule. The single error thus captures the whole debate: it is inexplicable by input alone, it demonstrates an internal generative rule, and it is corrected by social input, which is exactly why the interactionist synthesis is accepted.

INDIA

Milestone screening in Indian practice relies on locally validated tools rather than the raw Gesell ages: the Trivandrum Developmental Screening Chart and the developmental sections of instruments such as the Vineland Social Maturity Scale (Indian adaptation) are in routine use, and the RBSK (Rashtriya Bal Swasthya Karyakram) programme screens for developmental delay at anganwadi and school level. The language red flags need cultural adjustment too: many Indian children grow up bilingual or multilingual, and a transient "delay" in one language with normal total vocabulary across languages is not developmental language disorder. Assess the child's language across all the languages it hears, not just the clinic language.

MNEMONIC

"Smile at 2 months, Sit at 6, Stranger at 8, Speak at 12"

The four social-motor anchors in month order: social *smile* at about 6 to 8 weeks (~2 months), *sits* without support at about 6 months, *stranger* anxiety at about 8 months, and first *words* ("speak") at about 12 months. For the copy-a-shape ladder: circle 3, cross 4, square 5, triangle 6, diamond 7, each a year apart.

GOOD TO REMEMBER

- **Social smile:** 6 to 8 weeks (~2 months); earliest social milestone.
- **Head control:** 3 months (holds head, 90 degrees prone). Recognises mother 3 months.
- **Rolls over / sits with support:** about 5 to 6 months; babbles ~6 months.
- **Sits without support:** about 6 to 8 months (straight back, steady).
- **Stranger anxiety:** about 8 months (range 7 to 9); marks discriminated attachment.
- **Pincer grasp:** 9 to 10 months (thumb-index opposition).
- **First words (meaningful):** around 12 months; understands "where is mama?" by 10 months.
- **Walks well without support:** 14 to 15 months; wider normal range 12 to 15 months.
- **Two-word (telegraphic) phrases:** 18 to 24 months; ~10 words by 18 months.
- **Copy-a-shape ladder:** circle 3 y, cross 4 y, square 5 y, triangle 6 y, diamond 7 y.
- **Language red flags (ICD-11):** no single words by 2 years; no two-word phrases by 3 years; any loss of skill (regression) at any age is abnormal.
- **Motor red flags:** no head control by 4 mo, not sitting by 9 mo, not walking by 18 mo, no social smile by 3 mo.
- **Language stages:** cooing ~2 mo, babbling (canonical) 4 to 7 mo, holophrastic (one-word) ~12 mo, telegraphic (two-word) 18 to 24 mo.
- **Skinner (1957):** operant / learning account; language shaped by reinforcement and imitation; no special faculty.
- **Chomsky (1959 review; LAD 1975):** nativist; language acquisition device, universal grammar, poverty-of-stimulus argument.
- **Interactionist / social-pragmatic:** currently accepted; innate capacity realised through responsive social input (Bruner LASS, Vygotsky scaffolding).
- **Neural correlate:** left perisylvian network, Broca (production/syntax), Wernicke (comprehension), arcuate fasciculus; critical period closing around puberty.

Discriminate

21 · Discriminate: the theories side by side

The step that turns a list of theorists into an answer that scores. these notes reward one skill above all others: the ability to hold two or more rival theories in the same frame and name the one line that separates them. Examiners do not ask "describe Erikson"; they ask "compare Freud and Erikson", "which theory says the body changes first", "how does assimilation differ from accommodation". This topic gathers the three comparisons the exam returns to again and again and lays them out as tables, because a table is exactly the form a discrimination question wants back. Read the individual theory topics for depth; read this one to **compare** them cold.

Three grids do the work. The first and most important is the **aligned developmental-stages** grid, which stacks Freud, Erikson, Piaget and Kohlberg down a single shared age axis so you can read across a row and see what each theorist says is happening in the same child at the same age. The second sets the four emotion theories against each other on the single axis of *sequence*, the order in which arousal, cognition and feeling arrive. The third arranges the intelligence models on the single axis of *number*, one general capacity against many. A closing trap box collects the classic mix-ups that cost marks. Ground text throughout is Kaplan and Sadock (2024), with the

New Oxford Textbook, Tasman (2015) and the Companion to Psychiatric Studies behind the individual entries.

Age	Freud psychosexual	Erikson psychosocial	Piaget cognitive	Kohlberg moral
0 to 1 infancy	Oral	Trust vs mistrust	Sensorimotor	(pre-moral)
1 to 3 toddler	Anal	Autonomy vs shame, doubt	sensorimotor to preoperational	Preconventional emerging
3 to 6 preschool	Phallic Oedipus	Initiative vs guilt	Preoperational	Preconventional stages 1 to 2
6 to 12 school age	Latency	Industry vs inferiority	Concrete operational	Conventional stages 3 to 4
12 to 18 adolescence	Genital	Identity vs role confusion	Formal operational	Conventional to postconventional
19 to 40 young adult	Genital mature	Intimacy vs isolation	formal operational	Postconventional stages 5 to 6
40 to 65 midlife	(complete)	**Generativity vs stagnation**	(complete)	(complete)
65 plus old age	(complete)	**Integrity vs despair**	(complete)	(complete)

Fig 4.17 The four stage theories aligned down one shared age axis, the flagship figure of these notes. Reading across any row shows what each theorist claims is happening at that age: at 3 to 6 years, for instance, Freud's phallic conflict, Erikson's initiative crisis, Piaget's preoperational thought and Kohlberg's earliest preconventional morality all coincide. Reading down a column gives that theorist's full sequence. The single most examinable point is visible at a glance: Freud, Piaget and Kohlberg complete their sequences by early adulthood, while only Erikson's psychosocial stages (marigold) carry through midlife and old age.

21.1 The aligned developmental-stages grid: four theorists, one age axis

The flagship comparison of the whole set of notes. Four great stage theorists mapped childhood and beyond, each along his own dimension: Freud on the moving **erogenous zone** (psychosexual), Erikson on the widening **social** task (psychosocial), Piaget on the growing **cognitive** structure, and Kohlberg on the maturing basis of **moral** reasoning. Because they share a rough age spine, they can be aligned so that a single column, say the preschool child of 3 to 5, shows Freud's phallic-oedipal drama, Erikson's initiative-versus-guilt, Piaget's preoperational egocentrism, and Kohlberg's preconventional obedience all at once. Learning the grid down the age axis, rather than four separate ladders, is the single highest-yield move for these notes, and it is the figure to draw from memory in the exam (Kaplan and Sadock 2024).

Two alignment caveats before the grid. Kohlberg's stages are keyed to moral *reasoning* and therefore lag the others: preconventional reasoning runs to roughly age 9, and the higher levels

open only in adolescence and adulthood, so the moral column is deliberately coarser than the rest. And Freud's ladder simply *stops* at the genital stage in adolescence, whereas Erikson, Piaget (formal operations) and, above all, Erikson's three adult stages carry the developmental story across the entire lifespan. The empty lower-left of the Freud column is itself an examinable fact.

AGE BAND	FREUD (PSYCHOSEXUAL)	ERIKSON (PSYCHOSOCIAL: CRISIS / VIRTUE)	PIAGET (COGNITIVE)	KOHLBERG (MORAL)
Infancy (birth to ~1.5 y)	**Oral**	Trust vs mistrust / hope	**Sensorimotor (object permanence)**	(pre-moral)
Toddler (~1.5 to 3 y)	**Anal**	Autonomy vs shame and doubt / will	**Sensorimotor into preoperational**	(pre-moral)
Preschool (~3 to 5 y)	**Phallic (oedipal)**	Initiative vs guilt / purpose	**Preoperational (egocentrism)**	Level I Preconventional (to ~age 9): punishment-obedience, then self-interest
School-age (~6 to 12 y)	**Latency**	Industry vs inferiority / competence	**Concrete operational (conservation)**	
Adolescence (~12 to 18 y)	**Genital**	Identity vs role confusion / fidelity	**Formal operational (hypothetico-deductive)**	Level II Conventional: good-boy, then law-and-order
Young adulthood	**(Freud stops here)**	Intimacy vs isolation / love	Formal operational (mature)	Level III Postconventional (only ~10 to 15%): social contract, then universal principles
Middle adulthood (~40 to 65 y)	**(no Freudian stage)**	Generativity vs stagnation / care	Formal operational	
Old age (~65 y to death)	**(no Freudian stage)**	Ego integrity vs despair / wisdom	Formal operational	

Read across a row for the same-aged child through four lenses; read down the Freud column to see it end at adolescence while Erikson runs to death. Ages are the standard textbook bands (Kaplan and Sadock 2024), not sharp cut-offs.

How to use the grid in an answer. The examiner's favourite cross-sectional question is "what is happening developmentally at age X". At the preschool column you can now say, in one breath, that the phallic-stage child working through the Oedipus complex is simultaneously exercising Eriksonian initiative, thinking in egocentric preoperational terms (three-mountains task), and reasoning morally only from fear of punishment. That four-lens sentence is worth more than any single ladder recited in isolation, and it is exactly what the aligned grid trains.

TRAP Do not expect Freud's ladder to continue past adolescence. Freud, Piaget and Kohlberg **finish by early adulthood; only Erikson runs to death**, and the empty lower-left of the Freud column is itself an examinable fact.

21.2 Emotion theories on the axis of sequence: which comes first?

One question orders all four: body-first or cognition-first? Given a bear on the path, does the pounding heart come before the fear, at the same time, or after an appraisal? Each named theory is a different answer, and the whole set is best held as a single spectrum from pure body-first (james-lange) to pure cognition-first (lazarus), with cannon-bard and schachter-singer between them (Kaplan and Sadock 2024). The discriminator is always the *order* of the three ingredients: physiological arousal, cognitive interpretation, and conscious feeling.

THEORY (AUTHOR, YEAR)	SEQUENCE IT PROPOSES	THE ONE DISCRIMINATOR
James-Lange (James 1884, Lange)	Stimulus, then bodily arousal, then perception of it = the emotion	**Body first; feeling is the read-out of the body ("we are afraid because we tremble"); needs a unique bodily pattern per emotion**
Cannon-Bard (Cannon 1927, Bard)	Stimulus, then arousal and feeling together, in parallel	**Simultaneous and independent; the thalamus fires body and cortex at once, neither causes the other**
Schachter-Singer (1962)	Stimulus, then arousal, then cognitive label = the emotion	**Two factors: undifferentiated arousal first, but cognition must name it; same arousal labelled fear or euphoria by context**
Lazarus appraisal (1966, 1991)	Stimulus, then appraisal, then feeling and arousal together	**Cognition first; appraisal of meaning-for-self is necessary and prior and generates both feeling and body**

The spectrum from body-first to cognition-first. Note the two easily-confused middle theories: cannon-bard is simultaneous-and-independent, schachter-singer is arousal-then-label (still body-first, but cognition specifies which emotion).

The pairing examiners exploit. The two most-confused theories are james-lange and cannon-bard, because both concern the body, yet they are opposites on sequence: james-lange makes the body *cause* the feeling (serial, body then feeling), cannon-bard makes body and feeling *parallel* and unlinked (simultaneous, neither causing the other). Cannon built cannon-bard precisely as a rebuttal of james-lange, on three grounds: isolating the viscera did not abolish emotion, injected arousal did not create a genuine emotion, and autonomic responses are too slow and too uniform to explain the speed and variety of feeling. Beyond the four, the *currently accepted* synthesis folds them together, appraisal (Lazarus) sets it off, interoception gives it its felt body (james-lange revived, via Damasio's somatic markers and the insula), and conceptual construction names it (Schachter-Singer's label, formalised by Barrett 2017), with the appraisal-versus-primacy tension resolved neurally by LeDoux's low and high roads (Kaplan and Sadock 2024).

21.3 Intelligence models on the axis of number: one thing or many?

The single question that orders the intelligence theories: how many intelligences are there? Every model is judged against one stubborn empirical fact, the **positive manifold**, that scores on

almost all cognitive tests correlate positively, which any theory denying a general factor has to explain away. The models run from Spearman's single *g* to Gardner's eight-or-nine, with the Cattell-Horn-Carroll hierarchy resolving the fight by making it a matter of levels rather than of count (Kaplan and Sadock 2024; Carroll 1993).

MODEL (AUTHOR, YEAR)	HOW MANY, AND WHAT	THE ONE DISCRIMINATOR
Spearman two-factor (1904)	One general factor g, plus a specific s per task	**Unitary: one g lifts every performance; explains the positive manifold directly**
Gardner multiple intelligences (1983)	Many (seven, then eight): linguistic, logical-mathematical, spatial, musical, bodily-kinaesthetic, interpersonal, intrapersonal, naturalistic	**Plural and independent; each dissociable, own neural substrate; critique: contradicts the positive manifold, abilities do correlate**
Sternberg triarchic (1985)	Three: analytical, creative, practical	**Real-world success, not just school; first to bring creativity formally inside intelligence**
Cattell-Horn-Carroll, CHC (1993)	All levels at once: g over ~8 to 10 broad abilities over many narrow abilities (three strata)	**Hierarchy dissolves the one-vs-many war; g at the apex (Spearman) above broad and narrow abilities (Thurstone); the currently accepted consensus**

The axis is number. Spearman says one, Gardner says many-and-independent, Sternberg says three-for-real-life, and CHC nests them all: g over broad over narrow. The pluralist theories that deny g cannot be the consensus because the positive manifold is real.

Why CHC wins and the pluralists do not. The exam rewards the counter-intuitive line: Gardner and Sternberg feel modern and inclusive, but they sit *outside* the empirical mainstream precisely because they deny or minimise g, which the positive manifold will not allow. CHC is the working consensus because it honours both halves of the century-old debate, a genuine general factor at the top (vindicating Spearman) sitting over a rich layer of broad and narrow abilities (vindicating Thurstone, Cattell and Horn), which is why modern tests report both a full-scale IQ and index scores (Kaplan and Sadock 2024).

21.4 The three axes in one sentence each

Carry these away. The developmental grid is organised by *age* (what four theorists say is happening in the same child), the emotion theories by *sequence* (body-first to cognition-first), the intelligence models by *number* (one general capacity to many independent ones). Name the axis first in any comparison answer and the discriminators fall into place, because each theory is only ever defined by where it sits on its axis relative to its neighbours.

HOLD THIS

Three axes: developmental theorists on age, emotion theories on sequence, intelligence models on number. Name the axis, place each theory on it, state the single discriminator; that is what converts a memorised list into a comparison answer.

COMMON TRAP

The four classic mix-ups the exam plants:

- **James-Lange vs Cannon-Bard (direction):** both are about the body, but james-lange is *serial* (arousal then feeling, the body causes the emotion) while cannon-bard is *parallel and independent* (arousal and feeling together, neither causes the other). Do not call schachter-singer "cognition-first": its arousal comes first, then the label.
- **Assimilation vs accommodation:** in *assimilation* the new input is bent to fit the existing schema (a dachshund fits "dog"); in *accommodation* the schema is bent to fit the new input (the schema changes when a cat will not fit "dog"). Assimilation keeps the schema, accommodation changes it.
- **Piaget vs Vygotsky:** Piaget is individual construction (the lone child acting on the world, development leads learning); Vygotsky is social mediation (a more-knowledgeable other scaffolds within the zone of proximal development, learning leads development). Scaffolding as a term is Wood, Bruner and Ross, not Vygotsky.
- **Freud vs Erikson stage names:** Freud's are psychosexual (oral, anal, phallic, latency, genital); Erikson's are psychosocial crises with virtues (trust-vs-mistrust / hope, and so on). They run in parallel through childhood; then Freud stops at genital while Erikson adds three adult stages (intimacy, generativity, integrity). Do not swap Erikson's virtues between stages: initiative gives *purpose*, industry gives *competence*.

PEARL

For any "compare X and Y" question, do three things in order: name the shared axis (age, sequence, or number), place each theory on it, and state the single discriminator between the two. That structure, axis then placement then discriminator, is what converts a memorised list into a comparison answer, and it is why examiners set discrimination questions in the first place.

MNEMONIC

Three axes: AGE, SEQUENCE, NUMBER

Developmental theorists align on **age** (Freud / Erikson / Piaget / Kohlberg across one child), emotion theories order on **sequence** (body-first james-lange to cognition-first lazarus), intelligence models split on **number** (one g to many). Name the axis, then the discriminator.

GOOD TO REMEMBER

- **Aligned grid, preschool column (~3 to 5 y):** Freud phallic, Erikson initiative-vs-guilt (purpose), Piaget preoperational, Kohlberg preconventional.
- **Aligned grid, school-age (~6 to 12 y):** Freud latency, Erikson industry-vs-inferiority (competence), Piaget concrete operational, Kohlberg preconventional into conventional.
- **Aligned grid, adolescence:** Freud genital (last Freudian stage), Erikson identity-vs-role-confusion (fidelity), Piaget formal operational, Kohlberg conventional.
- **Freud stops, Erikson continues:** Freud's ladder ends at the genital stage; Erikson adds intimacy (love), generativity (care), integrity (wisdom) across adult life.
- **James-Lange:** body-first, feeling is the perception of arousal ("afraid because we tremble").
- **Cannon-Bard:** arousal and feeling simultaneous and independent (thalamic theory); built as the rebuttal of james-lange.
- **Schachter-Singer (1962):** two-factor, arousal then cognitive label; same arousal, different emotion by context.
- **Lazarus (1966, 1991):** cognition-first, appraisal is prior and necessary; Zajonc (1980) counter = affective primacy.
- **Emotion axis:** body-first to cognition-first; currently accepted = appraisal + interoception + construction.
- **Spearman (1904):** one general factor g plus specific s; the positive manifold.
- **Gardner (1983):** multiple independent intelligences (seven then eight); critique = contradicts the positive manifold.
- **Sternberg (1985):** triarchic, analytical + creative + practical.
- **CHC (Carroll 1993):** three-stratum hierarchy (g over broad over narrow); the currently accepted consensus.
- **Intelligence axis:** number, one thing (g) to many; pluralists that deny g fall outside the mainstream.
- **Four classic traps:** james-lange vs cannon-bard (serial vs parallel); assimilation (keep schema) vs accommodation (change schema); Piaget (individual) vs Vygotsky (social); Freud psychosexual vs Erikson psychosocial names.

Apply and consolidate

22 · Apply: four psychology vignettes

The final step, where the theories become an answer. Psychology is only worth marks if the frameworks convert into reads of a described child or adult. Examiners increasingly favour the short clinical vignette: a two-line presentation, then "which stage", "which attachment type", "which theory explains this". This topic drills that conversion on four deliberately varied cases, one per major tool covered above, so that the *discriminator* (the single fact that decides the answer) is what you learn to hunt for. Each vignette follows the same discipline: read the presentation, name the tool the case is testing, apply it, and state the one line that carries the mark.

The four cases are chosen to span the whole of this material. The first is a **developmental-stage** read of a preschooler placed simultaneously through Piaget, Erikson and the milestone schedule. The second is a **goodness-of-fit** case pairing a difficult-temperament infant with a rigid

parenting environment. The third is an **attachment classification** from a Strange-Situation description, naming the type and the internal working model it encodes. The fourth is an **emotion-theory and intelligence** application, reading an arousal-then-label sequence by Schachter-Singer and placing a jagged ability profile on CHC and Gardner. Ground text is Kaplan and Sadock (2024), with Piaget (1952), Ainsworth and colleagues (1978) and Schachter and Singer (1962) behind the individual reads.

22.1 Vignette 1: the four-year-old who fails conservation and false belief

A developmental-stage read across three theorists at once. This case tests whether you can take a single age and place the child correctly on Piaget, Erikson and the milestone schedule together, which is exactly the four-lens sentence a cross-sectional question rewards. The discriminator is the pairing of the two failed tasks: a conservation failure and a false-belief failure are the twin signatures of preoperational thought.

CLINICAL ANCHOR

Case (vignette). A boy of 4 years is watched at play. When water from a short wide beaker is poured into a tall thin glass in front of him, he insists there is now "more water". Shown the Sally-Anne scenario, in which Sally hides a marble in a basket and leaves, Anne moves it to a box, and Sally returns, he says Sally will look in the box. He copies a cross on request but cannot yet copy a square. Place him.

The reasoning. Two failures anchor the Piagetian stage. The child cannot conserve liquid quantity because he *centrates* on the single salient dimension (the height of the column) and lacks the *reversibility* that would let him mentally pour the water back; conservation of quantity is not achieved until the concrete operational stage at about 7 years (Piaget 1952). He also fails the false-belief task, answering from his own privileged knowledge of where the marble truly is rather than tracking Sally's false belief, the marker of *egocentrism*; theory of mind on this task emerges at about 4 years (Wimmer and Perner 1983; Baron-Cohen, Leslie and Frith 1985), so at exactly 4 he can be on the cusp and still fail. Both features place him firmly in the **preoperational stage** (about 2 to 7 years).

The read. Piaget: preoperational, shown by non-conservation (centration, irreversibility) and egocentrism (false-belief failure). Erikson: at 4 the crisis is *initiative versus guilt*, virtue purpose (about 3 to 5 years). Freudian correlate: the phallic-oedipal stage. Milestones: copying a cross is the expected fine-motor item *at 4 years* (the square comes at 5), so his graphomotor development is on schedule and the cognitive "failures" are stage-appropriate, not delay. The whole answer in one line: a normally developing preoperational preschooler in Erikson's initiative-versus-guilt stage, whose conservation and false-belief failures are expected for his age.

HOLD THIS

At 4 years, non-conservation and false-belief failure are expected, not delay. The paired failure is the twin signature of preoperational thought; the milestone check (copies a cross at 4) confirms the child is on track.

22.2 Vignette 2: the difficult infant meeting a rigid parent

A temperament case that turns on goodness of fit, not on the temperament alone. The trap here is to answer "difficult temperament, poor outcome" and stop. The tool the case actually tests is Chess and Thomas' **goodness of fit**: outcome is predicted by the *match* between the child's style and the environment's demands, so the same infant does well or badly depending on the parenting it meets (Kaplan and Sadock 2024).

CLINICAL ANCHOR

Case (vignette). A 10-month-old feeds and sleeps on no predictable schedule, screams loudly and for a long time at each new food or face, takes many exposures to settle to any change, and is generally irritable. Her father, a punctual and orderly man, keeps a strict feeding and sleeping timetable, reads her intense crying as wilful defiance, and responds by tightening the routine and raising his voice. Classify the temperament and predict the trajectory.

The reasoning. The infant's profile is the classic **difficult child** constellation: irregular rhythmicity, withdrawal from novelty, poor (slow) adaptability, high intensity of reaction and predominantly negative mood (Chess and Thomas, New York Longitudinal Study). Difficult children are about 10 percent of the sample and carry the highest risk of later disturbance, but that risk is not fixed. The decisive variable is the environment she meets. Here the fit is *poor*: a rigid, timetable-driven parent who misreads intensity as defiance and escalates is maximally mismatched to an irregular, intense, slow-adapting infant, setting up a coercive cycle.

The read. Difficult temperament plus a rigid, mismatched caregiving environment equals a *poor goodness of fit*, and it is the poor fit, not the temperament, that predicts stress, escalating conflict and later behaviour problems. State the counterfactual to prove you understand the construct: the identical infant paired with a calm, flexible parent who paces transitions gently and reframes intensity as style rather than misbehaviour has a good fit and a favourable trajectory. The clinical move is to treat the dyad, not the child, and to reframe temperament for the father as a style to work with, not defiance to be disciplined out.

22.3 Vignette 3: the Strange-Situation reunion that names the type

An attachment classification read from reunion behaviour, plus the internal working model it encodes. The tool is Ainsworth's **Strange Situation**, and the whole discriminator lives in the *reunion* episode, not in how much the infant cries at separation (Ainsworth and colleagues 1978). Get the reunion behaviour, name the letter and label, then state the internal working model of self and other that the pattern encodes.

CLINICAL ANCHOR

Case (vignette). A 14-month-old in the standardised procedure explores the toys only a little and stays close to her mother. When the mother leaves she becomes intensely distressed and cannot be settled by the stranger. On the mother's return she rushes to be picked up but then arches away, kicks and cannot be comforted, alternately seeking and resisting contact, and does not return to play. The mother's caregiving history is described as warm but unpredictable. Classify.

The reasoning. Separation distress alone does not classify, since both secure and insecure-ambivalent infants are highly distressed; the answer is read from reunion. The signature here, seeking contact yet simultaneously resisting it (approaching to be held, then arching and pushing away), unsettled and not returning to exploration, is the **insecure-ambivalent / resistant** pattern, Ainsworth's *Type C*. The little pre-separation exploration and clinginess fit the same type. The typical caregiving is *inconsistent and unpredictable*, which matches the "warm but unpredictable" history: the child cannot form a stable expectation of availability, so it maximises proximity-seeking and protest to keep an unreliable caregiver engaged.

The read. Type C, insecure-ambivalent (resistant), read from the contradictory seek-and-resist reunion. Its **internal working model** (Bowlby's mental template built from repeated interactions) is a model of the caregiver as *unreliably available*, sometimes responsive and sometimes not, paired with a model of the self as having to escalate distress to secure care and as not confidently worthy of consistent comfort. Contrast to fix the answer: had she avoided and ignored the mother on reunion with little separation distress, that is Type A avoidant (a model of the caregiver as rejecting); had she sought the mother and been readily comforted then returned to play, that is Type B secure (a model of the caregiver as reliably available and the self as worthy of care). The adult counterpart of Type C on the Adult Attachment Interview is the preoccupied classification.

22.4 Vignette 4: the arousal that is labelled two ways, and the jagged ability profile

Two applications in one case: an emotion theory on the axis of sequence, and an intelligence model on the axis of number. The emotion half tests Schachter-Singer's two-factor account, where the same undifferentiated arousal is named by context; the intelligence half tests where a spiky ability profile sits on CHC versus Gardner. The discriminator for emotion is *same arousal, different label*; for intelligence it is *whether the peaks are truly independent or nest under g*.

CLINICAL ANCHOR

Case (vignette). A man is given an injection that races his heart and makes him sweat, but he is not told the drug is arousing. Placed with a cheerful companion he reports feeling euphoric; on another day, identically injected but placed with an angry companion, he reports feeling angry. Separately, a schoolboy is assessed: he reasons superbly through novel puzzles and has a large vocabulary, plays music with rare skill and is socially deft, yet on formal testing his musical and interpersonal talents do not stand apart from his general ability, which is uniformly high. Read the emotion, then place the profile.

The reasoning, part one (emotion). The arousal is constant across both days; only the available cognitive interpretation changes, and with it the reported emotion. This is **Schachter-Singer** two-factor theory (1962): undifferentiated physiological arousal supplies the intensity, and a cognitive *label* drawn from the context supplies the identity, so the same pounding heart is felt as euphoria beside a happy confederate and as anger beside a hostile one. Because the man was not informed of the drug's effects, he had an *unexplained* arousal to attribute, the origin of *misattribution of arousal*. Note the sequence to avoid the classic trap: arousal comes *first*, then the label, so this is still body-first, not cognition-first; had the case turned on an appraisal preceding any arousal it would be Lazarus.

The reasoning, part two (intelligence). The boy shows apparent peaks (music, social skill) on top of strong general reasoning and knowledge. **Gardner** would read the peaks as separate *musical* and *interpersonal* intelligences, largely independent modules an IQ test misses (Gardner 1983). But the case supplies the decisive fact: on testing his talents do *not* dissociate from his general ability, which is uniformly high. That is the **positive manifold**, the robust finding that cognitive abilities correlate positively, and it is precisely what Gardner's independence claim cannot accommodate. The profile therefore sits best on **CHC** (Cattell-Horn-Carroll): a high general factor *g* at the apex (Stratum III) expressed through strong broad abilities (Stratum II) and narrow abilities (Stratum I), so his novel-puzzle skill is fluid reasoning (Gf), his vocabulary is crystallised knowledge (Gc), and even his musical and social strengths, while real, correlate with the same underlying g rather than floating free.

The read. Emotion: Schachter-Singer two-factor, one arousal labelled two ways by context (body-first, arousal-then-label). Intelligence: a jagged-looking profile that nonetheless obeys the positive manifold belongs on the CHC hierarchy (g over broad over narrow), not on Gardner's independent multiple intelligences, because the peaks do not dissociate from g. CHC is the currently accepted consensus for exactly this reason.

COMMON TRAP

The four discriminators the vignettes turn on, and the wrong answers they punish:

- **Vignette 1:** do not call a stage-appropriate conservation or false-belief failure "developmental delay". At 4 years, non-conservation and egocentric false-belief errors are *expected* preoperational features; the milestone check (copies a cross at 4) confirms the child is on track.
- **Vignette 2:** do not answer "difficult temperament, therefore poor outcome". Temperament alone does not predict outcome; *goodness of fit* does. Name the poor fit, and state the counterfactual (same infant, flexible parent, good outcome).
- **Vignette 3:** do not classify from separation distress. Both secure (B) and ambivalent (C) infants are highly distressed at separation; the type is read from *reunion*. Seek-and-resist is C, not B.
- **Vignette 4:** do not call Schachter-Singer "cognition-first" (arousal comes first, then the label). And do not accept a spiky profile as proof of Gardner's independent intelligences unless the peaks actually *dissociate* from g; if they correlate (the positive manifold), the profile is CHC.

PEARL

Every vignette answer has the same skeleton: name the tool the case is testing, apply it to the described behaviour, and state the single discriminator that carries the mark, then prove mastery with the counterfactual (what a different answer would have looked like). The discriminator is nearly always one fact: the failed conservation-and-false-belief pair means preoperational; the poor match means bad goodness of fit; the reunion behaviour means the attachment type; the constant arousal with a changing label means Schachter-Singer; the peaks that still correlate with g mean CHC, not Gardner.

GOOD TO REMEMBER

- **Vignette 1, the tool:** developmental-stage read (Piaget + Erikson + milestones), placing one age through several lenses.
- **Vignette 1, the read:** a 4-year-old failing conservation (centration, no reversibility) and false belief (egocentrism) is *preoperational* (Piaget, about 2 to 7 y); Erikson crisis = initiative vs guilt (virtue purpose, about 3 to 5 y); copies a cross at 4 y (square at 5) = milestones on track.
- **Conservation of quantity:** achieved in concrete operational stage (about 7 y), not before.
- **False-belief / theory of mind:** emerges about 4 years (Sally-Anne, Baron-Cohen, Leslie and Frith 1985; paradigm Wimmer and Perner 1983).
- **Vignette 2, the tool:** temperament plus goodness of fit (Chess and Thomas, New York Longitudinal Study).
- **Difficult child:** irregular rhythmicity, withdrawal, poor adaptability, high intensity, negative mood; about 10 percent; highest risk of later disturbance.
- **Goodness of fit:** the match between child temperament and environmental demand is the real predictor of outcome, not the temperament alone; difficult infant plus rigid parent = poor fit = coercive cycle; same infant plus flexible parent = good fit.
- **Vignette 3, the tool:** attachment classification from the Strange Situation (Ainsworth and colleagues 1978), read from reunion.
- **Type C, insecure-ambivalent / resistant:** intense separation distress, seeks yet resists contact on reunion (approach then arch away), not settled; caregiving inconsistent/unpredictable; internal working model = caregiver unreliably available, self must escalate for care; adult counterpart preoccupied.
- **Reunion, not separation, classifies:** both B (secure) and C (ambivalent) are distressed at separation; A (avoidant) ignores caregiver on reunion; B seeks and is readily comforted.
- **Internal working model (Bowlby):** paired mental template of caregiver-availability and of self-worth, built from repeated interactions, largely outside awareness.
- **Vignette 4, emotion:** Schachter-Singer two-factor (1962), same undifferentiated arousal labelled euphoria or anger by context; body-first, arousal-then-label; origin of misattribution of arousal.
- **Vignette 4, intelligence:** a jagged ability profile whose peaks still correlate with g (the positive manifold) belongs on CHC (Cattell-Horn-Carroll, g over broad over narrow), not on Gardner's independent multiple intelligences; CHC is the currently accepted consensus.
- **Positive manifold:** cognitive abilities correlate positively; the fact any theory denying g must explain away.

23 · Consolidate: mnemonic, retrieval and synthesis

The last hour is where revision is made or lost. General and developmental psychology fails on exam morning not because the facts were never read but because they were never **consolidated** into a single retrievable structure. This closing topic does three specific jobs, each a distinct memory operation. First it gives one master **mnemonic** that chains every strand of this material, from the five schools through the general-psychology functions to the developmental theorists, so that pulling one thread pulls the rest. Second it converts the material into **retrieval practice**, a set of answer-free prompts to be worked with the answers covered, because the act of retrieving is itself what fixes a memory (Kaplan & Sadock 2024). Third it names a whole-chapter **synthesis map** to redraw from memory, aligning the developmental theorists on one age axis with the general-psychology functions and the depth-psychology schools as branches.

Why these three and not simple re-reading. The consolidation literature is unambiguous that the two most effective study strategies are **retrieval practice** (testing yourself) and **spaced practice**, and that re-reading and highlighting, though they feel productive, are among the weakest (Dunlosky et al. 2013). The **testing effect** is the finding that recalling material strengthens later retention more than restudying the same material for the same time (Roediger & Karpicke 2006). A good mnemonic supplies the retrieval cues, active recall exercises the retrieval itself, and a redrawn map forces the relations between items to be reconstructed rather than merely recognised. Use this topic as the closing loop: read the mnemonic, then cover the answers and self-test, then redraw the map on blank paper.

TRAP Re-reading and highlighting feel productive but are among the **weakest** study strategies; retrieval practice and spaced practice are the strongest, and the testing effect means recall beats restudy for the same time (Dunlosky et al. 2013).

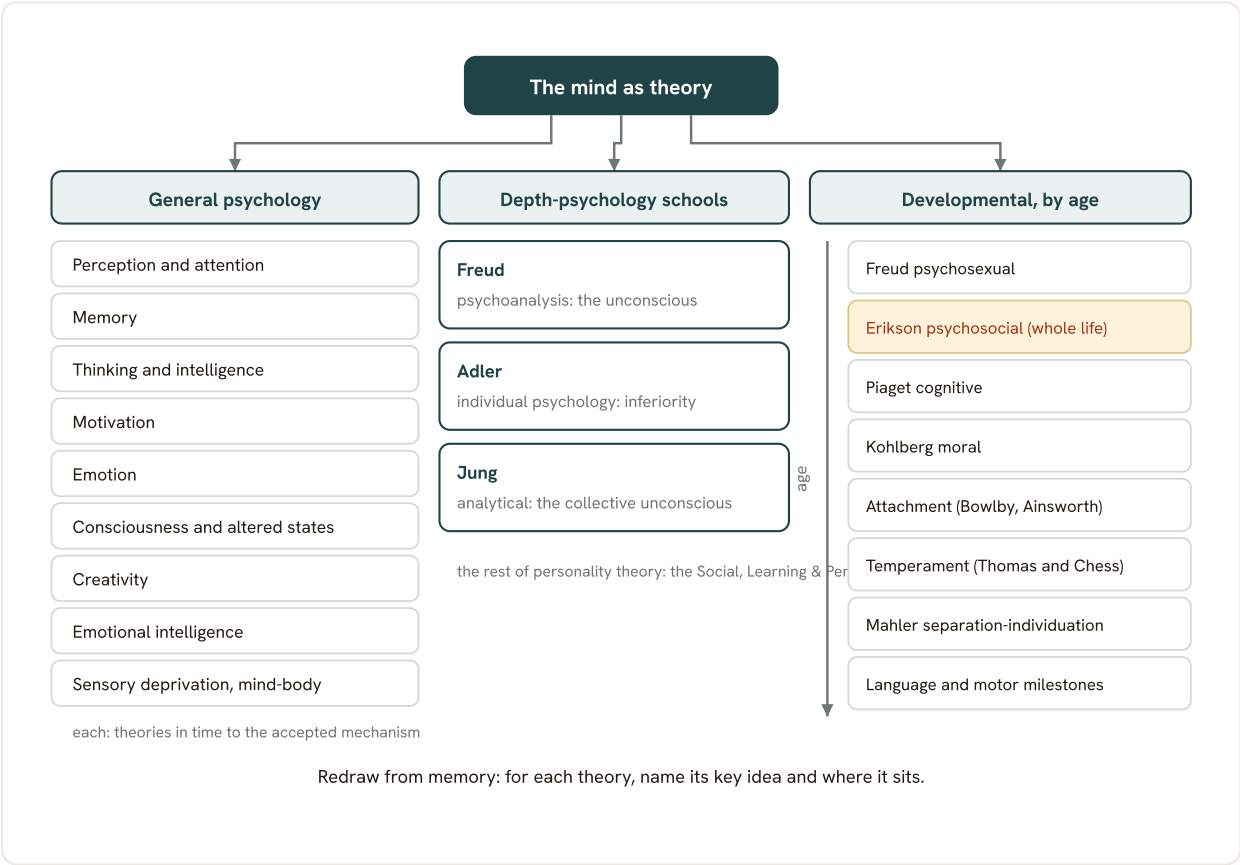


Fig 4.18 The whole chapter on one page. General psychology supplies the functions, each taught as a history of theories converging on the accepted mechanism; the three depth-psychology schools (Freud, Adler, Jung) supply the map of the unconscious; and the developmental theorists line up along a single age axis, with only Erikson spanning the whole lifespan. Cover the panels and rebuild this from memory as a retrieval test.

23.1 The master mnemonic for the whole set of notes

One chain from schools to functions to theorists. This is the single memory anchor for the chapter: a three-part device whose first line seeds the five schools, whose second line seeds the general-psychology functions, and whose third and fourth lines seed the depth-psychology schools and the developmental theorists. The letters are cues, not content; each is unpacked

below to the item it must recover. Rehearse the four lines until they run without effort, then use each letter as a hook to reel in its full topic.

MNEMONIC

Big Cats Bite Prey Hungrily · Please Make Time, Matey, Every Clever Creature Excels · Freud, Adler, Jung climb the iceberg · Every Playful Kid Anxiously Tests Mother's Milestones

Line 1, the five schools, in appearance-and-argument order (Big Cats Bite Prey Hungrily). Big = *Biological* (the brain: genes, neurotransmitters, circuits, evolution). **C**ats = *Cognitive* (the computer metaphor; Neisser 1967). **B**ite = *Behavioural* (the black box; Watson 1913, Skinner). **P**rey = *Psychodynamic* (the iceberg; Freud, Adler, Jung). **H**ungrily = *Humanistic* (the growing self; Maslow, Rogers; descendant positive psychology, Seligman).

Line 2, the nine general-psychology functions (Please Make Time, Matey, Every Clever Creature Excels). Please = *Perception* (currently accepted as predictive processing; neural correlate the sensory-association cortex and the two visual streams). **M**ake = *Memory* (Atkinson-Shiffrin then Baddeley then the systems synthesis; correlate hippocampus for declarative, basal ganglia and cerebellum for procedural, amygdala for emotional). **T**ime = *Thinking and intelligence* (currently accepted CHC model; correlate parieto-frontal integration theory and processing speed). **M**atey = *Motivation* (drive to incentive to the currently accepted multi-system view; correlate mesolimbic dopamine, hypothalamus). **E**very = *Emotion* (James-Lange to Cannon-Bard to Schachter-Singer to the currently accepted appraisal-plus-interoception-plus-construction synthesis; correlate the limbic system and Papez circuit, amygdala with LeDoux's two roads, insula for interoception). **C**lever = *Consciousness* (global workspace and its neural correlate). **C**reature = *Creativity* (the componential and systems view; correlate the default-mode, executive-control and salience networks). **E**xcels = *Emotional intelligence* (Salovey-Mayer ability model versus Goleman and Bar-On mixed models; correlate the "social brain," ventromedial prefrontal cortex, amygdala, insula), and the *mind-body* problem underneath them all (dualism to identity theory to functionalism).

Line 3, the three depth-psychology schools (Freud, Adler, Jung climb the iceberg). Freud = psychoanalysis: topographic and structural models, the psychosexual stages, defence and transference. **Adler** = individual psychology: organ inferiority, the inferiority feeling, striving for superiority, style of life, social interest. **Jung** = analytical psychology: the collective unconscious, archetypes (persona, shadow, anima and animus, self), complexes, introversion and extraversion.

Line 4, the developmental strands (Every Playful Kid Anxiously Tests Mother's Milestones). Every = *Erikson* (eight psychosocial crises, each with its virtue). **P**layful = *Piaget* (four cognitive stages: sensorimotor, preoperational, concrete operational, formal operational). **K**id = *Kohlberg* (three moral levels: preconventional, conventional, postconventional). **A**nxiously = *Attachment* (Harlow, Bowlby, Ainsworth; secure, avoidant, ambivalent, disorganised). **T**ests = *Temperament* (Chess and Thomas nine dimensions and three types; goodness of fit; Kagan's behavioural inhibition). **M**other's = *Mahler* (separation-individuation: the precursor phases autistic and symbiotic, then the four subphases differentiation, practising, rapprochement, consolidation). **M**ilestones = the *developmental milestones* ladder (social smile, sitting, pincer grasp, first words, walking, the copy-a-shape sequence, and their red flags). Freud's psychosexual stages, from Line 3, are the fifth stage theorist that runs down the same age axis.

23.2 Retrieval practice: work these with the answers covered

Test yourself, do not re-read. The following are deliberately answer-free. Use **active recall**: read each prompt, say or write the full answer from memory, and only then check it against the topic it came from. This is **retrieval practice**, the single highest-yield way to convert a day of reading into exam-durable memory, and it works only if you genuinely attempt recall before checking, so cover the answers.

RETRIEVAL PRACTICE, COVER THE ANSWERS

Retrieval practice, cover the answers. Answer each aloud or on paper before you look anything up. If a prompt is blank in your mind, flag it and return to that topic; a blank on a self-test now is a mark you would otherwise have lost in the exam.

1. Name the five schools of psychology and give each one's unit of analysis and its lead figure.
2. State the historical arc: which school fixed which gap, from introspection through behaviourism to the cognitive revolution, and where the psychodynamic and humanistic traditions sit.
3. For perception, give the evolution from the classical view to the currently accepted predictive-processing account, and name its neural correlate.
4. Lay out the memory systems and map each onto its structure: declarative versus procedural versus emotional, and the model sequence from Atkinson-Shiffrin to Baddeley's working memory.
5. State the currently accepted model of intelligence and its neural correlate, and distinguish fluid from crystallised ability.
6. Trace the emotion theories in order (James-Lange, Cannon-Bard, Schachter-Singer, appraisal, constructed emotion) and name the structures of the neural correlate.
7. Contrast the ability model of emotional intelligence with the mixed models, naming their authors.
8. Give Freud's topographic and structural models and list the psychosexual stages with their ages and zones.
9. State Adler's core concepts: organ inferiority, inferiority feeling, striving for superiority, style of life, and social interest.
10. Draw Jung's structure of the psyche and name the major archetypes, and state the boundary rule for complexes versus archetypes.
11. List Erikson's eight psychosocial stages with their ages and virtues.
12. Give Piaget's four stages with ages and one signature achievement or error each, then contrast Piaget with Vygotsky.
13. State Kohlberg's three levels and six stages, the dilemma used to elicit them, and the core scoring rule.
14. Name the four attachment classifications, the discriminator that separates them, and who added the fourth type.
15. List Chess and Thomas's three temperament types with their approximate proportions, define goodness of fit, and give Mahler's two precursor phases and four subphases of separation-individuation with their ages.

23.3 The whole-day synthesis map to redraw from memory

Reconstruct the relations, do not just recognise the items. The final consolidation act is to draw the whole set of notes as one **synthesis map** on a blank sheet and to redraw from memory until it flows without prompts. Put a single horizontal *age axis* across the page, from birth on the left to old age on the right. Along it, stack the five stage theorists who share that axis so their stages line up vertically: Freud's psychosexual stages, Erikson's eight psychosocial crises, Piaget's four cognitive stages, Kohlberg's three moral levels, and Mahler's separation-individuation sub-phases, with attachment phases and the motor-language milestone ladder threaded beneath as the relational and observable strands. Then branch upward off the map two further clusters that are not age-staged: the nine *general-psychology functions* (perception, memory, thinking and intelligence, motivation, emotion, consciousness, creativity, emotional intelligence, and the mind-body problem), each labelled with its currently accepted mechanism and neural correlate, and the three *depth-psychology schools* (Freud, Adler, Jung) as the roots feeding the psychodynamic lens. Redraw this from memory once and the material is genuinely consolidated: the age axis holds the developmental theorists in register, and the two branches keep the functions and the schools attached to the same single structure. A concept SVG of this map should be drawn to anchor the redraw.

HOLD THIS

One age axis holds five stage theorists in register (Freud, Erikson, Piaget, Kohlberg, Mahler), with the functions and the depth-schools branching off. Redraw it once from memory and the chapter is genuinely consolidated.

GOOD TO REMEMBER

- **Five schools (Line 1):** Biological (brain), Cognitive (computer; Neisser 1967), Behavioural (black box; Watson 1913, Skinner), Psychodynamic (iceberg; Freud, Adler, Jung), Humanistic (growing self; Maslow, Rogers; positive psychology, Seligman).
- **Nine functions (Line 2):** perception, memory, thinking and intelligence, motivation, emotion, consciousness, creativity, emotional intelligence, mind-body; each learned as evolution of theories to currently accepted mechanism to neural correlate.
- **Perception:** currently accepted = predictive processing; correlate = sensory-association cortex and the two visual streams (dorsal "where," ventral "what").
- **Memory:** Atkinson-Shiffrin then Baddeley working memory then systems synthesis; correlate = hippocampus (declarative), basal ganglia and cerebellum (procedural), amygdala (emotional).
- **Intelligence:** currently accepted = CHC (Cattell-Horn-Carroll); correlate = parieto-frontal integration theory and processing speed.
- **Emotion:** James-Lange to Cannon-Bard to Schachter-Singer to appraisal-plus-interoception-plus-construction; correlate = limbic system and Papez circuit, amygdala (LeDoux's two roads), insula.
- **Emotional intelligence:** Salovey-Mayer ability model vs Goleman and Bar-On mixed models; correlate = the "social brain," ventromedial prefrontal cortex, amygdala, insula.
- **Freud (Line 3):** psychoanalysis; topographic and structural models; psychosexual stages (oral, anal, phallic, latency, genital); staged by body zone.
- **Adler (Line 3):** individual psychology; organ inferiority, inferiority feeling, striving for superiority, style of life, social interest.
- **Jung (Line 3):** analytical psychology; collective unconscious; archetypes (persona, shadow, anima/animus, self); complexes; introversion/extraversion.
- **Erikson (Line 4):** eight psychosocial crises, each with a virtue (trust/hope to integrity/wisdom); psychosocial, added three adult stages beyond Freud's genital.
- **Piaget (Line 4):** sensorimotor (0 to ~2 y), preoperational (~2 to 7 y), concrete operational (~7 to 11 y), formal operational (~11 y onward).
- **Kohlberg (Line 4):** preconventional (to ~9 y), conventional (adolescence on), postconventional (only ~10 to 15% reach it); Heinz dilemma; reasoning fixes the stage.
- **Attachment (Line 4):** Harlow (contact comfort), Bowlby (behavioural system, secure base, internal working model), Ainsworth (Strange Situation); types A avoidant, B secure, C ambivalent, D disorganised (Main & Solomon).
- **Temperament (Line 4):** Chess and Thomas nine dimensions, easy (~40%), difficult (~10%), slow-to-warm-up (~15%); goodness of fit; Kagan behavioural inhibition (~10 to 15%).
- **Mahler (Line 4):** normal autistic (0 to ~1 mo), symbiotic (~1 to 5 mo), differentiation (~5 to 9 mo), practising (~9 to 16 mo), rapprochement (~16 to 24 mo), consolidation/object constancy (~24 to 36 mo).
- **Milestones (Line 4):** social smile ~6 to 8 wk, sits without support ~6 to 8 mo, pincer grasp 9 to 10 mo, first words ~12 mo, walks well 14 to 15 mo; copy-a-shape circle 3 y, cross 4 y, square 5 y, triangle 6 y, diamond 7 y.
- **Consolidation science:** retrieval practice and spaced practice are the highest-yield strategies (Dunlosky et al. 2013); the testing effect beats restudy (Roediger & Karpicke 2006); re-reading and highlighting are weak.

Previously asked

Real long-essay (25-mark) and short-note (10-mark) questions from the general and developmental psychology territory, most-recent year shown.

LONG ESSAYS (25 MARKS)

- Define emotions. Discuss the various theories of emotion and the psychopathological presentations related to emotion. MUHS 2017
- Describe the physiological basis of emotions. MUHS 2018
- Describe perceptual processes and the various disorders of perception. MUHS 2014
- Define the term consciousness. Describe the differential diagnosis of unconsciousness, and how you would investigate and manage a case of suspected dissociative (hysterical) unconsciousness. MUHS 2016

SHORT NOTES (10 MARKS)

- Erik Erikson and the stages of psychosocial development. MUHS 2021
- Theories of motivation and their application in psychiatry. MUHS 2021
- Psychological development in adolescence and its relation to psychiatric disorders. MUHS 2020
- Carl Gustav Jung. MUHS 2017
- Emotional intelligence. MUHS 2018
- Principles of Gestalt psychology. MUHS 2018
- Freud's concept of the id. MUHS 2013
- Implicit memory. MUHS 2013
- Working memory. MUHS 2012
- Jean Piaget. MUHS 2011
- Sigmund Freud and his contribution to psychiatry. MUHS 2011
- Tests used to assess intelligence. MUHS 2011

Psychology is a dependable examiner's quarry: emotion theories and the physiological basis of emotion recur as full essays, and Freud, Jung, Erikson, Piaget, motivation, working and implicit memory, emotional intelligence and Gestalt appear regularly as short notes. Prepare each theorist well enough to give the core idea, the stages or components, and one clinical link in a few lines. Learning and classical or operant conditioning, theories of personality, social perception, the psychology of aggression and the psychology of rape are examined from this same territory but are taught on the Social, Learning & Personality Psychology notes; intelligence testing is taken up on the Psychometry, Assessment and Descriptive Psychopathology notes.

Quick review

The whole picture in one table	
SCHOOLS OF PSYCHOLOGY	Five lenses on the same mind: biological (brain, genes), cognitive (information processing), behavioural (observable stimulus and response), psychodynamic (the unconscious), humanistic (growth and meaning). Each arose partly to fix what the previous lens left out. The general-psychology topics below each run the same way: the theories in the order they appeared, then the currently accepted mechanism and its neural correlate.
PERCEPTION AND ATTENTION	Sensation to perception; Gestalt organisation; Gibson direct bottom-up versus Gregory constructivist top-down, now reconciled as predictive perception; signal detection (d-prime, criterion). Attention: Broadbent early filter to Treisman attenuation to Deutsch-Norman late selection to Kahneman capacity. Hallucination theories evolve from perceptual release (Hughlings-Jackson) through source monitoring and aberrant salience to predictive coding. Neural: ventral what and dorsal where streams.
MEMORY	Ebbinghaus forgetting curve; Atkinson-Shiffrin multi-store (sensory, short-term, long-term); Baddeley working memory (central executive, phonological loop, visuospatial sketchpad, episodic buffer); levels of processing; Tulving long-term taxonomy (episodic, semantic, procedural; explicit, implicit). Forgetting by decay, interference, retrieval failure. Neural: hippocampus and medial temporal lobe for declarative, prefrontal for working memory.
THINKING AND INTELLIGENCE	Heuristics and biases (availability, representativeness, anchoring); dual-process. Intelligence models: Spearman g, Thurstone primary abilities, Cattell fluid and crystallised, the Cattell-Horn-Carroll consensus, Gardner multiple, Sternberg triarchic. The argument is one thing versus many; CHC is the working consensus. Neural: parieto-frontal integration (P-FIT). Testing is on the Psychometry, Assessment and Descriptive Psychopathology notes.
MOTIVATION	Instinct to drive-reduction (Hull) to arousal or optimal-level (Yerkes-Dodson) to incentive to Maslow's hierarchy (deficiency then growth needs) to Murray and McClelland to Deci and Ryan self-determination (intrinsic and extrinsic; autonomy, competence, relatedness). Homeostasis cannot explain curiosity or achievement. Neural: mesolimbic dopamine incentive-salience.

The whole picture in one table	
EMOTION	James-Lange (body first), Cannon-Bard (simultaneous, thalamic), Schachter-Singer two-factor (arousal plus label), Lazarus appraisal (appraisal first), then basic (Ekman) versus constructed emotion (Barrett). The enduring debate is body-first versus cognition-first. Neural: limbic system and Papez circuit, amygdala (LeDoux), insula for interoception.
CONSCIOUSNESS	Level (arousal) versus content (awareness); the hard problem. Global workspace (Baars) and integrated information (Tononi). Altered states: sleep and dreaming, hypnosis, meditation, drug-induced, and clinical (delirium, dissociation, coma). Neural: ascending reticular activating system, thalamocortical loops, default-mode network.
CREATIVITY	Guilford convergent versus divergent thinking (fluency, flexibility, originality, elaboration); Torrance tests; Wallas four stages (preparation, incubation, illumination, verification); the threshold hypothesis; the creativity-psychopathology question. Neural: reduced latent inhibition, default-mode and executive dynamics.
EMOTIONAL INTELLIGENCE	Mayer and Salovey four-branch ability model (perceive, use, understand, manage) versus Goleman mixed or trait model; Bar-On. Ability versus trait debate; MSCEIT versus self-report; incremental-validity critique. Neural: ventromedial prefrontal cortex, amygdala, insula.
SENSORY DEPRIVATION AND MIND-BODY	Sensory deprivation (Hebb and McGill, Lilly): perceptual and cognitive effects, hallucinations; relevance to solitary confinement and ICU. Mind-body problem: dualism (Descartes) versus monism (physicalism, functionalism, emergentism); the explanatory gap and qualia; the biopsychosocial synthesis (Engel) as the working clinical stance.
FREUD (PSYCHOANALYSIS)	Topographic (conscious, preconscious, unconscious) and structural (id, ego, superego) models; psychosexual stages oral, anal, phallic (Oedipus), latency, genital; techniques (free association, dream analysis, transference). The Wednesday Psychological Society became the Vienna Psychoanalytic Society; Adler, Jung, Stekel and Rank defected over the primacy of sexuality.
ADLER (INDIVIDUAL PSYCHOLOGY)	Inferiority feeling driving striving for superiority; the inferiority and superiority complexes; holism and fictional finalism; the style of life; social interest as the mark of health; birth order and family constellation. Broke from Freud over libido; influenced CBT and humanistic therapy.
JUNG (ANALYTICAL PSYCHOLOGY)	Ego, personal unconscious (complexes), collective unconscious with archetypes (persona, shadow, anima and animus, the Self); introversion and extraversion with four functions (the MBTI typology); individuation as the goal; the word-association test; synchronicity. Broke from Freud over libido as general psychic energy.

The whole picture in one table	
ERIKSON (PSYCHOSOCIAL)	Eight lifespan crises with virtues: trust versus mistrust (hope), autonomy versus shame (will), initiative versus guilt (purpose), industry versus inferiority (competence), identity versus role confusion (fidelity), intimacy versus isolation (love), generativity versus stagnation (care), integrity versus despair (wisdom). Epigenetic principle; Marcia identity statuses. The only stage theory to span the whole life.
PIAGET, VYGOTSKY, THEORY OF MIND	Piaget: assimilation and accommodation; sensorimotor (object permanence), preoperational (egocentrism, no conservation), concrete operational (conservation, reversibility), formal operational (abstract). Vygotsky: sociocultural, the zone of proximal development, scaffolding (social versus individual construction). Theory of mind: the false-belief task, emerging near age 4, relevant to autism.
KOHLBERG (MORAL)	Three levels via the Heinz dilemma: preconventional (punishment-obedience, instrumental exchange), conventional (interpersonal conformity, law and order), postconventional (social contract, universal principles). The reasoning defines the stage, not the answer; not all reach postconventional. Gilligan critique: care versus justice.
ATTACHMENT	Harlow contact comfort overturned cupboard-love. Bowlby: an evolved system, secure base, monotropy, internal working model, protest-despair-detachment. Ainsworth strange situation: secure (B), avoidant (A), ambivalent-resistant (C), disorganised (D, Main and Solomon). Disorganised attachment carries the greatest psychopathology risk.
TEMPERAMENT	Thomas and Chess (New York Longitudinal Study): nine dimensions (activity, rhythmicity, approach-withdrawal, adaptability, intensity, threshold, mood, distractibility, persistence); three types (easy, difficult, slow-to-warm-up); goodness of fit between temperament and environment predicts outcome. Kagan behavioural inhibition; Rothbart reactivity.
MAHLER (SEPARATION-INDIVIDUATION)	Normal autistic (0 to 1 month) and symbiotic (1 to 5 months) phases, then four subphases: differentiation, practising, rapprochement (the crisis), and consolidation with object constancy (to 36 months). Rapprochement-failure is linked to borderline pathology. Klein, Winnicott and Fairbairn (object relations) are taught on the Social, Learning & Personality Psychology notes.
LANGUAGE AND MOTOR MILESTONES	Verified ages: social smile 6 to 8 weeks, head control 3 months, sits 6 months, stranger anxiety 8 months, pincer grasp 9 to 10 months, first words about 12 months, walks 12 to 15 months, two-word phrases 18 to 24 months. Language theory: Skinner operant versus Chomsky nativist (language acquisition device, universal grammar) versus interactionist; cooing, babbling, holophrastic, telegraphic.
DISCRIMINATE AND APPLY	Align the stage theorists (Freud, Erikson, Piaget, Kohlberg) down one age axis; only Erikson spans the whole life. Tell the emotion theories apart by the

The whole picture in one table	
	order of arousal, cognition and feeling; place the intelligence models on the one-versus-many spectrum. Apply by reading a child by stage, a temperament by goodness of fit, and an attachment by the strange situation.

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This material is grounded in the standard texts (the source hierarchy below); each theory is attributed to its primary source, and landmark, contested or numeric claims carry a PubMed-verified journal citation. Every PMID here was checked against PubMed this build, and citations whose identifier did not resolve to the cited paper were corrected or dropped.

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PART V

V

Social, Learning & Personality Psychology

How people are moved by other people, how behaviour is learned, and how personality has been explained.

01 Orientation

02 Social psychology

03 Learning and behaviour

04 Personality and psychodynamic theory

05 Special topics

06 Discriminate

07 Apply and consolidate

Social, Learning & Personality Psychology

Seven sections · 20 topics · one complete notes document

These notes complete the psychology of the paper by covering the three domains the General and Developmental Psychology notes deliberately held back: the social, the learned and the theorised person. Where the General and Developmental Psychology notes taught the general functions and the developmental theorists, these notes cover **how people act on each other, how behaviour is shaped, and how personality is modelled.** Social psychology comes first (attitudes and their change, attribution and the biases of social thinking, conformity and obedience, prejudice, aggression, the crowd), then learning and behaviour (classical and operant conditioning, Bandura's social learning, and the therapies built directly on them), then the rest of psychodynamic and personality theory (the defences and the Vaillant hierarchy, the object-relations school, and the trait, type, humanistic and positive-psychology models). Freud's models, Adler and Jung are taught in full on the General and Developmental Psychology notes and only cross-referenced here. The examinable skill is discrimination: telling classical from operant from social learning, one personality model from another, and one social bias from the next, then placing a case in the right paradigm.

HOW TO USE THESE NOTES

The theory-heavy topics (attitudes, attribution, the learning paradigms, the personality models) follow the same flow as the General and Developmental Psychology notes: the idea in brief, then the **theories in the order they appeared** (what each fixed, what stayed debated), then the **currently accepted** position, then a **behavioural or neural correlate**, then a worked example. Figures declare one axis and code it in colour and shape: **petrol** marks structure and the neutral case, **coral** marks conflict, pathology or the point of debate, and **marigold** highlights the accepted answer. The boxes marked **Good to remember** gather every named theorist, mechanism and classification in one place, so the reference facts sit apart from the reasoning. One patient-facing note carries through the whole ecosystem: no diagnosis is named to a patient, but this is doctor-facing revision, so the full clinical vocabulary is used.

Orientation

1 · Orientation: the three domains as a map

The General and Developmental Psychology notes gave you the general functions of the mind and the developmental theorists, taught through five competing lenses. This material takes the territory that those lenses opened but did not pay off, and it turns out to be three large domains, each defined by a different **unit of analysis**. The **social** person is moved by the presence, judgement and pressure of *other people*; the **learned** person is behaviour *shaped by consequence and by observation*; the **theorised** person is personality itself, *modelled* by a succession of schools that each claimed to say what a person fundamentally is. Fix these three as a map before any of the detail, because the paper rarely asks you to defend one domain against another; it asks you to

recognise which domain a given experiment, effect or theorist belongs to, and to attach the right name (Kaplan & Sadock 2024).

The exam skill across this whole chapter is placement. An item about a subject who conforms to a unanimous but wrong majority is **social psychology** (Asch); an item about a response that grows or shrinks according to its consequence is **learning** (Skinner); an item asking which trait dimension captures anxiety-proneness is **personality** (neuroticism, in the Big Five). This orientation lays the three domains side by side, binds each to its unit of analysis and its key figures, and marks the two boundaries you must not cross: the psychodynamic *founders* (Freud's topographic and structural models, Adler, Jung) are taught in full on the General and Developmental Psychology notes and are only cross-referenced here, and the psychological *tests* (reliability, validity, the specific instruments) are the Psychometry, Assessment and Descriptive Psychopathology notes. The rest of these notes pays the map off.

1.1 Why three domains, and what each one counts as data

Each domain answers a different question about behaviour. Social psychology asks how the individual is changed by the real, imagined or implied presence of others, so its data are situations and the people in them. Learning and behaviour ask how experience lawfully changes what an organism does, so its data are stimuli, responses and their contingencies. Personality asks what stable internal structure makes one person reliably different from another across situations, so its data are consistencies over time. The same clinical fact sits differently in each: a patient's avoidance of a crowded market is, to social psychology, a matter of anticipated evaluation and the behaviour of the crowd; to learning, a conditioned fear response maintained by negative reinforcement (escape lowers anxiety, so avoidance is strengthened); to personality, an expression of high trait neuroticism and low extraversion. None is wrong; the discipline for the viva is to name the domain the question is pitched at (Kaplan & Sadock 2024; Tasman 2015).

1.2 The three domains as a map

Bind each domain to its unit of analysis and its key figures. This is the schema for the whole chapter: read the domain, hold what it counts as data, and attach the names examiners expect. Read the definitions once now as the index; every later topic is a special case of one of these three.

Social psychology

Unit of analysis: *the individual in the presence of others*. How attitudes form and change, how we explain behaviour (attribution), how the group bends the individual (conformity and obedience), and how intergroup processes produce prejudice, aggression and crowd behaviour. Key figures: Leon Festinger (cognitive dissonance, attitude change), Solomon Asch (conformity to a majority), Stanley Milgram (obedience to authority), Gordon Allport (attitudes, the nature of prejudice). This domain owns the attitudes, attribution, conformity, prejudice, aggression and crowd topics of these notes.

Learning and behaviour

Unit of analysis: *the lawful change in behaviour produced by experience*. Three paradigms: classical (Pavlovian) conditioning of a stimulus to a response, operant (instrumental) conditioning of a behaviour by its consequence, and observational learning by watching a model. Key figures: Ivan

Pavlov (classical conditioning), B. F. Skinner (operant conditioning, building on Thorndike's law of effect), Albert Bandura (observational or social learning). This domain grounds behaviour therapy and underwrites the conditioning topics.

Personality

Unit of analysis: *the stable internal structure that makes a person consistently themselves*. A succession of traditions: the psychodynamic (drives, defences, object relations), the trait (dimensions on which everyone can be scored), the type (discrete categories), the humanistic (the self striving toward growth), and the social-cognitive (person and situation in reciprocal interaction). Named anchors examiners want: the ego defence mechanisms, object relations, and above all the Big Five or Five Factor Model, the modern trait consensus (McCrae & Costa 1990).

> **PEARL**
>
> The three domains in one line: social psychology studies the person *between other people*, learning studies the person *shaped by consequences*, and personality studies the person *as a stable structure*. If you can say whether a claim is about the *situation*, the *contingency*, or the *trait*, you have placed the domain and can go looking for the right name.

1.3 The unit of analysis is the fastest discriminator

When an item could belong to two domains, decide by what it treats as the cause. The three domains overlap at the edges, and the paper exploits this. The reliable test is to ask what the explanation makes the cause of the behaviour. If the cause is *someone else* (a majority, an authority, an outgroup, an audience), it is social psychology. If the cause is a *past pairing or consequence* (a bell that once predicted food, a reward that followed an action, a model who was seen to be reinforced), it is learning. If the cause is a *durable internal disposition* that would show up across many situations, it is personality. The domains also hand off historically: behaviour therapy grew out of the learning domain in the 1950s and 1960s, social-cognitive personality theory borrowed observational learning from Bandura, and social psychology and personality meet in the person-situation debate. Knowing the seams is itself examinable (Kaplan & Sadock 2024).

DOMAIN	UNIT OF ANALYSIS (WHAT CAUSES THE BEHAVIOUR)	SIGNATURE PHENOMENA	KEY FIGURES
Social psychology	**Other people (real, imagined or implied)**	Attitudes and dissonance, attribution, conformity and obedience, prejudice, aggression, the crowd	Festinger, Asch, Milgram, Allport
Learning and behaviour	**Past pairings and consequences**	Classical conditioning, operant conditioning, observational learning	Pavlov, Skinner, Bandura
Personality	**A stable internal disposition**	Defences and object relations, traits, types, the striving self, reciprocal person-situation interaction	Freud (the General and Developmental Psychology notes), the Big Five (McCrae & Costa)

The three domains of these notes on one axis: the fastest discriminator is what each treats as the cause of behaviour. Signature phenomena and figures are paid off in the domain topics; here, hold the parallelism.

RULE **Place the item by its unit of analysis, not its content.** If the cause is other people it is social; if it is a past pairing or consequence it is learning; if it is a durable internal disposition it is personality.

HOLD THIS

Social = the person between others; learning = the person shaped by consequences; personality = the person as a stable structure. Name which of the three a stem is pitched at before reaching for any figure.

1.4 The boundary with the General and Developmental Psychology notes and with Psychometry

Know where each thread starts and stops. This chapter deliberately picks up threads the General and Developmental Psychology notes opened, so keep the cross-references clean and do not re-teach. The *founders* of the psychodynamic tradition are the General and Developmental Psychology notes material: Freud's topographic and structural models, Alfred Adler's individual psychology, and Carl Jung's analytical psychology are taught there in full, and the personality topic here uses them only as the psychodynamic tradition's starting point rather than re-deriving them. In the other direction, the personality domain names the Big Five and the defence mechanisms, but the *measurement* of personality (the NEO inventory, the MMPI, projective tests, and the reliability and validity of any scale) belongs to the Psychometry, Assessment and Descriptive Psychopathology notes. Likewise, learning here is the theory of conditioning; the clinical behaviour therapies that apply it (systematic desensitisation, exposure, token economy) are developed with the treatments. Treat this topic as the index page: when a later claim needs placing, flip back here, decide the domain by its unit of analysis, and then follow the cross-reference to where it is finished (Kaplan & Sadock 2024).

COMMON TRAP

Do not let the personality topic pull you back into re-teaching Freud, Adler and Jung; those are the General and Developmental Psychology notes and are only cross-referenced here. Equally, do not answer a personality-*testing* question (a scale's reliability, an inventory's validity) inside these notes; that is Psychometry. The personality topic here is about the *theories* of what a person is, not the *instruments* that measure it.

1.5 How these notes is wired, and the theory-evolution spine

The theory-heavy topics each run as an evolution of theories. Within each domain, the examinable topics that carry competing theories (attitudes and attitude change, attribution, the three learning paradigms, and the personality-theory topic) are best learned the same way the general functions were on the General and Developmental Psychology notes: the theories in the order they appeared, each stating what it fixed from the last and what it left debated, then the currently accepted position, its behavioural or neural correlate where one exists, and a worked example. So attitude change runs from balance and dissonance theories to the modern dual-process (elaboration-likelihood) account; attribution runs from the naive-scientist models to the recognition of the fundamental attribution error and modern social cognition; the learning paradigms run from Pavlov and Thorndike through Skinner to Bandura and the cognitive turn; and personality runs from the psychodynamic school through trait and type approaches to the humanistic and social-cognitive traditions and the Big Five consensus. Hold that spine now; the domain topics pay it off.

MNEMONIC

SLP: See, Learn, Portray

The three domains of these notes, in teaching order: **S**ocial psychology (how others *See* and move me), **L**earning and behaviour (how I *Learn* from consequence and model), **P**ersonality (how theory *Portrays* the stable self). SLP is the master mnemonic for this chapter: every topic here is a See, a Learn, or a Portray. Under each letter hang the lead names, Festinger-Asch-Milgram-Allport under S, Pavlov-Skinner-Bandura under L, and the psychodynamic-trait-type-humanistic-social-cognitive traditions ending in the Big Five under P.

GOOD TO REMEMBER

- **Social psychology (domain):** unit of analysis = the individual in the presence of others; owns attitudes, attribution, conformity and obedience, prejudice, aggression, the crowd.
- **Leon Festinger (1957):** cognitive dissonance and attitude change; the discomfort of holding an action and a belief that conflict, resolved by changing the attitude.
- **Solomon Asch:** conformity to a unanimous majority even when it is plainly wrong.
- **Stanley Milgram:** obedience to authority; ordinary people administer harm when instructed by a legitimate authority.
- **Gordon Allport:** attitudes and the nature of prejudice.
- **Learning and behaviour (domain):** unit of analysis = the lawful change in behaviour produced by experience; three paradigms below.
- **Ivan Pavlov:** classical (Pavlovian) conditioning; a neutral stimulus paired with a significant one comes to evoke the response.
- **B. F. Skinner:** operant (instrumental) conditioning; behaviour is controlled by its consequences, building on Thorndike's law of effect.
- **Albert Bandura:** observational (social) learning; behaviour acquired by watching a model.
- **Personality (domain):** unit of analysis = the stable internal structure that makes a person consistently themselves; five traditions, psychodynamic, trait, type, humanistic, social-cognitive.
- **Big Five / Five Factor Model (McCrae & Costa 1990):** the trait consensus; extraversion, agreeableness, conscientiousness, neuroticism, openness (mnemonic OCEAN).
- **Cross-references (do not re-teach):** psychodynamic founders (Freud topographic and structural, Adler, Jung) are the General and Developmental Psychology notes; the psychological tests and their reliability and validity are the Psychometry, Assessment and Descriptive Psychopathology notes.

Social psychology

2 · Attitudes, attitude change and cognitive dissonance

How the mind takes a stance, and how that stance is moved. An **attitude** is a learned evaluative disposition toward a person, object or idea, and the psychology of **attitude change** is the study of how such evaluations are formed, resist, and shift. The exam wants this as a chain of theories in the order they appeared: a first structural account of what an attitude is (the tripartite ABC model), the discovery that attitudes and behaviour often diverge (LaPiere), then successive theories of change, the **yale** communication approach, Leon **festinger**'s cognitive-dissonance theory, Bem's rival self-perception account, and finally Petty and Cacioppo's dual-route **elaboration likelihood** model of **persuasion**. Each fixed a limitation of the one before it, and the field settled on a dual-process synthesis that is now the **currently accepted** position.

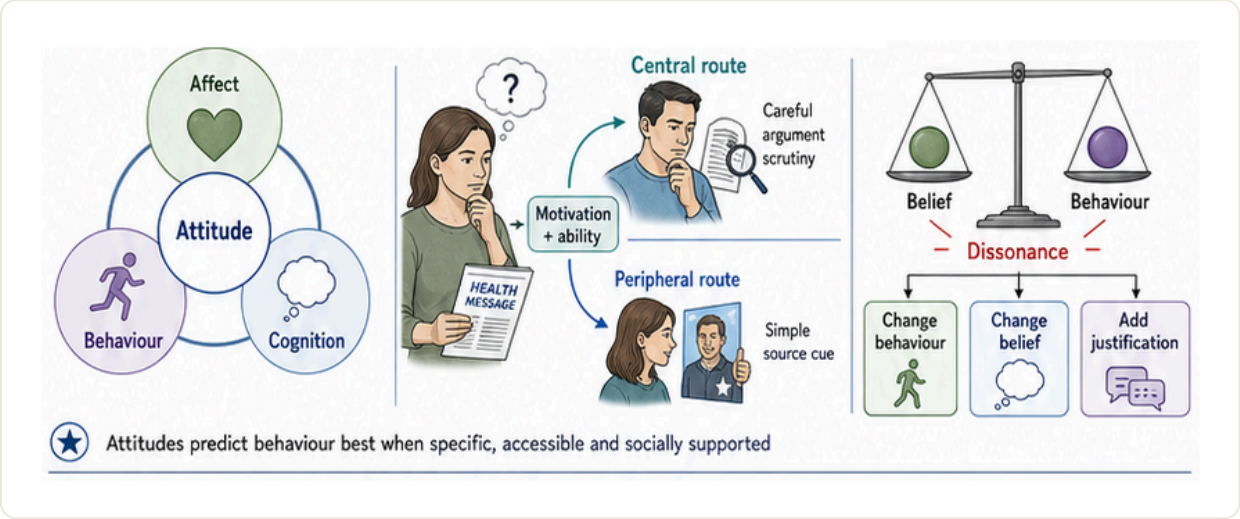


Fig 5.1 Attitudes, persuasion and cognitive dissonance.

This matters for psychiatry beyond social-science trivia. Attitude change is the engine of every psychoeducation programme, adherence intervention and public-health campaign; cognitive dissonance is the explicit mechanism of motivational interviewing and of the dissonance-based eating-disorder prevention programmes now in the guidelines (New Oxford Textbook of Psychiatry). Treat the persuasion structure and the dissonance paradigm as the two highest-yield items; treat the numeric details of the classic experiments as standard textbook figures to reproduce, not to over-claim.

2.1 What an attitude is: the tripartite ABC model

Affect, behaviour, cognition. The classic structural definition holds that an attitude has three components, the **ABC model**: an *affective* component (the feelings an object evokes, "I dislike smoking"), a *behavioural* component (the disposition to act, "I avoid smokers"), and a *cognitive* component (the beliefs held about the object, "smoking causes cancer"). An attitude is thus a relatively enduring, learned evaluation that predisposes a person to respond consistently, favourably or unfavourably, toward a class of objects. It is distinguished from a transient *mood* (no object), a *belief* (the cognitive element alone, without the evaluation), and a *value* (a broader, more abstract guiding principle under which many attitudes sit).

2.2 Attitude formation and function

How evaluations are acquired. Attitudes are learned, chiefly through three routes: *classical conditioning* (an object paired repeatedly with positive or negative affect acquires that valence, the basis of advertising and of the "mere exposure" effect, in which familiarity alone breeds liking); *operant conditioning* (attitudes that are rewarded or socially approved are retained); and *social/observational learning* (attitudes modelled by parents, peers and media are copied, Bandura). A complementary *functional* view (Katz) asks what an attitude does for the person: a *knowledge* function (organising a complex world), an *instrumental/utilitarian* function (maximising reward), an *ego-defensive* function (protecting self-esteem, the route by which prejudice can serve a defensive need), and a *value-expressive* function (signalling identity). The function an attitude serves predicts which persuasive appeal will move it.

2.3 The attitude-behaviour gap: LaPiere

Attitudes predict behaviour only weakly. The foundational problem that every later theory had to reckon with is that expressed attitudes and actual behaviour often diverge. Richard LaPiere's classic field study (LaPiere 1934) is the exam anchor: travelling the United States with a young Chinese couple, he found they were refused service at only one of over 250 hotels and restaurants, yet when he later wrote to the same establishments asking whether they would serve Chinese guests, the large majority said they would not. Attitude (expressed prejudice) and behaviour (actual courteous service) were sharply discordant. Later work (Ajzen and Fishbein; the theory of reasoned action and its successor the theory of planned behaviour) reconciled this: attitudes predict behaviour well only when they are *specific* to the behaviour, *strong*, *accessible*, and when perceived social norms and perceived control are added to the model. The gap is not a refutation of attitudes but a specification of when they bite.

> **COMMON TRAP**
>
> Do not read LaPiere as proving attitudes are irrelevant. The correct lesson is that general attitudes poorly predict specific acts, and that behaviour is co-determined by norms and situational constraint. This is exactly why a health campaign that shifts a general attitude ("smoking is bad") may fail to change a specific behaviour unless it also targets intention, norms and perceived control.

2.4 Theory one: the Yale/Hovland persuasion approach

Who says what to whom, through what channel. The first systematic theory of attitude change came from Carl Hovland and colleagues at Yale after the Second World War (the **yale** communication and attitude-change programme). It treated **persuasion** as a message-learning process and dissected it into four classes of variable, the durable exam checklist:

Source

The communicator. Persuasion rises with source *credibility* (expertise and trustworthiness), *attractiveness* and *similarity*. The *sleeper effect* is the Yale finding that a message from a low-credibility source can gain influence over time as the message dissociates from its discredited source.

Message

Its content and structure: one-sided versus two-sided arguments, the strength and order of arguments, and the calibrated use of *fear appeals* (moderate fear paired with a clear coping action persuades; overwhelming fear provokes denial).

Channel

The medium of delivery (face-to-face, print, broadcast), and its match to message complexity.

Audience

Recipient characteristics: prior attitude, intelligence, self-esteem, involvement, and forewarning (which mobilises resistance).

What it fixed and what it left open. The Yale model fixed the absence of any framework by giving a systematic, empirically testable taxonomy of persuasion variables. What it left unexplained was the *internal* process: it described which inputs move attitudes but not the

psychological mechanism by which a person changes their own mind, and it could not explain why the same variable (say, an attractive source) sometimes mattered and sometimes did not.

2.5 Theory two: Festinger's cognitive dissonance

The discomfort of holding inconsistent cognitions drives change. Leon Festinger (Festinger 1957, *A Theory of Cognitive Dissonance*, Stanford University Press) proposed that when a person holds two psychologically inconsistent cognitions, or acts in a way discrepant from a held belief or from the view of the self, they experience an aversive state of tension, **cognitive dissonance**, that they are motivated to reduce (Tasman Psychiatry). Because behaviour that has already occurred is usually the fixed element, the cheapest route to consonance is often to change the *attitude* to fit the act. Festinger's originating observation was a doomsday cult whose members, after the predicted apocalypse failed to arrive, did not abandon their belief but *intensified* their proselytising, reducing the dissonance between "I gave up everything for this prophecy" and "the prophecy was false" by recruiting others (Festinger 1957; Tasman Psychiatry). Dissonance is now often reframed as a *self* theory: the discomfort is sharpest when the discrepant act threatens the view of oneself as competent and moral (Aronson et al. 2007, cited in Tasman Psychiatry).

2.6 Festinger: the three classic dissonance paradigms

Induced compliance, effort justification, post-decision. Three experimental paradigms recur in exams and each demonstrates a distinct route by which dissonance shifts an attitude.

Induced compliance (the "one dollar / twenty dollar" study)

Festinger and Carlsmith (1959) had subjects perform a dull task and then paid them either a small or a large sum to tell a waiting person the task was enjoyable. Those paid the *small* sum later rated the task as more genuinely enjoyable than those paid the large sum. The small payment was insufficient external justification for the lie, so dissonance ("I said it was fun, but it was boring") was resolved by internally revising the attitude; the large payment supplied ample external justification, so no dissonance and no attitude change followed. Counter-attitudinal behaviour changes the attitude most when external incentive is minimal.

Effort justification

Aronson and Mills (1959): people who underwent a severe, embarrassing initiation to join a dull group later valued the group more highly than those admitted easily. High effort or suffering for a poor outcome creates dissonance that is resolved by inflating the outcome's worth ("I would not have gone through that for nothing"). This underlies the loyalty produced by harsh hazing and demanding training.

Post-decision dissonance

After a difficult choice between two similar options, the rejected option's attractive features and the chosen option's flaws generate dissonance, which is reduced by *spreading of alternatives*: the chosen option is subsequently rated more highly and the rejected one more poorly. This is why people rationalise a purchase or a career choice after committing to it.

RULE **In induced compliance, the smaller incentive produces the larger attitude change.** Too little external justification for the act forces the person to justify it internally by revising the attitude.

CLINICAL ANCHOR

Cognitive dissonance is the mechanism named inside motivational interviewing: the clinician selectively elicits and reflects the patient's own *change talk* so that the discrepancy between current behaviour (drinking, non-adherence) and a valued goal (health, family, self-respect) becomes salient, and the resulting dissonance is resolved in the direction of change rather than of defending the status quo. It also explains "effort justification" in therapy itself: a patient who has invested heavily in treatment is motivated to value its gains.

2.7 Theory three: Bem's self-perception, the rival account

Attitude inferred from behaviour, no inner tension required. Daryl Bem (1967) offered a behaviourist rival to dissonance. His **self-perception theory** proposes that people often do not consult a pre-existing internal attitude at all; instead, like an outside observer, they *infer* their attitude from watching their own behaviour and the circumstances in which it occurred ("I ate the whole salad, so I must like salad"). Applied to the Festinger and Carlsmith result, the small-payment subject observes "I said the task was fun for only a dollar, so I must actually have found it somewhat fun," with no aversive arousal needed. **What it fixed and what it left open.** Self-perception fixed dissonance theory's untestable reliance on an unobservable inner "tension." The debate was settled empirically rather than by one theory winning: dissonance operates when behaviour is clearly *counter-attitudinal* and produces measurable physiological arousal, whereas self-perception better describes attitude formation in *novel or weakly held* domains where no prior attitude exists to be contradicted. Both mechanisms are real; they occupy different regions of the same map.

2.8 Theory four: the Elaboration Likelihood Model (central vs peripheral routes)

Two roads to a changed attitude. Richard Petty and John Cacioppo's **elaboration likelihood** model (1986) is the integrative dual-process theory that reconciled the earlier work and remains the framework of choice. It proposes that persuasion travels one of two routes depending on how much a person is *motivated* and *able* to think about (elaborate) the message.

Central route

Engaged when motivation and ability are high (the issue is personally relevant, the person is undistracted and capable). The recipient effortfully scrutinises the *quality of the arguments*. Attitude change by the **central route** is strong, enduring, resistant to counter-persuasion, and predictive of behaviour.

Peripheral route

Engaged when motivation or ability is low (low involvement, distraction, time pressure). The recipient relies on simple *cues* outside the argument's merit, source attractiveness, expert credentials, message length, sheer number of arguments, or the mood of the moment. Attitude change by the **peripheral route** is weaker, more transient, and easily reversed.

FEATURE	CENTRAL ROUTE	PERIPHERAL ROUTE
Trigger	High motivation *and* ability to think	**Low motivation *or* low ability (distraction, low involvement)**
What is processed	Argument quality, effortful scrutiny (elaboration)	**Peripheral cues: source attractiveness/credibility, message length, number of arguments, mood**
Resulting attitude	Strong, enduring, resistant to counter-persuasion, predicts behaviour	**Weak, transient, easily reversed, poor behaviour prediction**
Parallel model	Systematic processing (Chaiken)	Heuristic processing (Chaiken)

The discriminator is the middle two rows: what the recipient actually processes (arguments vs cues) and how durable the resulting attitude is; the trigger is set by motivation and ability.

What it fixed. The ELM explained the previously puzzling inconsistency of the Yale variables: a peripheral cue such as an attractive source persuades only when elaboration is low, whereas under high elaboration argument quality dominates and the cue fades. It absorbed the Yale taxonomy, dissonance and self-perception into a single account of *when* each process operates. Chaiken's parallel heuristic-systematic model makes the same central distinction between systematic (effortful) and heuristic (cue-based) processing.

2.9 Currently accepted position

Dual-process persuasion and constructed, context-sensitive attitudes. The **currently accepted** synthesis is dual-process: attitude change proceeds through a thoughtful, elaboration-heavy central/systematic route or an automatic, cue-driven peripheral/heuristic route, with the balance set by motivation and cognitive capacity (Petty and Cacioppo 1986). Alongside this, contemporary social cognition treats attitudes not as fixed objects retrieved intact from memory but as *constructed* at the moment of judgement and sensitive to context, framing and momentary accessibility. The field also distinguishes *explicit* attitudes (deliberate, self-reported) from *implicit* attitudes (automatic, activated without intention and measured by reaction-time tasks such as the Implicit Association Test), which can diverge from explicit ones and independently predict spontaneous behaviour.

HOLD THIS

The persuasion arc is Yale to Festinger to Bem to the ELM. External input-output (Yale), then internal-motivation dissonance (Festinger), then a behaviourist rival (Bem's self-perception), resolved into the dual-process ELM (central = argument quality, peripheral = cues).

2.10 Behavioural and neural correlate

Where attitudes predict action, and the neurobiology of dissonance. Behaviourally, the attitude-behaviour link is strongest for accessible, specific, strongly held attitudes, and **implicit attitudes** add predictive power for fast, unmonitored behaviour where explicit attitudes fail. The *neural correlate* of dissonance is beginning to be mapped: functional imaging associates the aversive state of holding inconsistent cognitions, and its resolution, with the *dorsal anterior*

cingulate cortex and *anterior insula* (a conflict- and discomfort-detecting network), while the down-regulation of that signal as the attitude is revised engages *dorsolateral prefrontal cortex*; evaluative attitude signals themselves recruit *ventromedial prefrontal cortex* and the amygdala. These localisations are an emerging literature rather than a settled map, so treat them as direction-of-travel, not as fixed exam facts.

2.11 Worked example: a smoking-cessation campaign

The theories applied to one health-behaviour campaign. Take a district anti-smoking campaign and read it through the whole chain. *Attitude structure (ABC):* the target attitude has a cognitive component (beliefs about harm), an affective component (fear, disgust) and a behavioural component (buying, lighting up). *Attitude-behaviour gap:* a poster that shifts the general belief "smoking is harmful" will not, on LaPiere's lesson, change the specific act unless it also targets intention, injunctive norms ("people I respect disapprove") and perceived control (a quit-line, nicotine replacement). *Yale variables:* a credible source (a respected physician), a two-sided message pre-empting the "but my grandfather smoked to ninety" counter-argument, a moderate fear appeal *coupled with* a concrete coping action, delivered through a channel the audience uses. *Dissonance:* rather than lecturing, have smokers publicly argue the case for quitting to younger peers, the dissonance-based, induced-compliance move, so the discrepancy between their advocacy and their own smoking presses toward change; this is exactly the logic of the dissonance-based Body Project used for eating-disorder prevention (New Oxford Textbook of Psychiatry). *ELM routing:* for a highly involved smoker planning to quit, use the central route with strong argument quality for durable change; for a low-involvement teenager, peripheral cues (an admired influencer, vivid imagery) may be the only lever that lands, accepting that such change is more fragile and needs reinforcement.

INDIA

Persuasion variables are culturally weighted. In much of Indian practice, *source* credibility rests heavily on perceived authority and seniority (the treating consultant, the elder, the community leader), and *norms* are family- and community-level rather than individual, so an adherence or public-health message routed through the family and a trusted authority figure often out-performs an individually addressed appeal. Fear appeals on tobacco and alcohol must be paired with a locally reachable coping action, or they default to denial.

MNEMONIC

"ABC of attitudes; Yale asks Who-What-Which-Whom; dissonance = $1 > $20"

ABC: Affective, Behavioural, Cognitive components. **Yale:** Source (who), Message (what), Channel (which medium), Audience (to whom). **Dissonance direction:** the *smaller* incentive ($1) produces the *larger* attitude change, because low external justification forces internal justification. And for the ELM: *Central = think, Peripheral = cues.*

PEARL

The one-line arc for an examiner: the field moved from an external, input-output account of persuasion (Yale) to an internal-motivation account (Festinger's dissonance), met a behaviourist rival (Bem's self-perception), and resolved both into a dual-process model (Petty and Cacioppo's ELM, central versus peripheral) that specifies *when* each earlier mechanism operates. Name that sequence and you have framed the entire topic.

GOOD TO REMEMBER

- **Attitude (ABC model):** a learned evaluative disposition with Affective, Behavioural and Cognitive components.
- **Attitude formation:** classical conditioning, operant conditioning, social/observational learning (Bandura); mere-exposure effect; Katz's functions (knowledge, instrumental, ego-defensive, value-expressive).
- **LaPiere (1934):** Chinese-couple field study; expressed attitude (prejudice) discordant with actual behaviour (service given). The attitude-behaviour gap.
- **Ajzen and Fishbein:** theory of reasoned action / planned behaviour; attitudes predict behaviour via intention, norms and perceived control.
- **Yale / Hovland approach:** persuasion as message-learning; Source, Message, Channel, Audience; sleeper effect; fear-appeal calibration.
- **Festinger (1957):** cognitive dissonance; aversive tension from inconsistent cognitions drives attitude change; doomsday-cult origin; now a self theory (Aronson et al. 2007).
- **Festinger and Carlsmith (1959):** induced compliance, the $1 > $20 study; smaller incentive, larger attitude change.
- **Aronson and Mills (1959):** effort justification; severe initiation raises valuation of the group.
- **Post-decision dissonance:** spreading of alternatives after a hard choice.
- **Bem (1967):** self-perception theory; attitude inferred from own behaviour, no inner tension; rival to dissonance, better for novel/weak attitudes.
- **Petty and Cacioppo (1986):** elaboration likelihood model; central route (argument quality, high elaboration, durable) vs peripheral route (cues, low elaboration, transient); Chaiken's heuristic-systematic parallel.
- **Currently accepted:** dual-process persuasion; attitudes as constructed and context-sensitive; explicit vs implicit attitudes (Implicit Association Test).
- **Neural correlate (emerging):** dissonance signalled by dorsal anterior cingulate cortex and anterior insula; resolution via dorsolateral prefrontal cortex; evaluative attitude signals in ventromedial prefrontal cortex and amygdala.
- **Clinical use:** motivational interviewing exploits dissonance via change talk; dissonance-based prevention (Body Project) for eating disorders (New Oxford).

3 · Attribution theory and social cognition

Two questions, one machinery. **Social cognition** is the umbrella: how we perceive, encode, store, retrieve and use information about people and social situations, running largely on **schemas** (organised knowledge structures for persons, roles and events) and cognitive short-cuts called **heuristics**. **Attribution** is the best-studied slice of it: the process by which people explain the causes of behaviour and events, deciding whether an act sprang from the person (disposition) or from the situation. For the exam this topic is a clean historical spine (Heider to Weiner) that ends in a set of named **attribution biases**, and it is examined both as pure psychology and as the

cognitive substrate of depression (attributional style), paranoia (personalising bias) and prejudice (Kaplan & Sadock 2024; Tasman 2015).

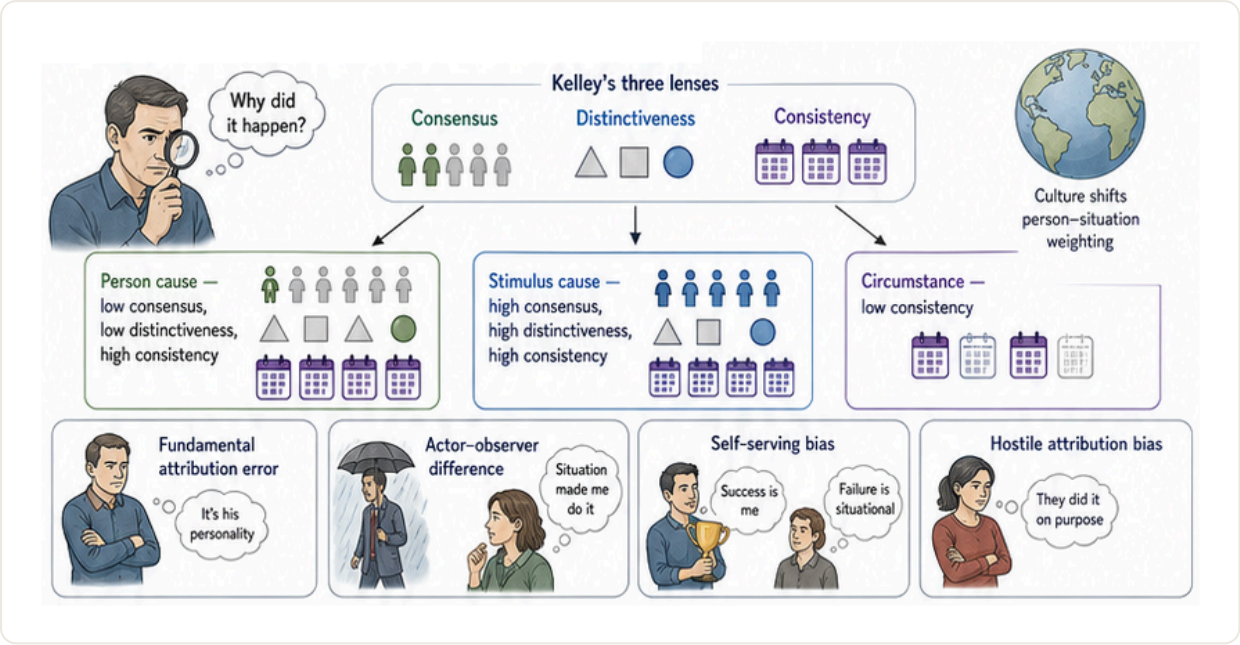


Fig 5.2 Attribution: how we infer causes.

The spine runs in strict date order, each theory fixing a gap left by the last: **Heider (1958)** named the person-versus-situation split; **Jones and Davis (1965)** asked when we may read a disposition off a single act; **Kelley (1967)** asked how we combine information across situations; **Weiner (1974)** re-cut attributions along abstract dimensions for achievement and emotion. The **currently accepted** position is not a further grand theory but the recognition that these normative models are systematically distorted by predictable errors, the attribution biases, whose neural substrate sits in the social-cognition (mentalizing) network. Because this topic names dated theorists, dimensions and hard classifications of bias, it closes with a good-to-remember box enumerating every one (Kaplan & Sadock 2024; Tasman 2015).

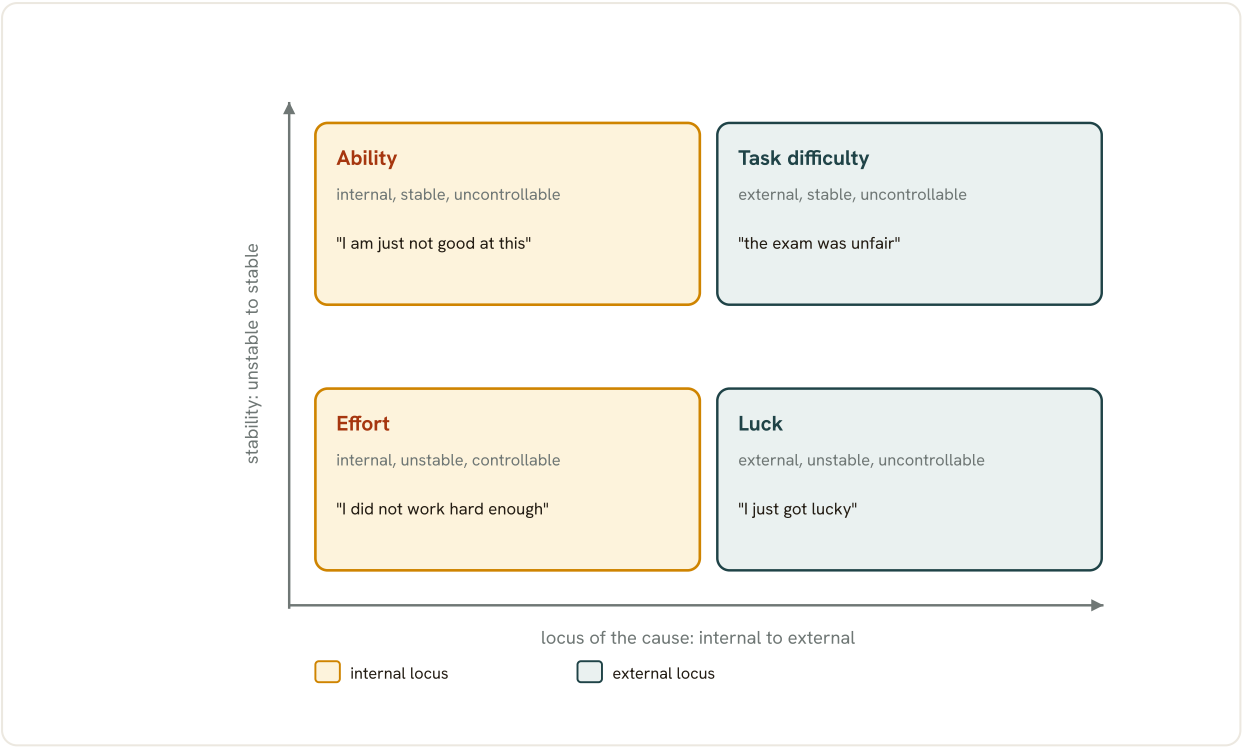


Fig 5.3 Weiner's dimensional model of attribution, shown on two of its axes: whether the cause is inside the person (internal) or outside (external), and whether it is stable or unstable across time. The four classic achievement attributions fall into the cells: ability (internal, stable), effort (internal, unstable), task difficulty (external, stable) and luck (external, unstable). A third axis, controllability, cuts across these: effort is controllable while ability and luck are not, which is why effort attributions carry the most motivational weight. Colour codes the locus: marigold for internal causes, petrol for external.

3.1 Social cognition: the frame the theories live inside

Attribution is one operation within social cognition, so define the frame first. Social cognition is the study of how people make sense of themselves and others: perceiving faces and emotions, inferring intentions and mental states (theory of mind), forming and applying impressions, and choosing behaviour on that basis. It is not a blank-slate computation. Incoming social data is filtered through **schemas**, pre-existing mental templates (a person schema, a role schema, a self-schema, an event schema or *script*) that let us fill gaps and predict, at the cost of stereotyping and confirmation bias. Because full rational analysis of every social act is impossible, the mind leans on **heuristics**, fast rules of thumb (representativeness, availability, anchoring), and on **dual-process** operation: fast, automatic, effortless System 1 judgements versus slow, controlled, effortful System 2 reasoning (Kahneman's framing, the modern default account). Attribution is precisely the schema-and-heuristic-driven machinery we use to answer one recurring social question: *why did that happen?* (Kaplan & Sadock 2024).

3.2 Heider (1958): naive psychology and the person-situation split

The founding move: treat the ordinary person as an intuitive scientist. Fritz Heider's *The Psychology of Interpersonal Relations* (1958) launched attribution theory with the idea of **naive** (or common-sense) **psychology**: everyday people continuously seek the causes of behaviour and do so with an implicit, lay causal theory. Heider's core distinction, which every later model inherits, is between **internal (personal or dispositional)** causes located in the actor (ability, effort, personality, mood) and **external (situational or environmental)** causes located outside the

actor (task difficulty, luck, social pressure, circumstance). Heider observed that perceivers tend to see behaviour as flowing from the person and to under-weight the situation, planting the seed of what would later be called **correspondent inference** and the fundamental attribution error. What he left debated: *when* and *how* the perceiver actually decides between the two, which the next theories set out to specify (Heider 1958; Kaplan & Sadock 2024).

3.3 Jones and Davis (1965): correspondent inference theory

What it fixed: it specified when a single act licenses a dispositional inference. Edward Jones and Keith Davis proposed **correspondent inference** theory: an observer makes a *correspondent* inference when they conclude that a behaviour corresponds to a stable underlying disposition (a hostile act means a hostile person). Their contribution was to list the conditions under which such an inference is warranted. It is stronger when the behaviour is *freely chosen* (not coerced), when it produces **non-common effects** (outcomes unique to that choice and not shared by the alternatives, which narrow down the actor's real motive), and when it is *low in social desirability* (unexpected, norm-violating behaviour is more informative about the person than conventional behaviour, since anyone would do the conventional thing). Hedonic relevance (the act affects the perceiver) and personalism (it seems aimed at the perceiver) further strengthen the dispositional reading. What it left debated: it handled inference from a *single* episode but said little about how we integrate information across *many* occasions, which Kelley then addressed (Jones & Davis 1965; Kaplan & Sadock 2024).

3.4 Kelley (1967): the covariation model and causal schemata

What it fixed: it gave a rule for combining information across situations and time. Harold Kelley's **covariation** model treats the lay perceiver as an intuitive statistician who attributes an effect to the cause with which it *covaries*. Given multiple observations, the perceiver weighs three kinds of information:

Consensus

Do *other people* behave the same way toward this stimulus? High consensus (everyone reacts this way) points *away* from the actor, toward the stimulus or situation.

Distinctiveness

Does this actor behave this way *only* toward this stimulus, or toward many stimuli? High distinctiveness (only this stimulus) points toward the stimulus; low distinctiveness (the actor does it to everything) points toward the person.

Consistency

Does the actor behave this way toward this stimulus *across time and settings*? High consistency is a precondition for a confident attribution of either kind; low consistency drives attribution to transient circumstance.

The classic pattern: high consensus + high distinctiveness + high consistency yields an *external (stimulus)* attribution ("the film really is funny, everyone laughs, he laughs only at it, and every time"); low consensus + low distinctiveness + high consistency yields an *internal (person)* attribution ("only he laughs, he laughs at everything, and always, so it is him"). When information is incomplete (a single observation), Kelley proposed that perceivers fall back on stored **causal**

schemata: pre-formed beliefs about how causes combine, such as the discounting principle (the role of a given cause is discounted if other plausible causes are present) and the augmentation principle (a cause is upgraded when it produces an effect despite an opposing force). What it left debated: covariation describes the ideal normative computation but not the systematic ways real perceivers deviate from it, nor the emotional consequences of attributions, which Weiner took up (Kelley 1967; Kaplan & Sadock 2024).

RULE **An external (stimulus) attribution needs all three Kelley cues high: consensus, distinctiveness and consistency.** Low consensus plus low distinctiveness plus high consistency points instead to the person.

3.5 Weiner (1974 onward): the dimensional model of achievement attributions

What it fixed: it abstracted attributions into dimensions and linked them to emotion, expectancy and motivation. Bernard Weiner reframed the field for *achievement* situations (success and failure at a task). Rather than cataloguing specific causes (ability, effort, task difficulty, luck), he classified any cause along orthogonal dimensions:

Locus (of causality)

Locus internal versus external: is the cause inside the person (ability, effort) or outside (task difficulty, luck)? Governs self-esteem and pride: internal success feels good, internal failure wounds.

Stability

Stability stable versus unstable: is the cause enduring (ability, task difficulty) or variable (effort, mood, luck)? Governs *expectancy* of future outcomes: a failure attributed to a stable cause predicts continued failure and breeds hopelessness; an unstable cause leaves hope.

Controllability

Controllable versus uncontrollable: could the person have altered the cause (effort is controllable; innate ability and luck are not)? Governs social emotions such as guilt, shame, anger, and pity, and others' willingness to help.

Crossing locus and stability gives Weiner's canonical two-by-two: *ability* (internal, stable), *effort* (internal, unstable), *task difficulty* (external, stable), and *luck* (external, unstable). This model is the bridge from attribution to clinical psychiatry: the *reformulated learned-helplessness* theory of depression (Abramson, Seligman and Teasdale 1978) holds that a depressogenic **attributional style** explains bad events by internal, stable, global causes ("it is me, it always will be, it ruins everything"), directly borrowing Weiner's locus and stability axes (Weiner 1985; Tasman 2015; Kaplan & Sadock 2024). What it left debated: like its predecessors it is a *normative* account of how attributions should be made and what they cause, which set up the corrective era of documented biases.

3.6 The currently accepted position: attribution is systematically biased

The modern consensus is not a new grand theory but a catalogue of predictable errors. The **currently accepted** view is that the elegant normative models above (correspondent inference, covariation, dimensional analysis) describe an ideal the mind rarely meets: real attribution is fast,

motivated and schema-driven, and it deviates in reliable directions. These are the **attribution biases**, and they are the highest-yield part of the topic.

GOOD TO REMEMBER

- **Fundamental attribution error (FAE):** the pervasive tendency, when explaining *others'* behaviour, to over-attribute it to disposition and under-weight the situation (also called correspondence bias; Ross 1977; Gilbert & Malone 1995).
- **Actor-observer asymmetry:** we explain *our own* behaviour situationally ("I snapped because the day was awful") but *others'* behaviour dispositionally ("he snapped because he is aggressive"); driven partly by differing perceptual focus and by richer self-knowledge (Jones & Nisbett 1972).
- **Self-serving bias:** we attribute our *successes* to internal, dispositional causes (ability, effort) and our *failures* to external causes (bad luck, unfair task), protecting self-esteem; its reversal (internal for failure, external for success) marks the depressive attributional style.
- **Just-world bias / hypothesis:** the belief that the world is fair, so people get what they deserve; leads to victim-blaming (Lerner).
- **False-consensus bias:** we over-estimate how far others share our own attitudes, choices and behaviour, treating our own view as the norm (Ross).

BIAS	WHOSE BEHAVIOUR	DIRECTION OF THE ERROR	FUNCTION OR DRIVER
Fundamental attribution error	Other person	**Over-weights disposition, under-weights situation**	Actor is the perceptual figure; automatic dispositional inference
Actor-observer asymmetry	Self vs other	**Self = situational, other = dispositional**	Different visual focus; more knowledge of one's own constraints
Self-serving bias	Self	**Success = internal, failure = external**	Self-esteem protection (motivational)
Just-world bias	Victim / other	**Blames the victim for their misfortune**	Need to believe outcomes are deserved and the world controllable
False-consensus bias	Self projected onto others	**Over-estimates how many share one's view**	Own position is cognitively available as the anchor

The five exam-standard attribution biases: what target they distort, the direction of the distortion, and why it happens (Kaplan & Sadock 2024; Tasman 2015).

HOLD THIS

The spine is Heider to Jones-Davis to Kelley to Weiner, and the modern answer is not a fifth theory but the biases. The reversed self-serving bias (failure read as internal, stable and global) is the depressive signature.

COMMON TRAP

Do not merge the **actor-observer** asymmetry with the **self-serving** bias. Actor-observer is about the *self-versus-other* contrast regardless of outcome (I am situational, you are dispositional). Self-serving is about the *success-versus-failure* contrast within the self (my wins are me, my losses are the world). They can be dissociated: the depressive shows a *reversed* self-serving bias (failure attributed internally, stably and globally) while the actor-observer pattern may persist. The **fundamental attribution error** is specifically about explaining *others*; it is not a self-versus-other contrast on its own.

3.7 Neural correlate: the social-cognition (mentalizing) network

Attribution has a definable neurobiology within the wider social brain. The **neural correlate** of attributing mental states and causes to others is the *mentalizing* or theory-of-mind network, whose reliably implicated nodes are the *medial prefrontal cortex*, the bilateral *temporo-parietal junction* (especially the right TPJ, engaged when representing another's beliefs and intentions), the *posterior superior temporal sulcus* (reading biological motion and gaze), the *precuneus and posterior cingulate*, and the *temporal poles* (social-semantic knowledge). The *amygdala* and *fusiform face area* feed the rapid, affective appraisal of faces and threat that biases attribution before deliberate reasoning engages. In psychiatry these systems are the substrate of the **social cognition** deficits catalogued in schizophrenia (impaired theory of mind, a *personalising* attributional bias that over-attributes negative events to other people rather than to circumstances, and jumping-to-conclusions), and they are the explicit target of Social Cognition and Interaction Training (SCIT) (Roberts, Penn & Combs 2016; Kaplan & Sadock 2024).

3.8 Culture: attribution is not universal

The fundamental attribution error is partly a Western phenomenon. A major qualification to the whole tradition is cross-cultural: people from *individualist* (typically Western) cultures, which foreground the autonomous person, show a stronger dispositional bias and a more robust fundamental attribution error, whereas people from *collectivist* (many East Asian and South Asian) cultures, which foreground the group, relationships and context, attribute behaviour more readily to *situational* and relational causes and show a weaker FAE. The self-serving bias is likewise attenuated, and sometimes a *self-effacing* pattern appears, in collectivist settings where modesty is normative. The lesson for the exam and for Indian practice is that the "fundamental" error is not a fixed feature of human cognition but is shaped by culturally transmitted models of the person (Nisbett and colleagues; Kaplan & Sadock 2024).

INDIA

India is a broadly collectivist, family-embedded context, and this reshapes attribution in the clinic. Distress is often explained through situational, relational and supernatural or karmic frames (family conflict, evil eye, planetary influence, fate) rather than through internal, dispositional or biomedical ones. A clinician who reads a patient's situational explanation as denial, or who imposes a Western dispositional-illness model, will mis-attune. It also predicts a softer fundamental attribution error in how families explain a relative's behaviour: an act is more likely read as caused by circumstances and relationships than by fixed character, which can protect the patient from blame but can also delay recognition of illness.

3.9 Worked example: reading one late arrival five ways

Run one everyday event through the whole apparatus. A colleague, Ravi, arrives thirty minutes late to a meeting you are chairing.

Heider

You immediately sort the cause into internal (Ravi is careless, disorganised) or external (the traffic, a prior emergency). The pull toward the internal reading is Heider's seeded observation.

Jones and Davis

If Ravi *freely* chose to leave home late and lateness is socially undesirable, you make a correspondent inference: he is an unreliable person. If he was ordered to finish another task first (coerced, low choice), the inference weakens.

Kelley (covariation)

You consult three streams. Consensus: do others also arrive late to *your* meetings (high consensus points to your meeting or its timing, an external cause)? Distinctiveness: is Ravi late only to this meeting or to everything (low distinctiveness points to Ravi)? Consistency: is he late to this meeting every week (high consistency licenses a firm attribution)? Low consensus + low distinctiveness + high consistency yields "it is Ravi."

Weiner

If you frame lateness as a performance failure, you locate its cause by **locus** and **stability**: "lazy" (internal, stable) predicts he will always be late and invites anger; "stuck in unusual traffic" (external, unstable) predicts nothing and invites sympathy. Controllability decides whether you feel anger (he could have left earlier) or pity (he could not).

The biases (currently accepted)

The **fundamental attribution error** makes you leap to "Ravi is unreliable" and ignore the flooded road. The **actor-observer** asymmetry means that when *you* were late last week you blamed the traffic, but when Ravi is late you blame Ravi. Had it been *your* lateness excused by traffic and *your* punctuality credited to your discipline, that is the **self-serving** bias. If you assume most people would judge Ravi as harshly as you do, that is false-consensus; if you conclude he "deserves" the reputational cost, that edges toward just-world thinking. In a collectivist frame, a colleague may instead default to "something must have happened at home," a situational reading and a softer FAE.

PEARL

If four things survive into the exam: (1) the *date-ordered spine* Heider (person vs situation) to Jones and Davis (correspondent inference from one act) to Kelley (covariation: consensus, distinctiveness, consistency) to Weiner (locus, stability, controllability); (2) Kelley's rule that *external* attribution needs high consensus + high distinctiveness + high consistency; (3) the five biases, with the *fundamental attribution error* as the flagship and the reversed self-serving bias as the depressive signature; (4) that the FAE is culturally softened in collectivist settings.

MNEMONIC

Kelley = CDC (Consensus, Distinctiveness, Consistency)

The three covariation cues, read like the disease-control acronym so it sticks. Pair it with the external-attribution rule "**all three high** (consensus + distinctiveness + consistency) points **out** to the stimulus." For Weiner, remember the two-by-two by its four cells: **A**bility, **E**ffort, **T**ask difficulty, **L**uck ("AETL"), read as internal-stable, internal-unstable, external-stable, external-unstable.

GOOD TO REMEMBER

- **Social cognition:** how we perceive, store and use social information; runs on schemas, heuristics and dual-process (System 1 automatic / System 2 controlled) cognition.
- **Attribution:** the sub-process of explaining the causes of behaviour, internal (dispositional) versus external (situational).
- **Heider (1958):** naive (common-sense) psychology; person-versus-situation split; seeded correspondent inference and the FAE.
- **Jones and Davis (1965):** correspondent inference theory; a dispositional inference is warranted when behaviour is freely chosen, has non-common effects, and is low in social desirability.
- **Kelley (1967):** covariation model; three cues = consensus, distinctiveness, consistency; external attribution needs all three high; causal schemata with discounting and augmentation principles for incomplete data.
- **Weiner (1974 onward):** dimensional model of achievement attribution; locus (internal/external), stability (stable/unstable), controllability; four cells = ability, effort, task difficulty, luck; locus drives self-esteem, stability drives expectancy, controllability drives social emotion.
- **Attributional style (Abramson, Seligman, Teasdale 1978):** depressogenic style attributes bad events to internal, stable, global causes (reformulated learned helplessness).
- **Fundamental attribution error (Ross 1977):** over-attributing others' behaviour to disposition; also called correspondence bias (Gilbert & Malone 1995).
- **Actor-observer asymmetry (Jones & Nisbett 1972):** self explained situationally, others dispositionally.
- **Self-serving bias:** success internal, failure external (self-esteem protection); reversed in depression.
- **Just-world bias (Lerner):** belief the world is fair, so victims must deserve their fate; drives victim-blaming.
- **False-consensus bias (Ross):** over-estimating how far others share one's own views.
- **Currently accepted:** the normative models are systematically distorted by these biases; attribution is fast, motivated and schema-driven.
- **Neural correlate:** mentalizing (theory-of-mind) network = medial prefrontal cortex, temporo-parietal junction (esp. right TPJ), posterior superior temporal sulcus, precuneus/posterior cingulate, temporal poles; amygdala and fusiform face area for rapid affective appraisal.
- **Clinical link:** personalising attributional bias and theory-of-mind deficits in schizophrenia; target of SCIT.
- **Culture:** individualist cultures show a stronger FAE and self-serving bias; collectivist cultures attribute more situationally and show a weaker FAE (Nisbett).

4 · Group dynamics: conformity, obedience and group processes

Why this matters. Social psychology studies the **typical** forces that govern how the social world shapes behaviour, where clinical psychiatry studies the atypical (Tasman 2015). Its central lesson, running from Sherif through Milgram, is that much of what looks like character is actually **situational**: ordinary people conform, obey and diffuse responsibility when the situation pulls for it. This is the counterweight to the **fundamental attribution error** (over-crediting internal traits), and it is why a psychiatrist reads a patient's behaviour against its social field, not only against personality.

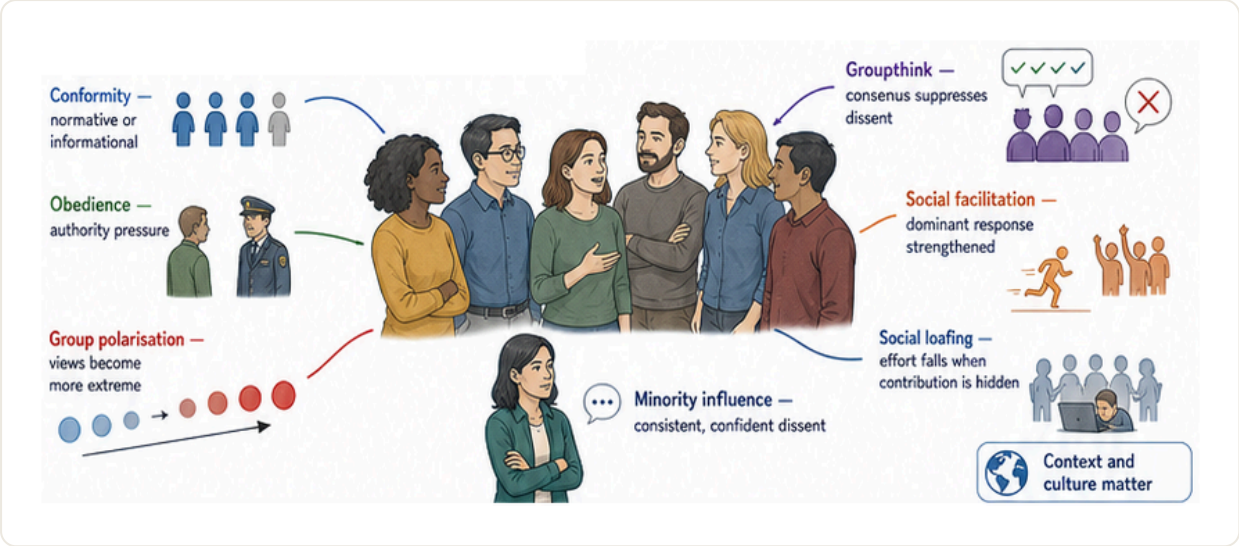


Fig 5.4 Social influence in groups.

The topic is a reliable exam staple: examiners want the **named experiment** matched to the **named mechanism** (Asch to normative influence, Milgram to the agentic state, Janis to groupthink, Zajonc to social facilitation). Build the answer as a spine of classic studies in the order they appeared, then close with the currently accepted situationist synthesis and its neural correlate.

4.1 What a group is: norms, roles, cohesion

A **group** is two or more people who interact, are interdependent, share goals and perceive themselves as a unit (a distinction from a mere aggregate, such as a bus queue). Three structural properties organise it and generate all the phenomena below.

Norms

Shared, often implicit rules about how members should behave and think; the reference point people default to when a situation is ambiguous.

Roles

Expected patterns of behaviour attached to a position in the group (leader, scapegoat, guard, prisoner); powerful enough to override individual disposition.

Cohesion

The sum of forces binding members to the group and to one another. Moderate cohesion aids function; excessive cohesion breeds loss of individuality, seen as fusion, contagion and groupthink (Tasman 2015).

Status and communication structure

The hierarchy of prestige and the channels through which information flows; both shape who conforms to whom.

4.2 Conformity, era 1: Sherif and the birth of a norm

Sherif, autokinetic effect (1935). A stationary pinpoint of light in a dark room appears to move (an **autokinetic** illusion). Asked individually how far it moved, people gave idiosyncratic estimates; placed in groups, their estimates **converged on a shared group norm** that then persisted when they were tested alone again. Sherif showed that in a genuinely ambiguous

situation a norm is **internalised**, not merely complied with. What it **fixed**: it demonstrated norm *formation* experimentally. What it **left debated**: because the stimulus was ambiguous, it could not tell us whether people would conform against the plain evidence of their own eyes. That question is Asch's.

4.3 Conformity, era 2: Asch and the line-judgement studies

Asch, line-judgement paradigm (1950s). A naive participant judged which of three comparison lines matched a standard, a task with an **unambiguous** correct answer, while a group of confederates unanimously gave the wrong answer on set trials. Roughly a third of naive responses went along with the majority, and about three-quarters of participants conformed at least once, while a control group erred almost never. Asch proved that people will publicly deny plain perceptual evidence under group pressure. Two mechanisms were later separated (Deutsch and Gerard 1955).

Normative influence
Conforming to be liked or accepted and to avoid rejection; produces public compliance without private belief change. Dominant in Asch, where the answer was obvious.

Informational influence
Conforming because others are treated as a source of valid information; produces private acceptance. Dominant in Sherif, where the answer was ambiguous.

Factors that raise conformity: unanimity of the majority; larger majority size up to about three or four, after which it plateaus; higher group cohesion and attractiveness; task difficulty or ambiguity; public rather than private responding; lower individual status or expertise. **Factors that lower it:** a single dissenting ally who breaks unanimity (the strongest single reducer); private or anonymous responding; higher personal competence on the task; and cultural individualism relative to collectivism.

~1/3	~75%	3-4
OF RESPONSES CONFORMED (ASCH)	CONFORMED AT LEAST ONCE	MAJORITY SIZE WHERE EFFECT PLATEAUS

RULE **A single dissenting ally who breaks unanimity is the strongest single reducer of conformity.** It is unanimity, not sheer numbers, that does most of the pressing.

COMMON TRAP
Sherif is *not* the same as Asch. Sherif used an **ambiguous** stimulus and demonstrated **informational** influence with genuine norm internalisation; Asch used an **unambiguous** stimulus and demonstrated **normative** influence with mere public compliance. Examiners deliberately swap the two.

4.4 Obedience: Milgram and the shock experiments

Milgram, obedience to authority (1963 onward; Milgram 1974). Prompted by the trial of Adolf Eichmann and Arendt's thesis that the Holocaust's perpetrators were ordinary bureaucrats rather than sadistic monsters (Tasman 2015), Milgram tested how far ordinary people would go

under instruction. A participant, cast as "teacher," was ordered by an experimenter to deliver escalating "electric shocks" to a "learner" (a confederate) for wrong answers. A striking majority continued to the maximum voltage when told to do so by the authority figure, and none of the minority who refused insisted the study be stopped or checked on the victim (Tasman 2015). Obedience is **compliance with a direct order from a perceived authority**, and is distinct from conformity to peers.

Milgram's two explanations (Tasman 2015): first, *conformism* from a lack of a reference point about how to behave in an unfamiliar situation; second, and central, **agentic state** theory. In the agentic state the obedient person redefines himself as an **instrument carrying out another's wishes** and feels minimal personal responsibility for the outcome. A contemporary parallel is **moral disengagement**, documented in prison guards assigned to execution teams (Osofsky, Bandura and Zimbardo 2005).

Situational factors that changed obedience rates: *proximity of the victim* (obedience fell as the learner became more physically present, and fell sharply when the teacher had to press the learner's hand onto a plate); *proximity and presence of the authority* (obedience dropped when the experimenter gave orders by telephone rather than in the room); *legitimacy of the authority* (a prestigious institutional setting raised obedience; an ordinary setting or an ordinary-man "experimenter" lowered it); and the presence of *disobedient peers*, whose defiance freed the participant to refuse. The lineage runs back to the **authoritarian personality** construct (Adorno et al. 1950), which had tried, less successfully, to locate obedience in a trait rather than the situation.

4.5 Roles, deindividuation and the Stanford prison experiment

Zimbardo, Stanford prison experiment (1971). Screened, ordinary young men were randomly assigned to be "guards" or "prisoners" in a simulated prison. Guards rapidly became abusive and prisoners passive and distressed, and the study, planned for two weeks, was halted early. Zimbardo read it as evidence of the **power of situations and assigned roles** to transform behaviour, mediated by **deindividuation**: a loss of individual self-awareness and self-restraint under anonymity, uniforms and group immersion, which lowers accountability and releases behaviour the person would not otherwise show. The same construct underlies the aggression of anonymous crowds.

COMMON TRAP

Modern critique, stated soberly: the Stanford study is now read cautiously. It had **no control condition**, a tiny non-representative sample, and, on later evidence, the experimenter and guards were **coached and led** toward the cruel behaviour rather than it emerging spontaneously; some guard conduct appears to have been demand characteristics and performance. Cite it as a *demonstration and a cautionary tale about roles and situational power*, not as clean experimental proof. Milgram, with its manipulated variables and control comparisons, is the sturdier evidence of situational power.

4.6 Group decision processes: polarisation and groupthink

Groups do not simply average their members' views; they systematically shift them.

Group polarisation

After discussion, a group's decision becomes **more extreme in the direction the members already leaned** (the older "risky shift" is one instance, but caution can be amplified too). Driven by informational influence (hearing more arguments on the favoured side) and normative influence (aligning with the group's valued position).

Groupthink (Janis 1972)

A mode of thinking in **highly cohesive, insulated groups under directive leadership and stress**, where the drive for unanimity overrides realistic appraisal of alternatives, degrading decision quality. Janis drew it from foreign-policy fiascos (the Bay of Pigs is the classic case).

Janis's symptoms of groupthink cluster into three groups: *overestimation of the group* (an illusion of invulnerability; belief in the group's inherent morality); *closed-mindedness* (collective rationalisation; stereotyping of outgroups and opponents); and *pressure toward uniformity* (self-censorship of doubts; a shared illusion of unanimity; direct pressure on dissenters; and self-appointed **mindguards** who shield the group from discordant information). Antidotes: a designated devil's advocate, leaders withholding their own view early, and inviting outside critique.

4.7 Presence of others: social facilitation and social loafing

Social facilitation (Zajonc 1965). The mere presence of others (as audience or co-actors) raises **arousal**, which strengthens the **dominant response**. The consequence depends on the task: on *easy or well-learned* tasks the dominant response is correct, so performance **improves**; on *difficult or novel* tasks the dominant response is often wrong, so performance **worsens**. This drive-arousal account resolved a century of contradictory audience findings into one rule.

Social loafing. When individual contributions are **pooled and cannot be identified**, people exert less effort than when working alone (the effect first noted in group rope-pulling). It is the near-opposite of facilitation, driven by the same diffusion logic as the bystander effect: identifiability, evaluation and personal accountability all reduce it.

4.8 Minority influence: how the few change the many

Moscovici (1969 onward). Against the majority-centred tradition above, Moscovici showed that a **consistent, confident minority** can convert the majority. The critical variable is **behavioural consistency** over time and across members; a wavering minority has no effect. Minority influence tends to produce **conversion** (genuine, often private and delayed attitude change through informational processing) rather than the surface **compliance** that majorities extract. This is the mechanism behind social innovation and the slow success of dissenting movements.

4.9 Currently accepted position and its neural correlate

The **currently accepted** synthesis is **situationism** tempered by interactionism: behaviour is a joint product of person and situation, but classic social psychology corrected a durable bias by showing how strongly the situation pulls, and how routinely observers underweight it (the

fundamental attribution error). Modern work reframes conformity within **social-identity** and self-categorisation theory (people conform to norms of groups they identify with, not to strangers indiscriminately) and within dual-process models separating fast normative alignment from slower informational persuasion.

HOLD THIS

Match each named study to its named mechanism: Asch to normative influence, Milgram to the agentic state, Zimbardo to deindividuation, Janis to groupthink, Zajonc to social facilitation, Moscovici to minority conversion. Much that looks like character is situation.

Neural correlate. Conformity has a measurable **neurobiology**. When a person's judgement conflicts with the group, activity in the **posterior medial frontal cortex / dorsal anterior cingulate** and **anterior insula** tracks the "social prediction error," the felt cost of deviating; the size of this signal predicts subsequent conforming. Reward circuitry, the **ventral striatum and ventromedial prefrontal cortex**, updates value toward the group's position when one aligns, giving conformity the signature of reinforcement learning. Obedience and moral disengagement engage reduced **medial prefrontal** self-agency signalling, consistent with the agentic state (the sense of acting as another's instrument). These are localisation claims to verify against a current source before quoting in a viva.

4.10 Worked example and the clinical read

Everyday. A junior doctor on a ward round privately doubts a senior's plan but stays silent (Asch normative pressure and Milgram's legitimate authority), the team's shared confidence hardens into an illusion of unanimity (groupthink), and no one calls the near-miss because "someone senior will have checked" (diffusion of responsibility). The fix is structural: name a devil's advocate, invite the most junior view first, and make each check individually accountable.

CLINICAL ANCHOR

Group phenomena are the working material of **group psychotherapy**: cohesion is a curative factor (Kaplan and Sadock 2024), but the same cohesion can tip into pretend-mode groupthink where patients answer for one another and stop mentalising (Bateman and Fonagy). Ward culture, family systems and treatment teams all show conformity, role capture and diffusion, and the clinician's job is often to restore individual accountability and dissent.

INDIA

In hierarchical, collectivist and family-centred settings, normative conformity and deference to authority (senior clinician, elders, the joint family) run high, which raises both helpful cohesion and the risk of unspoken dissent in consent and treatment decisions. Explicitly soliciting the quietest voice and separating family consensus from the patient's own view is a practical counter to culturally amplified groupthink.

MNEMONIC

SAME ZOO: Groups Just Zap Loafers, Minorities Convert

Sherif (norm formation), **A**sch (conformity), **M**ilgram (obedience), **E**ffect-bystander (Latané and Darley), **Z**imbardo (roles), **ZOO** reminds you these are the caged classics. Then the processes: **G**roup polarisation, **J**anis (groupthink), **Z**ajonc (social facilitation), **L**oafing, **M**oscovici (minority conversion).

GOOD TO REMEMBER

- **Group:** interacting, interdependent, shared-goal unit; structured by norms, roles, cohesion, status.
- **Sherif (1935), autokinetic effect:** ambiguous stimulus, group norm forms and is internalised; informational influence.
- **Asch (1950s), line judgement:** unambiguous stimulus, about a third of responses conform, roughly three-quarters conform at least once; normative influence.
- **Normative vs informational influence (Deutsch and Gerard 1955):** to be accepted (public compliance) vs to be correct (private acceptance).
- **Conformity raisers:** unanimity, majority size to about three, cohesion, ambiguity, public response; single ally is the strongest reducer.
- **Milgram (1974), shock experiments:** majority obey an authority to maximum shock; obedience is compliance with an order, not peer conformity.
- **Agentic state:** obedient person feels an instrument of another's will, minimal own responsibility.
- **Milgram situational factors:** victim proximity, authority proximity and legitimacy, and disobedient peers all move obedience.
- **Authoritarian personality (Adorno et al. 1950):** earlier trait account of blind acceptance of authority, superseded by the situationist reading.
- **Zimbardo (1971), Stanford prison:** roles and situational power; deindividuation; modern critique = no control, coached guards, demand characteristics.
- **Deindividuation:** loss of self-awareness and restraint under anonymity, releasing disinhibited behaviour.
- **Group polarisation:** discussion pushes the group further in its pre-existing direction (risky shift is one case).
- **Groupthink (Janis 1972):** cohesive, insulated, stressed group sacrifices appraisal for unanimity; symptoms = invulnerability, rationalisation, out-group stereotyping, self-censorship, illusion of unanimity, pressure on dissenters, mindguards.
- **Social facilitation (Zajonc 1965):** mere presence raises arousal, boosts easy tasks, impairs hard ones (dominant-response rule).
- **Social loafing:** reduced effort when contributions are pooled and unidentifiable; countered by accountability.
- **Minority influence (Moscovici 1969):** a consistent minority produces conversion (deep, private change), not mere compliance.
- **Bystander effect and diffusion of responsibility (Latané and Darley 1970):** less helping when others are present; belongs with prosocial and aggression behaviour (see the aggression and prosocial behaviour topic), cross-referenced here.
- **Situationism (currently accepted):** behaviour = person plus situation; fundamental attribution error over-weights traits; neural correlate in dorsal anterior cingulate, anterior insula and ventral striatum for conformity.

5 · Prejudice, stereotypes and intergroup relations

Why this sits on the exam spine. Intergroup psychology is the social-psychology chapter that maps directly onto the clinician's daily reality: the **stigma** of mental illness is, mechanically, prejudice applied to a psychiatric out-group. Examiners want the clean triad (thought, feeling, action), the named theories in the order they emerged, and the one intervention with the strongest evidence base behind it (the contact hypothesis). Answer it as an evolution of theories, each fixing the previous one's blind spot, and land it on the stigma application.

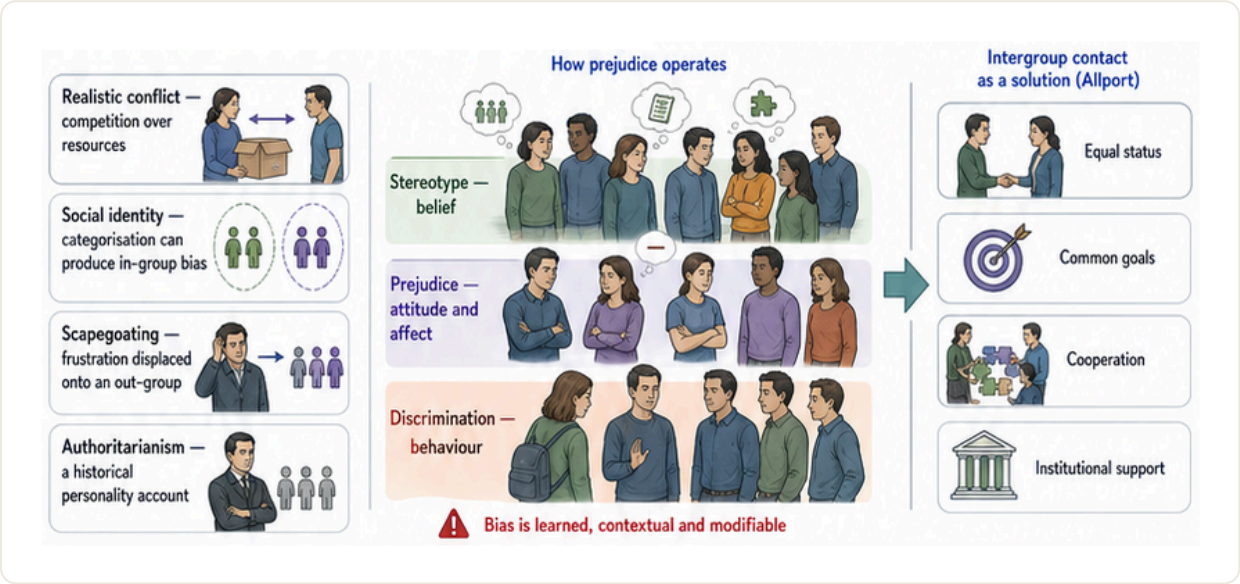


Fig 5.5 Prejudice and intergroup relations.

The organising move is to separate three things that lay usage blurs. A **stereotype** is a belief, a **prejudice** is a feeling or attitude, and **discrimination** is a behaviour. They correlate but dissociate: a clinician can hold an accurate-seeming stereotype without hostile affect, or feel prejudice yet not discriminate when institutional rules forbid it. Keeping the three levels distinct is what turns a vague answer into a scorable one (Kaplan & Sadock 2024).

5.1 The triad: stereotype, prejudice, discrimination

Three levels, one target group. The cognitive, affective and behavioural components of an intergroup attitude. Allport (1954) framed prejudice as "an antipathy based on a faulty and inflexible generalisation," which already fuses the belief (generalisation) with the feeling (antipathy).

Stereotype (cognitive)

An over-generalised, relatively fixed belief about the attributes of a social group, applied to its members regardless of individual variation. A cognitive schema, and therefore cognitively economical: it lets the perceiver "go beyond the information given." Can be positive or negative in content but is error-prone by construction.

Prejudice (affective attitude)

A pre-judgement, a negative (occasionally positive) attitude and emotional orientation toward a group and its members, held in advance of, and resistant to, disconfirming evidence. The evaluative, feeling-toned layer sitting on the stereotype.

Discrimination (behaviour)
The overt differential treatment (usually unfavourable) of individuals on the basis of their group membership. The behavioural output; the level at which law and institutions intervene.

COMPONENT	PSYCHOLOGICAL LEVEL	EVERYDAY MARKER
Stereotype	**Cognition (belief / schema)**	"People with schizophrenia are unpredictable"
Prejudice	**Affect (attitude / feeling)**	Discomfort, fear or dislike toward that group
Discrimination	**Behaviour (action)**	Refusing to rent a room to a psychiatric patient

The cognition to affect to behaviour spine: stereotype feeds prejudice, prejudice licenses discrimination, but the links are probabilistic, not automatic.

HOLD THIS
Stereotype is a belief (cognition), prejudice is a feeling (affect), discrimination is an act (behaviour). Keeping the three levels apart is what turns a vague answer into a scorable one; the stigma of mental illness is this triad applied to a psychiatric out-group.

5.2 Allport's classic account (1954): the foundational text

Where the field starts. Gordon Allport's *The Nature of Prejudice* (1954) is the origin point examiners expect you to name. He defined prejudice as antipathy from faulty, inflexible generalisation, located its cognitive engine in normal **categorisation** (the mind sorts the social world into groups to save effort, and prejudice is the pathological overreach of this normal process), and proposed a scale of acting-out from mild to lethal: antilocution (hostile talk), avoidance, discrimination, physical attack, and extermination. His lasting bequest was two-fold: prejudice grows out of ordinary cognition rather than a special pathology, and it can be reduced by structured intergroup contact (the **contact hypothesis**, 5.7). *What it left debated:* Allport described the individual and cognitive roots richly but did not fully explain why prejudice tracks group competition and group identity, which the next theories addressed.

5.3 The authoritarian personality (Adorno, 1950): prejudice as personality

Locating prejudice inside the person. Adorno and colleagues (1950), working in the shadow of fascism and from a psychodynamic frame, argued that prejudice is an expression of a personality type forged by harsh, status-anxious parenting. The **authoritarian** personality shows submission to authority, aggression displaced onto weaker out-groups, rigid conventional thinking and intolerance of ambiguity, indexed by the F-scale (F for fascism). *What it fixed:* it explained the individual differences Allport's cognitive account under-weighted, why some people are far more prejudiced than others in the same culture. *What it left debated:* a personality-only account cannot explain how whole populations shift into or out of prejudice rapidly, or why prejudice appears even among people with no authoritarian traits, which pushed the field toward situational and group-level theories.

5.4 Realistic conflict theory (Sherif): prejudice from competition

Prejudice as rational group interest. Muzafer Sherif's **realistic conflict** theory holds that intergroup hostility arises when groups compete for scarce, mutually exclusive resources; cooperation for shared goals dissolves it. The evidence is the **Robbers Cave** field experiment (1954): two groups of boys at a summer camp, once placed in competition, rapidly developed **in-group** solidarity and **out-group** hostility (name-calling, raids, flag-burning). Crucially, simple contact did not repair it; hostility only fell when the experimenters imposed **superordinate goals**, problems (a broken water supply, a stuck truck) that neither group could solve alone. *What it fixed:* it grounded prejudice in real group dynamics rather than individual pathology, and it foreshadowed the contact conditions. *What it left debated:* Robbers Cave showed competition is *sufficient* for hostility, but later work showed it is not *necessary*, group identity alone can produce bias without any conflict, which social identity theory demonstrated.

5.5 Social identity theory (Tajfel): prejudice from categorisation alone

The minimal condition for bias. Henri Tajfel's **social identity** theory (Tajfel & Turner) argues that people derive part of their self-esteem from the groups they belong to, and therefore favour the in-group to enhance a positive social identity. The decisive evidence is the **minimal-group paradigm**: when participants are sorted into groups on a trivial, arbitrary basis (a coin toss, a preference for one abstract painter), with no history, no contact and no competition, they still allocate more reward to anonymous in-group members. **In-group** favouritism emerges from mere categorisation. The mechanism runs categorisation, then identification, then social comparison, with a drive to see one's own group as positively distinct. *What it fixed:* it proved prejudice does not require competition (fixing the gap RCT left) or an authoritarian personality; a bare "us and them" split suffices. *What it left debated:* it explains the readiness to divide but is often paired with realistic conflict and cognitive-schema accounts to explain the *content* and *intensity* of specific prejudices.

5.6 Scapegoating: prejudice as displaced frustration

The out-group as a target of convenience. The **scapegoating** account (frustration-aggression tradition, Dollard and colleagues; taken up by Allport) holds that frustration or economic hardship generates aggression that cannot safely be aimed at its true or powerful cause, so it is displaced onto a weaker, visible minority. Historically this fits the correlation between economic downturn and rising hostility toward minorities. It complements rather than competes with the other theories: it supplies a motive (displaced frustration) that categorisation (5.5) and the authoritarian dynamic (5.3) then channel toward a particular out-group.

GOOD TO REMEMBER

- **Allport (1954), *The Nature of Prejudice*:** prejudice = antipathy from faulty, inflexible generalisation; roots in normal categorisation; scale of acting-out (antilocution to extermination); proposed the contact hypothesis.
- **Adorno et al. (1950), authoritarian personality:** prejudice as a personality type (submission, displaced aggression, rigidity), indexed by the F-scale; harsh parenting origin.
- **Sherif, realistic conflict theory / Robbers Cave (1954):** competition for scarce resources drives in-group vs out-group hostility; superordinate goals reduce it.
- **Tajfel & Turner, social identity theory:** in-group favouritism from mere categorisation; minimal-group paradigm; categorise to identify to compare.
- **Scapegoating (frustration-aggression, Dollard et al.):** displaced aggression onto a weaker visible out-group.
- **Pettigrew & Tropp (2006):** meta-analysis of 500+ studies confirming contact reduces prejudice; optimal conditions helpful but not essential.

5.7 Reducing prejudice: the contact hypothesis and Allport's conditions

The currently accepted intervention. The **contact hypothesis**, first set out by Allport (1954), is the position with the strongest evidence and is the **currently accepted** account of prejudice reduction: bringing groups into contact reduces prejudice, but only reliably when the contact meets certain conditions. Allport specified four: **equal status** between the groups within the contact situation, **common (superordinate) goals**, intergroup **cooperation** rather than competition, and **institutional / authority support** (norms and sanction that endorse the contact). Robbers Cave (5.4) is the field demonstration of the goal and cooperation conditions. Without these conditions, mere proximity can entrench hostility rather than dissolve it.

CLASSIC TRAP Post Pettigrew and Tropp (2006), Allport's four conditions are **facilitating and optimising, not strict prerequisites**; contact still reduces prejudice, more weakly, without them, so do not state them as absolute requirements.

MNEMONIC

E C C I

Allport's four contact conditions: **E**qual status, **C**ommon goals, **C**ooperation, **I**nstitutional support.

5.8 The modern evidence: Pettigrew and Tropp (2006)

What the meta-analysis actually showed. Pettigrew and Tropp's (2006) meta-analysis pooled several hundred studies and confirmed that intergroup contact reliably reduces prejudice, with effects generalising beyond the specific individuals met. Their refinement of Allport matters for exams: the four optimal conditions *enhance* the effect but are **not strictly necessary**, contact reduces prejudice even without the full set, and a large part of the effect is mediated by reduced anxiety and increased empathy / perspective-taking rather than by belief change alone. This is the modern, currently accepted picture: contact works, the conditions optimise it, and affect (anxiety, empathy) is a key mediating pathway.

COMMON TRAP

Do not state Allport's four conditions as strict prerequisites for any effect at all. Post Pettigrew and Tropp (2006), the examiner-correct line is that the conditions are *facilitating and optimising*, not absolutely necessary; contact still reduces prejudice, more weakly, without them. Conversely, do not claim "mere contact always helps": Robbers Cave shows unstructured contact under competition can worsen hostility.

5.9 Neural correlate of intergroup bias

The neurobiology of us-and-them. The **neural correlate** of prejudice centres on threat and social-cognition circuitry. The **amygdala** shows differential activation to out-group faces (a rapid, often implicit threat response), modulated by top-down control; the **medial prefrontal cortex** is engaged less when perceiving extreme, dehumanised out-groups (reduced mentalising, the neural signature of failing to attribute a full mind to the other); and the **anterior cingulate cortex** and **dorsolateral prefrontal cortex** support the effortful regulation and override of automatic bias. The reading is dual-process: a fast, amygdala-linked implicit reaction and a slower, prefrontally mediated controlled evaluation, the same fast-versus-controlled architecture that runs through modern social cognition.

5.10 Worked example: the stigma of mental illness as applied prejudice

The clinical application. The **stigma** of mental illness is the textbook clinical instance of the triad (cross-reference the community psychiatry / stigma material). Map it directly: the **stereotype** is the belief that people with mental illness are dangerous, incompetent or to blame; the **prejudice** is the fear and desire for social distance those beliefs generate; the **discrimination** is the concrete harm, denial of housing, employment, insurance and even parity in medical care. Link (2001) and Corrigan's work distinguish *public stigma* (the community's endorsement of the stereotype and resulting discrimination) from *self-stigma* (the patient internalising it, with loss of self-esteem and the "why try" effect that erodes help-seeking and adherence). The anti-stigma toolkit is exactly the intergroup-theory toolkit: education corrects the stereotype, protest challenges discrimination, and structured *contact* with people who have lived experience, framed with equal status and cooperation per Allport, is the most effective single lever, consistent with Pettigrew and Tropp (2006).

CLINICAL ANCHOR

When a discharged patient cannot get a job or a rented room, name the mechanism precisely: that is *discrimination* (behaviour) driven by *prejudice* (affect) built on a *stereotype* (belief). It anchors the anti-stigma plan, and it enforces the system rule that a diagnostic label is never handed to a patient as a bare word, because labelling amplifies self-stigma and the "why try" effect.

INDIA

The Mental Healthcare Act 2017 explicitly prohibits discrimination against persons with mental illness and asserts a right to equality and non-discrimination in treatment and services, translating the discrimination limb of the triad into statutory protection. In practice, marriage-related and family stigma remain dominant drivers of concealment and delayed care in Indian settings.

PEARL

One-line thread for the whole topic: prejudice is a normal cognitive process (categorisation) gone wrong (Allport), sharpened by personality (Adorno), competition (Sherif) and mere group identity (Tajfel), and the one evidence-based cure is optimal-condition contact (Allport's ECCI, validated by Pettigrew and Tropp), which is also the front-line tool against the stigma of mental illness.

6 · Aggression and prosocial behaviour

Two mirror-image questions. Social psychology asks why humans harm each other and why they help each other, and the exam pairs them as two halves of one topic. Both halves are examined the same way: as a **succession of theories**, each fixing a flaw in the one before, converging on a modern integrative account with a named neural substrate. For **aggression** the arc runs from Freud's death instinct and Lorenz's ethology, through the **frustration-aggression** hypothesis and Berkowitz's revision, through Bandura's social learning, to the general aggression model, with serotonin, the amygdala and prefrontal cortex as the biology. For **prosocial** behaviour and **altruism** the arc runs from the puzzle of the unhelpful crowd (the **bystander** effect) to the competing motivational accounts (**empathy-altruism** versus **social exchange**) and the evolutionary accounts (**reciprocity** and kin selection).

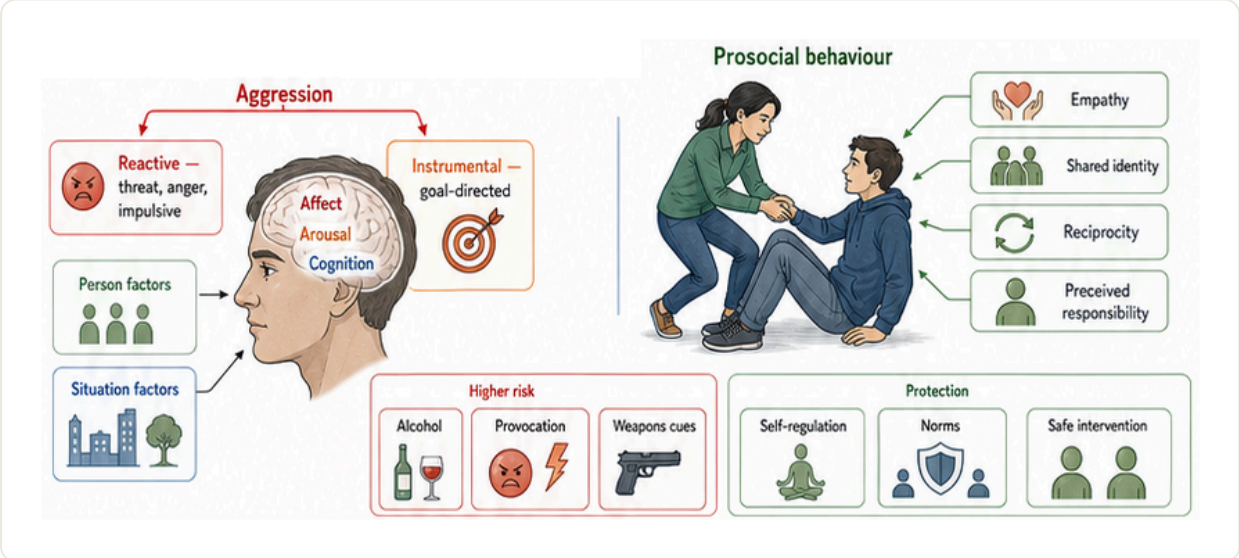


Fig 5.6 Aggression and prosocial behaviour.

The topic matters clinically because these are the mechanisms behind violence risk, impulsive aggression in personality disorder and intermittent explosive disorder, and the diffusion of responsibility that lets a ward or a bystander fail to act in an emergency; the empathy and reciprocity accounts also underpin how the therapeutic and helping relationship works (Kaplan &

Sadock 2024; Tasman 2015). Treat the theory sequence below as a system to enumerate: state what each theory added and what it left debated.

6.1 Defining aggression: reactive versus instrumental

Behaviour intended to harm. **Aggression** is behaviour carried out with the intent to harm another who is motivated to avoid it; intent is what separates it from accidental injury (Kaplan & Sadock 2024). The single most useful clinical division is by function. **Reactive (affective, impulsive) aggression** is hot: it is unplanned, arises from frustration, threat or anger, is accompanied by autonomic arousal, and serves no goal beyond discharge; **instrumental (proactive, predatory) aggression** is cold: it is deliberate, calculated and goal-directed, with low arousal, and is used as a means to an end (Bateman & Fonagy 2016). The distinction maps onto psychopathology: reactive aggression is sensitised by trauma and dominates in impulsive and borderline presentations, whereas planned instrumental aggression is the form that best distinguishes psychopathy from ordinary antisocial behaviour (Bateman & Fonagy 2016). Keep this pair in mind, because the early drive and frustration theories explain reactive aggression well but instrumental aggression poorly.

RULE **The reactive-versus-instrumental split drives management.** Hot, serotonin-linked reactive aggression (borderline, intermittent explosive disorder) responds to SSRIs and skills work; cold instrumental aggression in psychopathy does not, and is a risk-management problem.

6.2 Instinct and ethological theories: Freud and Lorenz

Aggression as an innate drive that must discharge. The earliest accounts treated aggression as a built-in biological force. Sigmund Freud, after the First World War, proposed a death instinct, **Thanatos**, a drive toward destruction that is either turned outward as aggression or inward as self-harm and depression; on this view aggression is an inevitable internal pressure seeking release (Kaplan & Sadock 2024). Konrad Lorenz, from ethology, argued in parallel that aggression is an evolved instinct with survival value (spacing out competitors, establishing dominance hierarchies, defending the young), driven by an accumulating internal energy that is released by an external **releasing stimulus**. Both are **hydraulic** models: pressure builds and must be let out, which gave rise to the (now discredited) idea of **catharsis**, that venting aggression harmlessly lowers it. *What they fixed:* nothing before them; they established aggression as biologically rooted, not merely learned. *What they left debated:* the drive was untestable, the hydraulic energy was never measured, and the catharsis prediction failed empirically (venting tends to increase, not reduce, later aggression). This pushed the field toward a specifiable trigger.

6.3 The frustration-aggression hypothesis: Dollard and Miller

Every frustration breeds aggression. The Yale group, John Dollard, Neal Miller and colleagues, proposed the **frustration-aggression** hypothesis (Dollard, Doob, Miller, Mowrer & Sears 1939), translating the psychoanalytic drive into testable learning-theory terms (Kaplan & Sadock 2024). Its original strong claim was reciprocal: frustration (the blocking of goal-directed behaviour) always produces a readiness for aggression, and all aggression presupposes frustration. It introduced **displacement** (aggression is redirected onto a safer, substitute target when the true

source is too powerful or unavailable, the classic account of scapegoating) and **catharsis** as the reduction of the aggressive drive after an aggressive act. *What it fixed:* it gave aggression an identifiable, manipulable cause (frustration) in place of an unmeasurable instinct. *What it left debated:* the strong form was quickly falsified, because frustration often yields not aggression but withdrawal, sadness or renewed effort, and aggression frequently occurs with no frustration at all. Neal Miller himself softened it in 1941 to say frustration produces instigations to a number of responses, of which aggression is only one.

6.4 Berkowitz's cue-arousal reformulation

Frustration produces readiness, cues pull the trigger. Leonard Berkowitz revised the hypothesis into the **cue-arousal** (later cognitive-neoassociation) model (Berkowitz 1989). Frustration, he argued, does not directly produce aggression; it produces **negative affect** and a readiness to aggress, but whether aggression actually occurs depends on the presence of **aggressive cues** in the situation, learned stimuli associated with aggression. His **weapons effect** demonstration showed that the mere presence of a gun in the room increased aggressive responding in provoked participants (Berkowitz & LePage 1967). The mature cognitive-neoassociation account holds that any aversive event (frustration, pain, heat, foul odour), not just goal-blocking, generates negative affect, which automatically primes an associative network of aggression-related feelings, thoughts and motor responses; higher-order appraisal can then amplify or inhibit the impulse. *What it fixed:* it explained why frustration only sometimes leads to aggression (cues and appraisal moderate it) and widened the cause from frustration to all aversive stimulation. *What it left debated:* it still centred on internal affect and said little about how aggressive behaviour is acquired in the first place.

6.5 Social learning of aggression: Bandura and the Bobo doll

Aggression is learned by watching. Albert Bandura's **social learning** theory answered the acquisition question: aggression, like other behaviour, is learned through **observation** and **imitation** of models, and does not require the observer to be reinforced directly (Bandura 1973; cross-referenced in the social-learning topic). In the famous **Bobo doll** experiments, young children who watched an adult model attack an inflatable Bobo doll later reproduced the specific aggressive acts when given access to the doll, while children who had not seen the model did not (Bandura, Ross & Ross 1961); a follow-up showed the effect transferred from a filmed model and even to a live clown (Bandura, Ross & Ross 1963). This was evidence for learning by observation in the absence of direct reinforcement (Companion to Psychiatric Studies). Whether the child then performs the learned aggression depends on **vicarious reinforcement** (seeing the model rewarded raises imitation; seeing the model punished lowers it) and on the child's **self-efficacy** for the act. Optimal conditions for observational learning include a live model, perceived similarity to the model, seeing the model reinforced, and familiarity with the model (Companion to Psychiatric Studies). *What it fixed:* it explained the transmission of aggression across people and generations (family violence, media violence) that instinct and frustration theories could not. *What it left debated:* it needed integration with the affect and arousal mechanisms, which the next model supplied.

6.6 The currently accepted position: the general aggression model

An integrative input-route-outcome framework. The **currently accepted** synthesis is the **general aggression model** (GAM) of Anderson and Bushman (Anderson & Bushman 2002), which folds the earlier theories into one cyclical process rather than replacing them. *Inputs* are of two kinds: **person factors** (trait aggressiveness, sex, beliefs, attitudes, genetic loading) and **situation factors** (provocation, frustration, aggressive cues such as weapons, pain, heat, alcohol). These act through three interacting *internal routes*, the present **cognition** (hostile thoughts and scripts), **affect** (anger, negative affect, from Berkowitz), and **arousal**. Appraisal and decision processes, immediate and automatic or reappraised and controlled, then yield the *outcome*: a thoughtful or an impulsive action, whose social consequences feed back to update the person's knowledge structures across encounters. GAM thereby contains Berkowitz's affect, Bandura's learned scripts and knowledge structures, and the older arousal notions inside a single loop. *What it fixed:* it unifies previously rival theories and accommodates both reactive and instrumental aggression. *What it leaves debated:* its breadth makes it hard to falsify, and the relative weight of each input remains contested.

6.7 Neurobiology of aggression

The neural correlate: a serotonin-limbic-prefrontal circuit. The **neural correlate** of impulsive aggression is a triad. First, low central **serotonin** (5-HT) function is the most replicated neurochemical correlate: reduced cerebrospinal-fluid 5-HIAA (the main serotonin metabolite) is associated with impulsive aggression, violent suicide attempts and low behavioural inhibition, supporting the model of serotonin as a brake on impulsive aggressive responding (Kaplan & Sadock 2024). Second, the **amygdala** generates the threat-driven reactive aggressive response, and its regulation by the **ventromedial and orbitofrontal prefrontal cortex** is what normally restrains it; reduced prefrontal control over an over-reactive amygdala is the circuit-level signature of reactive aggression, and reduced grey-matter volume has been reported in violent individuals with comorbid psychopathy and antisocial personality disorder (Bateman & Fonagy 2016). Third, **testosterone** correlates modestly with dominance-seeking and aggression, most consistently in interaction with low serotonin and low cortisol rather than as a simple main effect. A well-known gene-environment example is the low-activity **MAOA** variant, which predicts later antisocial and aggressive behaviour chiefly in men who were also maltreated in childhood (Caspi et al. 2002), illustrating that biology sets a threshold that experience then moves.

- **Low serotonin** - the most replicated neurochemical correlate: reduced CSF 5-HIAA marks impulsive aggression, so serotonin acts as a brake.
- **Amygdala under prefrontal control** - the amygdala drives the reactive aggressive response; reduced ventromedial/orbitofrontal restraint is the circuit signature of reactive aggression.
- **MAOA x maltreatment (Caspi 2002)** - the low-activity MAOA variant predicts later aggression chiefly in men maltreated in childhood: biology sets a threshold, experience moves it.

CLINICAL ANCHOR

The reactive versus instrumental split drives management. Reactive, serotonin-linked impulsive aggression (borderline personality disorder, intermittent explosive disorder) responds to SSRIs, mood stabilisers and skills-based work on arousal and appraisal; cold instrumental aggression in psychopathy does not respond to these and is a risk-management, not a pharmacological, problem (Kaplan & Sadock 2024; Bateman & Fonagy 2016). Note also that the catharsis idea, that letting a patient vent anger discharges it, is empirically wrong and is not a therapeutic technique.

6.8 Prosocial behaviour and the bystander effect

Why a crowd fails to help. **Prosocial** behaviour is voluntary action intended to benefit another; **altruism** is the special case of prosocial behaviour motivated by concern for the other rather than for self-gain. The founding finding is the **bystander** effect: an individual is significantly less likely to help a person in need when other potential helpers are present, because the responsibility to act is distributed across everyone present, termed **diffusion of responsibility** (Latané & Darley 1970; Tasman 2015). Prompted by the 1964 Kitty Genovese case, Latané and Darley showed experimentally that help becomes slower and less likely as group size rises. The effect operates through three social-cognitive processes: *diffusion of responsibility* (each onlooker feels less personally obliged), **pluralistic ignorance** (each reads the inaction of others as a signal that no emergency exists), and *evaluation apprehension* (fear of intervening wrongly and being judged). The lesson, carried into resuscitation training, is to defeat diffusion by assigning responsibility to one named person.

6.9 The bystander decision tree

Five sequential yes-or-no steps to helping. Latané and Darley modelled helping as a **decision tree**: help occurs only if the bystander clears every step, and a no at any step ends the process (Latané & Darley 1970).

STEP	THE QUESTION	WHAT BLOCKS A "YES" (FAILURE MODE)
1. Notice	Do I notice something is happening?	**Distraction, hurry, self-absorption**
2. Interpret	Is this an emergency?	**Pluralistic ignorance: others look calm, so I under-read it**
3. Responsibility	Is it my responsibility to act?	**Diffusion of responsibility across the crowd**
4. Decide how	Do I know what to do?	**Lack of competence or knowledge of the right action**
5. Act	Do I implement help?	**Evaluation apprehension, fear of danger or cost**

Each stage is a filter; the more people present, the more likely the process stalls at steps 2 and 3, which is the bystander effect.

6.10 Why we help: empathy-altruism versus egoistic accounts

Is helping ever truly selfless? Once someone decides to help, the debate is about motive. Two families of theory compete. The **empathy-altruism** hypothesis (Batson) holds that feeling genuine *empathic concern* for a sufferer produces truly altruistic motivation, a desire to relieve the other's distress as an end in itself, not to relieve one's own; Batson's experiments dissociated the two by making escape easy, showing that high-empathy participants still helped even when they could walk away, which a purely selfish account cannot explain (Batson 1991). Against this stand the **egoistic** accounts, which argue all helping ultimately serves the self. The **negative-state relief** model (Cialdini) proposes that witnessing distress makes the observer feel bad and that helping is a way to repair one's own mood, so the real goal is self-soothing. The **social exchange** account frames helping as a cost-benefit transaction: we help when the rewards (reciprocation, social approval, relief of distress, self-esteem) outweigh the costs, so apparent altruism is disguised self-interest. The debate is not fully resolved, but the empathy-altruism evidence is generally taken to show that genuinely other-directed motivation exists alongside egoistic motives.

6.11 The evolutionary accounts: reciprocity and kin selection

How can selfish genes build a helper? Evolutionary biology explains the paradox that costly helping persists. Two mechanisms do most of the work (Kaplan & Sadock 2024). **Kin selection** (William Hamilton) shows that a gene causing an individual to sacrifice for relatives can spread because relatives carry copies of that gene: Hamilton's rule states an altruistic act is favoured when $C < B \times r$, the cost to the actor is less than the benefit to the recipient times the coefficient of relatedness (r = **0.5** for a parent, child or full sibling), a concept captured by **inclusive fitness**. It explains parental sacrifice and why one would risk more for two siblings or eight cousins than for one. **Reciprocity**, or reciprocal altruism (Robert Trivers), explains helping between *non-kin*: I help you now because you are likely to help me later, an exchange that pays off when repeated interactions allow cheaters to be detected and excluded, modelled by the **prisoner's dilemma** (Trivers 1971; Kaplan & Sadock 2024). On this view social emotions are the enforcement machinery of reciprocity: gratitude and friendship reward cooperators, while anger, guilt and the urge to punish defectors police cheating (Kaplan & Sadock 2024). Together, kin selection and reciprocity supply the ultimate (evolutionary) explanation, while empathy and social exchange supply the proximate (psychological) one.

HOLD THIS

Catharsis is empirically false: venting tends to raise, not lower, later aggression. The examinable current model of aggression is Berkowitz's (frustration is one aversive input creating a readiness that cues and appraisal then shape), folded into the general aggression model.

TRAP Batson's empathy-altruism argues **for** genuinely other-directed helping; negative-state relief and social exchange are the egoistic rebuttals, not versions of it.

6.12 Worked example

One scene, every theory. A junior doctor is jostled and insulted by an intoxicated relative in a crowded casualty. His flash of anger and impulse to shove back is *reactive aggression*, primed by the aversive provocation (Berkowitz's negative affect) and the aggressive cues around him, gated by his prefrontal control over the amygdalar threat response; that he learned to keep his hands down comes partly from having modelled senior colleagues who de-escalate (Bandura). Moments later the relative collapses. The dozen onlookers freeze: each reads the others' stillness as evidence it is not serious (pluralistic ignorance) and assumes someone else will act (diffusion of responsibility), the *bystander* effect. The doctor overrides it by pointing at one nurse and saying "you, call the code," collapsing diffusion onto a named person. Whether he then feels genuine *empathic concern* for the patient (empathy-altruism) or is partly relieving his own distress (negative-state relief) and expecting professional credit (social exchange) is the motive debate, but the deep reason a species evolved to help a stranger at all traces to *reciprocity* and, for his own child at home, to *kin selection*.

COMMON TRAP

Do not confuse the two aggression subtypes with the two theory families: reactive aggression is not the same as the frustration-aggression theory, and instrumental aggression is not social learning. Also, the frustration-aggression hypothesis in its original strong form (frustration always causes aggression, all aggression follows frustration) is *wrong*; the examinable current form is Berkowitz's, where frustration is one aversive input producing a readiness that cues and appraisal then shape. And empathy-altruism is Batson's claim *for* genuine altruism; negative-state relief and social exchange are the egoistic rebuttals, not versions of it.

MNEMONIC

"NIRA-DA" for the bystander decision tree

Notice, **I**nterpret as emergency, take **R**esponsibility, decide how to **A**ct, then **DA**re to do it. Five sequential gates; a single "no" ends the sequence and no help is given.

INDIA

Diffusion of responsibility is a live problem in Indian public spaces: crowded roads and railway platforms where accident victims are watched but not helped are the bystander effect in the field. The Supreme Court's Good Samaritan guidelines (2016) were designed precisely to remove the cost side of the helping decision, protecting a helper from legal and procedural harassment so that steps 4 and 5 of the decision tree become easier to clear.

GOOD TO REMEMBER

- **Freud (Thanatos):** death instinct, aggression as an innate drive turned outward or inward.
- **Lorenz (ethology):** aggression an evolved instinct with an accumulating energy released by a releasing stimulus; hydraulic model.
- **Catharsis idea:** venting lowers aggression; empirically false (venting tends to increase it).
- **Dollard & Miller et al. 1939 (frustration-aggression):** frustration always breeds aggression; introduced displacement and scapegoating. Strong form falsified.
- **Miller 1941:** softened it, frustration instigates several responses, aggression being one.
- **Berkowitz (cue-arousal / cognitive-neoassociation):** frustration and any aversive event create negative affect and readiness; aggressive cues (the weapons effect, Berkowitz & LePage 1967) release it.
- **Bandura (social learning):** Bobo doll (1961; filmed and live-clown versions 1963), learning by observation and imitation without direct reinforcement; vicarious reinforcement governs performance.
- **Anderson & Bushman 2002 (general aggression model):** currently accepted; person and situation inputs act via cognition, affect and arousal, through appraisal, to a thoughtful or impulsive outcome, then feed back.
- **Reactive vs instrumental aggression:** hot, impulsive, frustration-driven (borderline, IED) versus cold, planned, goal-directed (psychopathy).
- **Neurobiology:** low serotonin (reduced CSF 5-HIAA) disinhibits impulsive aggression; amygdala drives reactive aggression under ventromedial/orbitofrontal control; testosterone modestly linked; low-activity MAOA x childhood maltreatment (Caspi 2002).
- **Latané & Darley 1970 (bystander effect):** help less likely as onlookers increase; diffusion of responsibility, pluralistic ignorance, evaluation apprehension; five-step decision tree.
- **Batson (empathy-altruism):** empathic concern produces genuinely altruistic motivation (helping persists even when escape is easy).
- **Cialdini (negative-state relief):** egoistic; helping repairs the helper's own bad mood.
- **Social exchange / reciprocity:** helping is a cost-benefit transaction; apparent altruism serves the self.
- **Trivers 1971 (reciprocal altruism):** helping non-kin because of expected later return; modelled by the prisoner's dilemma; social emotions enforce it.
- **Hamilton (kin selection):** altruism to relatives favoured when $C < B \times r$ ($r = 0.5$ for parent/child/sibling); inclusive fitness.

7 · Crowd and mob psychology

What happens to the individual mind when it is dissolved into a crowd. A **crowd** is a large, temporary, co-present gathering of people; a **mob** is a crowd that has turned to intense, often aggressive, collective action. The psychology of the crowd asks a single durable question: does a person in a crowd lose their individual judgement and become swept along by the mass, or do crowds behave in a patterned, meaningful way that reflects who the people in them are? The exam wants this as a chain of theories in the order they appeared: Gustave **le bon**'s original account of the crowd as a primitive collective mind, the mid-century theory of **deindividuation**, Turner and Killian's **emergent-norm** theory, and finally Reicher's **social identity** model, which is the modern corrective. Each theory fixed a limitation of the one before it.

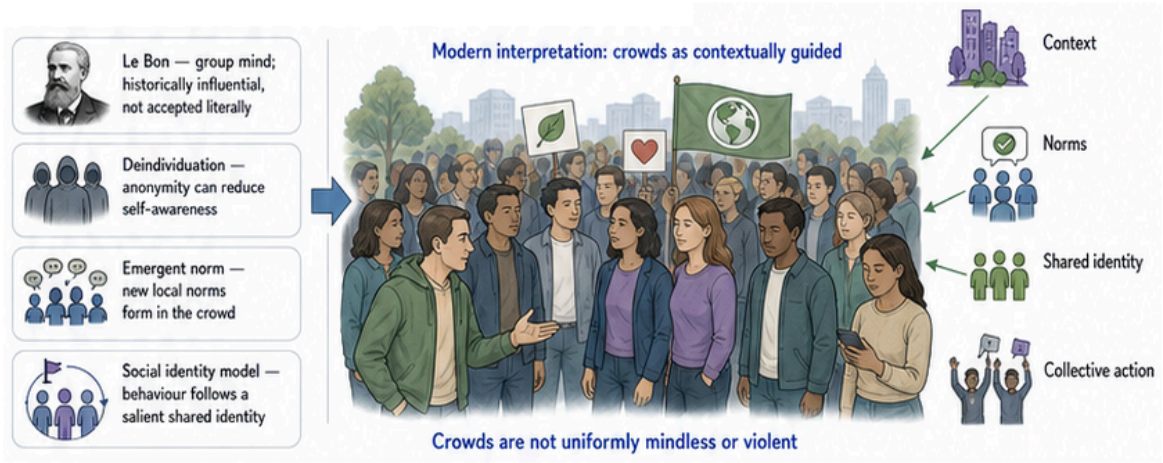


Fig 5.7 Crowd psychology: from group mind to shared identity.

This matters clinically and forensically, not as social-science trivia. Crowd dynamics underlie **mass psychogenic illness** (epidemic hysteria), the panic and crush injuries of stampedes, and the behaviour of riots, all of which a psychiatrist may be asked to explain in a medico-legal report or a public-health inquiry (Companion to Psychiatric Studies). Treat the four-theory sequence and the Le Bon-to-Reicher shift as the highest-yield items; treat mass hysteria as the clinical anchor.

7.1 Defining the crowd, the mob and collective behaviour

A vocabulary before the theories. *Collective behaviour* is the umbrella term for the relatively spontaneous, unstructured action of people responding together to a common situation. Within it, a *crowd* is defined by physical co-presence and a shared focus of attention; a *mob* is an emotionally aroused crowd acting toward a target (a lynch mob, a riot); a *panic* is a crowd in flight from a perceived threat. Two mechanisms recur across every theory and are worth fixing first: *suggestibility*, the readiness to accept and act on ideas or emotions coming from others without critical appraisal, and *contagion*, the rapid, seemingly automatic spread of an emotion or behaviour through a gathering. Le Bon put both at the centre; the later theories progressively reinterpreted them.

7.2 Theory one: Le Bon and the group mind (1895)

The crowd as a single primitive organism. Gustave Le Bon's *The Crowd: A Study of the Popular Mind* (Le Bon 1895) is the founding text and the classic exam anchor. Writing in the wake of the French revolutionary crowds, he argued that when individuals gather, a *collective* or **group mind** forms and the person is transformed. Three mechanisms drive this:

Anonymity

Submerged in the crowd and feeling unidentifiable, the individual loses the sense of personal responsibility that normally restrains conduct, and yields to instincts they would otherwise control.

Contagion

Emotions, ideas and acts spread through the crowd like an infection, each person imitating the next, so that feeling and behaviour sweep through the mass with little resistance.

Suggestibility

The crowd enters a hypnotic, quasi-trance state in which critical faculties are suspended; the person becomes highly open to suggestion and is driven by the images and slogans put before them.

The result, in Le Bon's picture, is a crowd that is impulsive, irritable, intellectually inferior to its members, prone to extremes of emotion, and morally regressed to a "primitive" level: the individual "descends several rungs on the ladder of civilisation." **What it fixed and what it left debated.** Le Bon fixed the absence of any theory by naming the phenomenon and giving it mechanisms, and his account was enormously influential on later thinking about propaganda and on Freud's group psychology. What it left debated, and what every later theory attacked, was its assumption that the crowd is uniformly irrational, mindless and homogeneous, that it destroys the individual's identity rather than expressing it, and its politically loaded contempt for the "masses."

7.3 Theory two: deindividuation (Festinger, Zimbardo, Diener)

Anonymity and lost self-awareness lower restraint. The mid-twentieth-century response kept Le Bon's core insight that the crowd loosens restraint but recast it in the testable language of experimental social psychology as **deindividuation**. Festinger, Pepitone and Newcomb (1952) coined the term for a state in which people in a group are not seen or attended to as individuals, which reduces inner restraints and increases behaviour that would ordinarily be inhibited. Philip Zimbardo (1969) systematised the antecedents: anonymity, diffusion of responsibility, large group size, arousal and altered states all reduce self-observation and evaluation-apprehension, releasing impulsive, often antisocial action; in his study, hooded, unidentifiable participants delivered more apparent shocks than clearly identified ones. Ed Diener (1976, 1980) sharpened the mechanism to *reduced self-awareness*: it is the loss of *private* self-focus, of attention to one's own standards, that de-regulates behaviour, not mere anonymity to others. A widely cited naturalistic illustration is that anonymity-promoting conditions such as darkness and disguise are associated with more disinhibited behaviour, for example the finding that trick-or-treating children were more likely to steal extra sweets when anonymous and in a group than when alone and identified (Diener et al. 1976).

What it fixed and what it left debated. Deindividuation fixed Le Bon's untestable "group mind" by replacing it with measurable variables (anonymity, group size, self-awareness) that could be manipulated in the laboratory. What it left debated is that anonymity does not reliably produce *antisocial* behaviour at all: anonymous, deindividuated crowds sometimes become more generous, more helpful or more conformist to a peaceful norm, which a theory of pure restraint-loss cannot explain. The direction of behaviour, not just its intensity, needed a theory.

7.4 Theory three: emergent-norm theory (Turner and Killian)

Crowds are not norm-less; they build a new norm on the spot. Ralph Turner and Lewis Killian's **emergent-norm** theory (Turner and Killian, *Collective Behavior*, 1957) rejected the idea that crowds are uniform and driven by contagion. In the ambiguous, unstructured situation a crowd faces, no existing rule tells people how to act; a few distinctive individuals then behave in a salient way (for example, throwing the first stone or beginning to flee), their conduct is taken as defining "what people here are doing," and it crystallises into a *new, situation-specific norm* that the

rest feel pressure to follow. The crowd only *appears* unanimous and contagious; in reality members differ in motive, and it is normative social pressure and the desire not to deviate visibly, not hypnotic contagion, that produces the observed uniformity. **What it fixed and what it left debated.** Emergent-norm theory fixed the assumption of mindlessness: crowd action is now rational and norm-governed, just governed by a norm that emerged in the moment rather than one brought in from outside. What it left debated is *where the new norm comes from* and why particular crowds converge on particular norms, hostile in one case, festive in another; the theory describes the process of norm formation but not its content, and it still treats the crowd as a set of strangers negotiating from scratch.

7.5 Theory four: the social identity model (Reicher), the modern corrective

Crowds act on a shared social identity, not on lost identity. Stephen Reicher's **social identity** model of crowd behaviour (Reicher 1984, building on Tajfel and Turner's social identity and self-categorisation theory) is the decisive correction to Le Bon and the position the field now holds. Its central claim inverts Le Bon: in a crowd the person does not *lose* identity but *shifts* from personal identity to a shared *social* identity, categorising the self as a member of the relevant group ("we, the protesters"; "we, the fans"). Behaviour then becomes not random or de-regulated but *patterned by the norms and values of that group identity*. This explains what deindividuation could not: crowds are selective, not indiscriminate. In Reicher's analysis of the 1980 St Pauls riot in Bristol, the crowd's violence was bounded and targeted, directed at police and symbols of the state and confined to the neighbourhood, not a blind orgy of destruction, precisely because it expressed a specific community identity and its grievances. The later *elaborated social identity model* (ESIM, Reicher, Stott, Drury) adds that crowd conflict is often *generated by the interaction* with an out-group such as the police: indiscriminate, heavy-handed control that treats a whole peaceful crowd as hostile can create a new, oppositional shared identity and escalate disorder that did not initially exist. **What it fixed.** The social identity model fixed the deepest error in the whole tradition, the equation of "crowd" with "irrational" and "identity-less." It shows crowd behaviour to be socially meaningful, group-normed and, crucially, shaped by how the crowd is policed, which is why it now underpins evidence-based public-order policing.

7.6 Currently accepted position

The social identity account, with deindividuation demoted to a special case. The **currently accepted** position is that crowd behaviour is not the loss of the rational individual to a primitive group mind but the shift to a shared social identity whose norms then guide conduct (Reicher; Reicher, Stott and Drury). Le Bon's contagion is reinterpreted: what looks like automatic emotional spread is the rapid, mutual recognition and enactment of a common in-group norm among people who now categorise themselves together. Deindividuation is retained only in a limited, reinterpreted form, the SIDE model (Social Identity model of Deindividuation Effects, Reicher, Spears and Postmes), which holds that anonymity in a group does not abolish norms but *strengthens adherence to the salient group norm* by making personal individuality less salient than group membership. The through-line is decisive: crowds are norm-governed and identity-driven, not mindless.

HOLD THIS

The crowd sequence rescues the crowd's rationality: Le Bon (group mind) to deindividuation to emergent-norm to Reicher's social identity model. In a crowd the person does not lose identity but shifts from personal to shared social identity, and behaviour follows that group's norms.

7.7 Neural and behavioural correlate

Where restraint and self-monitoring live. There is no single "crowd centre," but the mechanisms the theories describe map onto known systems. The reduced self-monitoring and behavioural disinhibition of deindividuation are consistent with attenuated engagement of the *medial and lateral prefrontal cortex*, the substrate of self-referential processing and of top-down inhibitory control over prosocial norms; reduced private self-awareness is, in effect, reduced recruitment of these self-monitoring circuits. Emotional contagion, the rapid spread of affect through a crowd, is linked to fast, automatic *affect-sharing and mirroring processes* (limbic structures including the amygdala and the anterior insula, and the human mirror-neuron system), which transmit fear and arousal person-to-person below the level of deliberation. Social categorisation, the engine of the social identity model, engages the same *medial prefrontal and temporoparietal* "social brain" regions that distinguish in-group from out-group. The behavioural correlate at the level of the crowd is the crush dynamics of a panicking mass: as density rises, individual locomotion is overridden by physical coupling between bodies, producing turbulent, wave-like "crowd quakes" in which people are injured by compressive asphyxiation rather than by trampling.

TRAP Do not label every stampede death "mass panic": most are **physical crush and compressive asphyxia at critical density**, and survivors usually behaved cooperatively until physically overwhelmed.

CLINICAL ANCHOR

Mass psychogenic illness (epidemic or mass hysteria). This is contagious dissociative or conversion phenomena spreading rapidly through a group under conditions of shared anxiety, with no organic cause found (Companion to Psychiatric Studies). It classically strikes closed, stressed institutions, most often schools, where fainting, dizziness, breathlessness or non-epileptic collapse spread from person to person, typically along lines of sight and friendship. A famous, still-debated example is the 1955 outbreak among nurses at the Royal Free Hospital during a polio epidemic, read by some as atypical infection and by others as mass hysteria (McEvedy and Beard 1970, cited in Companion to Psychiatric Studies). The clinical task is a careful differential from a genuine toxic or infectious outbreak: mass psychogenic illness shows rapid onset and remission, spread by sight and sound rather than by a plausible physical vector, a preponderance of subjective symptoms with normal investigations, and often an index case with a visible acute symptom. Management is calm separation of affected individuals, avoidance of dramatic medical spectacle that amplifies suggestion, credible reassurance, and correcting the anxiety-laden rumour that feeds it.

INDIA

Crowd crush at mass religious gatherings and festivals is a recurring public-health problem in India, where enormous congregations converge on constrained spaces (narrow temple approaches, riverbank ghats, festival grounds). Fatal stampedes at such events illustrate the crowd-dynamics point exactly: deaths are overwhelmingly from progressive crowd compression and asphyxia at critical density, often triggered by a rumour, a sudden surge toward a darshan or a blocked exit, not by generalised "panic" in the Le Bon sense. The psychiatric and forensic contribution is to resist the lazy "mass panic" narrative and point instead to identifiable failures of crowd management, density control, flow direction, communication, and to the behavioural finding that people in crushes typically continue cooperative, help-seeking behaviour until physically overwhelmed. Mass psychogenic illness outbreaks in Indian residential schools and factories are also periodically reported and follow the same anxiety-and-suggestion pattern.

COMMON TRAP

Do not present Le Bon as the correct modern account. In an exam, name Le Bon (1895) as the historically foundational but now-superseded theory, and be explicit that the contemporary consensus is the social identity model (Reicher): crowds are not mindless, contagion-driven and identity-less, they act on a shared social identity and its norms. A second trap: do not equate every crowd death with "panic." Most stampede fatalities are physical crush and compressive asphyxia at high density, and survivors usually behaved cooperatively; the label "mass panic" is often a post-hoc misattribution.

MNEMONIC

Le Bon's Dogs Emerge Social

The four theories in the order they appeared: **Le Bon** (group mind, 1895), **D**eindividuation (Festinger, Zimbardo, Diener), **E**mergent-norm (Turner and Killian), **S**ocial identity (Reicher, the modern corrective). Read the sequence as a steady rescue of the crowd's rationality: from a primitive group mind, to lost restraint, to a norm built on the spot, to a shared identity that was there all along.

GOOD TO REMEMBER

- **Le Bon (1895), *The Crowd*:** first theory; anonymity + contagion + suggestibility create a primitive, irrational "group mind" and loss of individual responsibility. Now superseded.
- **Deindividuation (Festinger, Pepitone and Newcomb 1952; coined the term):** group immersion reduces inner restraints and inhibited behaviour is released.
- **Zimbardo (1969):** anonymity, diffusion of responsibility, group size and arousal drive deindividuated, disinhibited action.
- **Diener (1976, 1980):** the core mechanism is reduced *private self-awareness*, not mere anonymity to others.
- **Emergent-norm theory (Turner and Killian 1957):** in ambiguous situations crowds create a new, situation-specific norm; uniformity comes from normative pressure, not contagion.
- **Social identity model (Reicher 1984):** in a crowd the person shifts from personal to shared *social* identity; behaviour is patterned by group norms, not lost. The modern corrective to Le Bon.
- **ESIM (Reicher, Stott, Drury):** crowd conflict is often generated by out-group (police) action; indiscriminate control creates oppositional identity and escalates disorder.
- **SIDE model (Reicher, Spears, Postmes):** anonymity in a group strengthens adherence to the salient group norm rather than abolishing norms.
- **Contagion:** rapid automatic spread of emotion/behaviour through a gathering; reinterpreted by modern theory as mutual enactment of a shared in-group norm.
- **Mass psychogenic illness / epidemic (mass) hysteria:** contagious dissociative-conversion symptoms in an anxious group with no organic cause; classic in schools; Royal Free Hospital 1955 (McEvedy and Beard 1970).
- **Currently accepted position:** social identity account (Reicher, Stott, Drury); deindividuation retained only as the reinterpreted SIDE effect.
- **Stampede mechanism:** deaths are from crowd compression and asphyxia at critical density ("crowd quakes"), not from Le Bon-style mass panic.

Learning and behaviour

8 · Classical conditioning

The oldest theory in learning, still the model of fear. **Classical conditioning** (also called Pavlovian or respondent conditioning) is the associative process by which a neutral stimulus, through repeated pairing with a biologically significant event, comes itself to elicit an anticipatory response. It is the first of the two great learning paradigms (the other being operant/instrumental conditioning) and the one the exam ties most tightly to psychopathology: conditioned fear is the working model of phobia, conditioned nausea is the model of anticipatory vomiting in chemotherapy, and conditioned cue reactivity is the model of relapse in addiction (cross-refer SUD). For a CORE answer you must trace the theory in date order, from Pavlov's reflex physiology, through Watson and Rayner's demonstration that human emotion obeys the same law, to the modern cognitive turn (Rescorla and Wagner) that redefined conditioning as prediction rather than mere pairing (Kaplan & Sadock 2024; Tasman 2015).

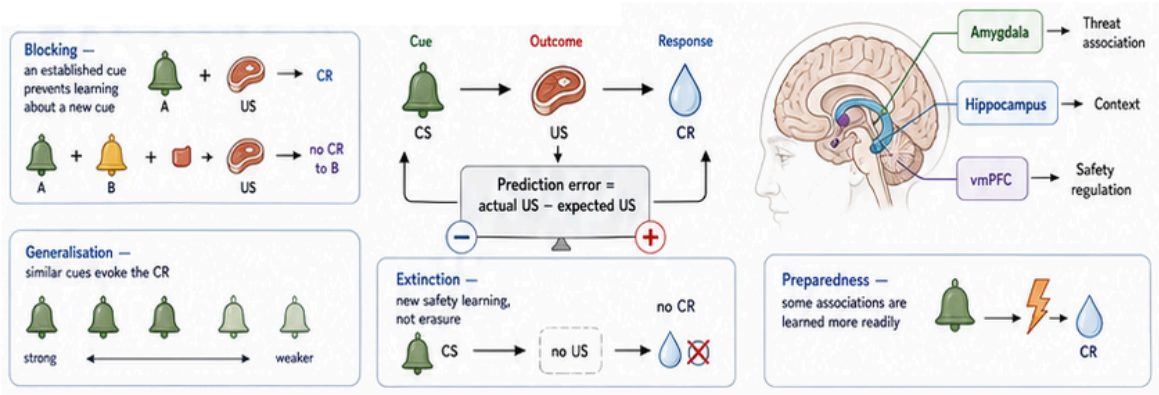


Fig 5.8 Classical conditioning is prediction.

The spine runs in strict historical order, each stage fixing what the last left open: **Pavlov (1927)** gave the reflex vocabulary (US, UR, CS, CR) and the four core phenomena (acquisition, extinction, spontaneous recovery, generalisation); **Watson and Rayner (1920)** proved the law applied to human fear (Little Albert) and launched the behaviourist manifesto; the mid-century **timing analysis** specified how the CS and US must be arranged in time; and the **Rescorla and Wagner (1972)** model overturned the naive idea that contiguity alone is enough, recasting learning as driven by surprise and contingency, with **preparedness** (Seligman; the Garcia effect) adding an evolutionary constraint. The **currently accepted** view is that classical conditioning is prediction-error learning under biological constraint, and its clearest **neural correlate** is amygdala-based fear conditioning with prefrontal control of extinction. Because this topic names dated theorists, defined phenomena and a hard timing classification, it closes with a good-to-remember box enumerating every one (Kaplan & Sadock 2024).

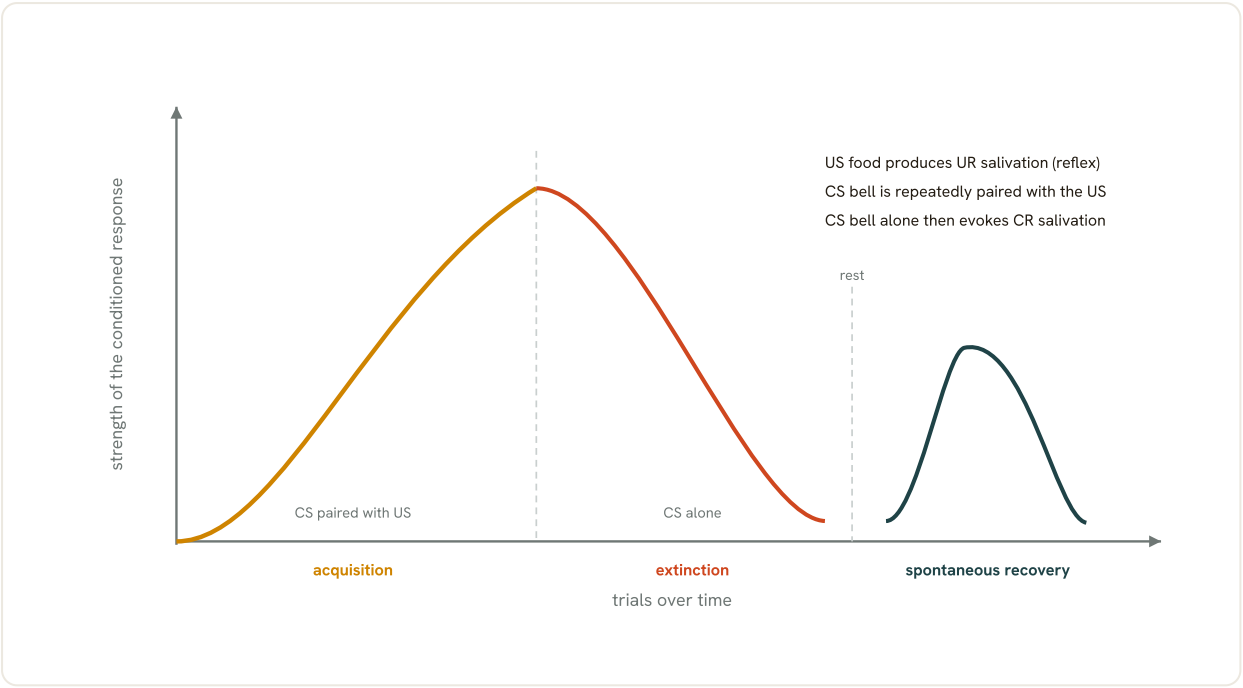


Fig 5.9 The course of classical conditioning. During acquisition the conditioned stimulus (the bell) is repeatedly paired with the unconditioned stimulus (food), and the conditioned response grows to an asymptote. Presenting the conditioned stimulus alone produces extinction, a fall in the response. After a rest the response returns, weaker, as spontaneous recovery, showing that extinction suppresses rather than erases the learning. The unconditioned stimulus and response are the inborn reflex; the conditioned stimulus and response are what the animal learns.

8.1 Pavlov (1927): the reflex vocabulary

The founding move: an automatic reflex can be transferred to an arbitrary signal. The Russian physiologist Ivan Pavlov, working in the reflex tradition, rang a bell and then gave a dog food; after a few pairings the dog salivated to the bell alone, anticipating the food (Kaplan & Sadock 2024). The events are named so the paradigm applies anywhere:

Unconditioned stimulus (US, UCS)

The stimulus that *unconditionally* elicits a response before any learning: the food.

Unconditioned response (UR, UCR)

The innate, reflexive response to the US: salivation to food.

Neutral stimulus (NS)

A stimulus that initially elicits no relevant response: the bell before pairing.

Conditioned stimulus (CS)

The former neutral stimulus *after* pairing, which now elicits the response conditional on the CS to US pairing: the bell.

Conditioned response (CR)

The learned, anticipatory response to the CS: salivation to the bell (usually weaker than the UR).

Read the arithmetic once and it never confuses: US produces UR by nature; NS produces nothing; pair NS with US repeatedly; the NS becomes a CS and now produces a CR. What Pavlov left open was *why* pairing sometimes works and sometimes does not, which the twentieth-century revisions answered (Tasman 2015).

8.2 The four core phenomena of Pavlovian learning

Every classical-conditioning answer must name these four. They are examined as pure psychology and as the mechanics of exposure therapy.

Acquisition

Acquisition is the initial learning phase in which the CR is established and strengthened over successive CS to US pairings; it is faster when the US is intense or salient and when the CS is novel.

Extinction

Extinction is the weakening and eventual disappearance of the CR when the CS is presented repeatedly *without* the US. It does not erase the original learning; it lays down new "the CS is safe" learning on top of it. Extinction is the theoretical engine of exposure therapy (Kaplan & Sadock 2024).

Spontaneous recovery

After extinction and a rest interval, presenting the CS again elicits the CR in diminished strength, proving the original association was not destroyed. Clinically it is the model for the return of a treated phobia after a symptom-free gap.

Stimulus generalisation and discrimination

Generalisation is the spread of the CR to stimuli resembling the CS (a child bitten by a spaniel fears all dogs). *Discrimination* is the complementary narrowing: the organism learns to respond only to the exact CS and not to similar stimuli, achieved by pairing the true CS with the US while presenting similar stimuli without it.

A fifth, higher-order (second-order) conditioning, extends the reach of a CS: once a CS reliably elicits a CR, pairing a *new* neutral stimulus with that established CS (with no US present) makes the new stimulus a CR-eliciting signal in its own right, which is how conditioned fear can spread to cues never once paired with the original trauma (Kaplan & Sadock 2024).

8.3 Watson and Rayner (1920): Little Albert and the behaviourist manifesto

What it fixed: it proved human emotion obeys Pavlov's law, not just canine salivation. John B. Watson, who had declared in his 1913 behaviourist manifesto that psychology should study only observable behaviour and treat consciousness as outside its scope, set out with Rosalie Rayner to show that a human emotion could be conditioned. In the **Little Albert** experiment (1920) an eleven-month-old infant was shown a white rat (initially neutral, even pleasant) while a steel bar was struck loudly behind his head (the US, producing the UR of startle and fear). After a few pairings the rat alone (now the CS) elicited crying and withdrawal (the CR of conditioned fear). Crucially the fear *generalised* to a rabbit, a dog, a fur coat and a Santa Claus mask, demonstrating stimulus generalisation of a conditioned emotion (Kaplan & Sadock 2024). Watson thereby claimed emotions are built by conditioning, not inherited fully formed, the empirical anchor of his environmentalist manifesto ("give me a dozen healthy infants..."). The complementary case, *Peter* (deconditioned of an animal fear by pairing a caged rabbit, moved gradually closer, with a favourite food), is the historical seed of systematic desensitisation (Kaplan & Sadock 2024). What it left debated: *which* arrangements of CS and US in time actually produce learning, and why some pairings fail, taken up next.

CLINICAL ANCHOR

Little Albert is the textbook model of specific phobia: a neutral object becomes a fear cue by pairing with an aversive event, then generalises. The mirror image, Peter, is the model of exposure-based cure. Both together make the two-line clinical story the exam wants: fear is conditioned in and extinguished out.

8.4 The timing of CS and US: delay, trace, simultaneous, backward

What it fixed: it specified the temporal arrangement that makes conditioning strong or absent. Because the CS works by *predicting* the US, its onset must precede the US for good learning. The four classic arrangements, in descending order of effectiveness, are a high-yield MCQ:

PARADIGM	TEMPORAL ARRANGEMENT	STRENGTH OF CONDITIONING
Delay conditioning	CS begins, then continues (overlaps) until the US is delivered	**Strongest; the standard optimal arrangement**
Trace conditioning	CS begins and *ends*, then a gap (trace interval), then the US	Weaker; must hold a memory trace of the CS across the gap
Simultaneous conditioning	CS and US presented at the same instant	Poor; the CS predicts nothing new
Backward conditioning	US precedes the CS (CS comes after)	**Weakest, often inhibitory; the CS signals the US is over**

The four Pavlovian timing paradigms ordered by efficacy: delay is best, backward is worst, and the rule is that the CS must come before and predict the US (Kaplan & Sadock 2024).

RULE **The CS must come before and predict the US.** Efficacy runs delay > trace > simultaneous > backward, with backward (US first) often inhibitory because the CS then signals the US is over.

8.5 Rescorla and Wagner (1972): conditioning is prediction, not contiguity

What it fixed: it replaced "pairing causes learning" with "surprise causes learning". Research from the late 1960s showed that a CS to US pairing does *not* guarantee conditioning. Two findings forced the change. In **blocking** (Kamin), if one CS already reliably predicts the US, a second CS added to it acquires little conditioning, because it carries no new information. In the *contingency* experiments (Rescorla), the organism treats the CS as a signal only when the US is *more probable* in the presence of the CS than in its absence; if the US occurs equally often with and without the CS, no conditioning develops despite many pairings. The lesson is that **contingency** (predictive relationship), not mere **contiguity** (co-occurrence), drives learning (Kaplan & Sadock 2024). The *Rescorla-Wagner model* made this formal: the change in a CS's associative strength on any trial is proportional to the discrepancy between the US that *actually* occurs and the US already *predicted* by all cues present, that is, the **prediction error** (or surprise). A fully predicted US drives no further learning (error is zero); an unexpected US drives strong learning; a US smaller than predicted drives inhibitory learning. This "learning is driven by prediction error" idea is the direct ancestor of the dopaminergic reward-prediction-error account

in modern computational psychiatry. What it left debated: *which* CS to US associations form easily and which resist, answered by preparedness (Kaplan & Sadock 2024).

HOLD THIS

Conditioning is driven by contingency (prediction), not mere contiguity (co-occurrence). A fully predicted US drives no further learning; surprise does, which is why blocking occurs and why classical conditioning is now read as prediction-error learning under biological constraint.

8.6 Preparedness: Seligman, taste aversion and the Garcia effect

What it fixed: not all pairings are equal; evolution biases which associations form. The Rescorla-Wagner era treated the CS and US as interchangeable, but Seligman's concept of **preparedness** (1971) holds that organisms are biologically *prepared* to associate certain CS to US combinations far more readily than others, because those associations were adaptive over evolutionary time. The decisive evidence is *conditioned taste aversion*, the *Garcia effect* (Garcia and Koelling): a rat that becomes ill hours after tasting a novel flavour will avoid that flavour thereafter, and this learning violates the ordinary rules, because it forms after a *single* trial and across a delay of hours between CS (taste) and US (nausea) that would abolish any normal Pavlovian pairing. Critically, tastes are readily associated with *illness* but not with shock, whereas audio-visual cues are readily associated with *shock* but not illness (belongingness). Preparedness explains why human phobias cluster on evolutionarily threatening objects (snakes, spiders, heights, blood) rather than on modern dangers (electric sockets, cars) that are as often paired with pain (Kaplan & Sadock 2024).

CLINICAL ANCHOR

The Garcia effect is the direct model of *anticipatory nausea and vomiting* in chemotherapy: the clinic, the smell of the infusion suite or a particular food eaten before a cycle becomes a CS that elicits nausea (CR) before the cytotoxic drug (US) is even given. Single-trial, delay-bridging taste-aversion learning is exactly why patients develop food aversions after one bad cycle.

8.7 The currently accepted position and its neural correlate

Conditioning is prediction-error learning under biological constraint, and fear conditioning has a mapped circuit. The **currently accepted** synthesis keeps Pavlov's phenomena but reinterprets them: acquisition is the accrual of associative strength driven by prediction error; extinction is *new inhibitory learning* (not erasure), which is why the response returns as spontaneous recovery, renewal (context change) and reinstatement; and preparedness sets which associations form. The **neural correlate** is best defined for conditioned fear: the *amygdala*, specifically the basolateral complex, is where CS and US converge and the fear memory is stored, with the central nucleus driving the autonomic and behavioural fear output; the *hippocampus* encodes the context (essential for context-dependent renewal); and the *ventromedial prefrontal cortex* drives extinction learning and top-down inhibition of the amygdala (the LeDoux and Milad-Quirk circuitry). Extinction being new learning rather than unlearning is precisely why exposure therapy relapses when the patient leaves the treatment context, and why extinction is

now augmented pharmacologically (for example D-cycloserine facilitating NMDA-dependent extinction consolidation) (Kaplan & Sadock 2024; Stahl 2021).

> **PEARL**
>
> Extinction is not forgetting. The CR that "disappeared" in the clinic can come back three ways: *spontaneous recovery* (time passes), *renewal* (the CS is met in a new context) and *reinstatement* (the US is encountered again). This single fact explains post-exposure phobia relapse, and it is the highest-value clinical pearl of the whole topic.

8.8 Clinical yield: phobia, chemotherapy nausea, addiction cue reactivity

Three disorders, one mechanism. Classical conditioning is examinable chiefly as the substrate of three clinical phenomena (Kaplan & Sadock 2024; New Oxford Textbook 2020):

Conditioned fear to phobia

A neutral object paired with an aversive event becomes a fear CS, generalises, and is maintained by avoidance (which prevents extinction). Treatment is extinction by graded exposure.

Conditioned nausea in chemotherapy

Anticipatory nausea and vomiting is a prepared, taste-aversion-like CR to clinic cues; treatable by behavioural desensitisation and by minimising cue salience.

Cue reactivity in addiction

Drug-paired cues (paraphernalia, places, people, the sight of a needle) become CSs that, via Pavlovian conditioning, elicit conditioned craving, autonomic arousal and conditioned compensatory (tolerance-like) responses, driving relapse. Cue-exposure therapy attempts extinction; the renewal effect explains why extinction in a clinic often fails to transfer to the street (cross-refer SUD).

8.9 Worked example: the dental phobia, read through the whole apparatus

Run one everyday fear through every term. A man tenses and feels his knees weaken merely on entering the waiting room of a dentist he is visiting for a routine cleaning (Tasman 2015).

Acquisition

A previous painful procedure (the US) elicited a fear-and-pain response (the UR). The dentist's office, paired with that pain, became a CS.

Conditioned response

Now the office alone (CS) elicits fear (the CR): sweating, weak knees, dread, before any drilling.

Generalisation

The fear spreads: the smell of antiseptic, the sound of a drill next door, even a white coat can now trigger it.

Higher-order conditioning

The appointment-reminder text, paired only with the already-feared office and never with pain, itself starts to trigger dread.

Preparedness

Pain-linked cues condition readily and fast; a single bad extraction can establish the phobia, echoing prepared, few-trial fear learning.

Extinction and its limits

Repeated painless visits (CS without US) extinguish the fear. But after a year's gap the dread can return (*spontaneous recovery*), or reappear at a *new* clinic (*renewal*), because extinction added a "safe" meaning without deleting the "dangerous" one.

Neural correlate

The office-fear association is held in the basolateral amygdala; the return of fear in a new clinic reflects hippocampal context coding; successful exposure depends on ventromedial prefrontal cortex driving extinction over the amygdala.

COMMON TRAP

Do not confuse classical with operant conditioning. In *classical* conditioning a *stimulus* comes to elicit an involuntary, reflexive response (the response is *elicited* by an antecedent CS: salivation, fear, nausea). In *operant* conditioning a *voluntary behaviour* is strengthened or weakened by its *consequences* (reinforcement or punishment). A second frequent slip: "extinction" means different things in the two paradigms only superficially; in both it is the decline of the response when the maintaining event (the US, or the reinforcer) is withheld, but in neither does it erase the original learning.

MNEMONIC

Timing efficacy: "Delay Dominates, Backward is Broken" (D > T > S > B)

Delay (overlapping CS) is strongest, then Trace (gap), then Simultaneous, then Backward (weakest, often inhibitory). The single rule underneath: the CS must come **before** and **predict** the US. For the reflex terms, remember the US to UR pair is *unlearned* (both begin with the natural reflex) and the CS to CR pair is *conditional* on training.

INDIA

Cue-reactivity conditioning is directly usable in Indian addiction practice, where alcohol and tobacco (including gutka and khaini) dependence is highly cue-bound: the tea-shop, the after-meal ritual, the paan corner and specific companions act as powerful CSs for craving. Relapse-prevention counselling that identifies and plans around these conditioned cues (a behavioural, low-cost intervention) fits resource-limited settings well, and the renewal effect warns that skills learned in an inpatient de-addiction ward may not transfer home unless practised in the patient's own high-risk contexts.

GOOD TO REMEMBER

- **Classical (Pavlovian, respondent) conditioning:** a neutral stimulus paired with a US comes to elicit an anticipatory CR; the model of conditioned fear, nausea and craving.
- **Pavlov (1927):** reflex vocabulary (US, UR, CS, CR) and the core phenomena; the dog-bell-salivation paradigm.
- **US / UR:** unconditioned (unlearned) stimulus and its innate reflex response (food to salivation).
- **CS / CR:** conditioned (learned) stimulus and its trained response (bell to salivation); the CR is usually weaker than the UR.
- **Acquisition:** the initial phase of learning and strengthening the CR over CS to US pairings.
- **Extinction:** decline of the CR when the CS is repeatedly presented without the US; new inhibitory learning, not erasure; basis of exposure therapy.
- **Spontaneous recovery:** reappearance of an extinguished CR (diminished) after a rest interval; proves the original learning survives.
- **Stimulus generalisation / discrimination:** spread of the CR to similar stimuli / learned narrowing to the exact CS.
- **Higher-order (second-order) conditioning:** a new neutral stimulus paired with an established CS becomes CR-eliciting without the US.
- **Watson and Rayner (1920), Little Albert:** conditioned fear of a white rat (US = loud noise) that generalised; empirical anchor of the behaviourist manifesto (Watson 1913).
- **Timing paradigms:** delay (strongest) > trace > simultaneous > backward (weakest); CS must precede and predict the US.
- **Rescorla-Wagner (1972):** learning is driven by prediction error (surprise); explains blocking; contingency, not mere contiguity, produces conditioning.
- **Blocking (Kamin):** a CS that predicts nothing new (a second cue already predicts the US) acquires little conditioning.
- **Preparedness (Seligman 1971):** organisms are biologically biased toward some CS to US associations; explains the object-selectivity of phobias.
- **Garcia effect / conditioned taste aversion:** single-trial, long-delay taste-to-illness learning; belongingness (taste with illness, not shock); model of chemotherapy anticipatory nausea.
- **Neural correlate:** basolateral amygdala stores the fear CS to US association; hippocampus codes context (renewal); ventromedial prefrontal cortex drives extinction.

9 · Operant conditioning and reinforcement schedules

Learning by consequence, and the timetables that shape it. Where classical conditioning is about associations between stimuli, **operant conditioning** (also called instrumental conditioning) is about how the consequences of a voluntary action change the future probability of that action. A behaviour that operates on the environment is an **operant**; if its consequence strengthens it, the consequence is a **reinforcement**, and if the consequence weakens it, the consequence is a **punishment**. The exam wants this as an evolutionary sequence of ideas: Thorndike's law of effect from the puzzle box, Skinner's formalisation of the operant and the four-cell reinforcement-versus-punishment matrix, the derived techniques (shaping, chaining, extinction, stimulus control), the four schedules of reinforcement with their signature response patterns, and the modern reward-learning synthesis anchored to dopamine.

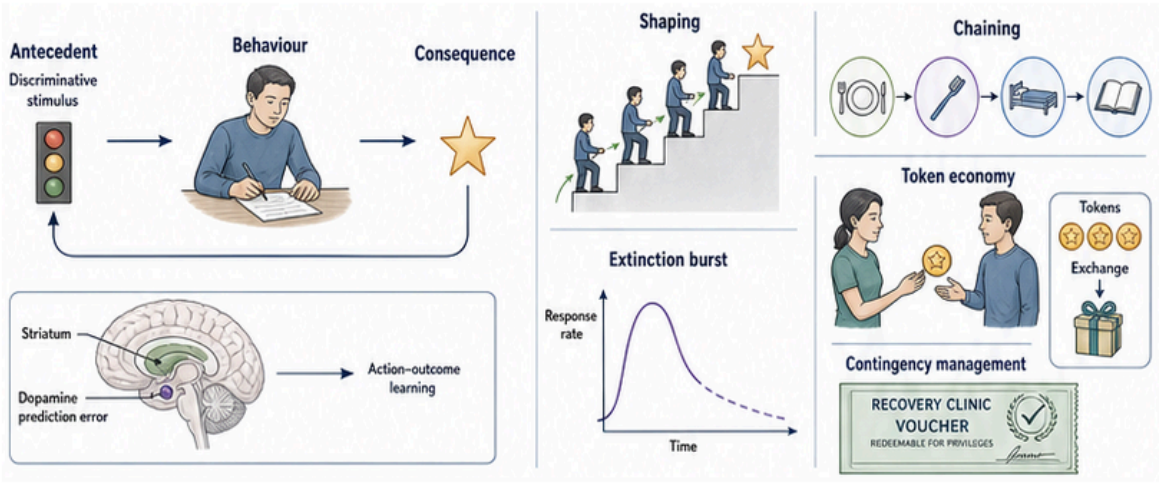


Fig 5.10 Operant learning: consequences select behaviour.

This is one of the highest-yield theory blocks in the behavioural-science paper because the whole of behaviour therapy, applied behaviour analysis, token economies and contingency management is built on it (Kaplan & Sadock 2024). Treat the four-cell matrix and the four schedules as the two must-reproduce items; the clinical arm (token economy, contingency management) is developed in the behaviour-therapy topic and is only cross-referenced here.

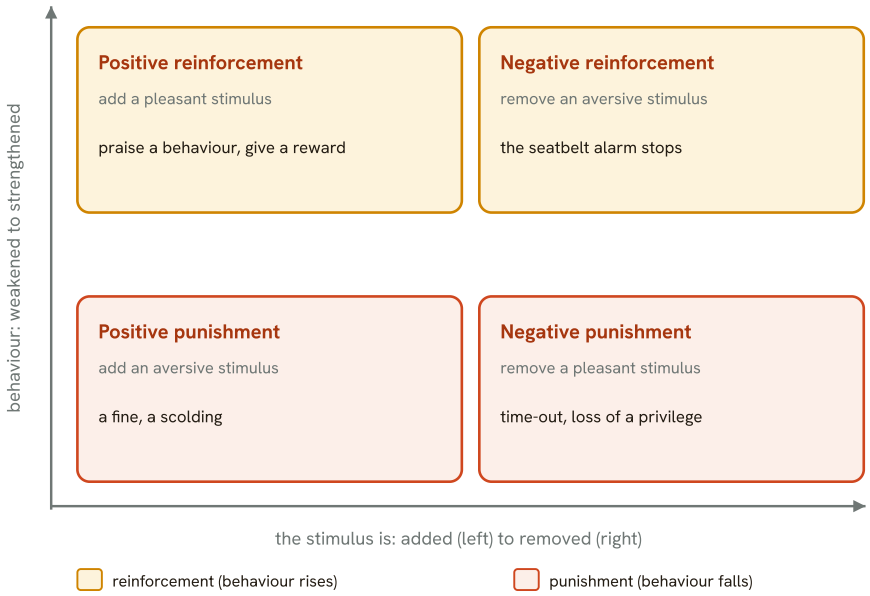


Fig 5.11 The operant matrix. "Positive" and "negative" mean the stimulus is added or removed, not good or bad; "reinforcement" and "punishment" mean the behaviour is strengthened or weakened. Reading the two axes gives the four operations: positive reinforcement (add a pleasant stimulus), negative reinforcement (remove an aversive one), positive punishment (add an aversive one) and negative punishment (remove a pleasant one). The commonest exam trap is confusing negative reinforcement, which strengthens behaviour, with punishment, which weakens it.

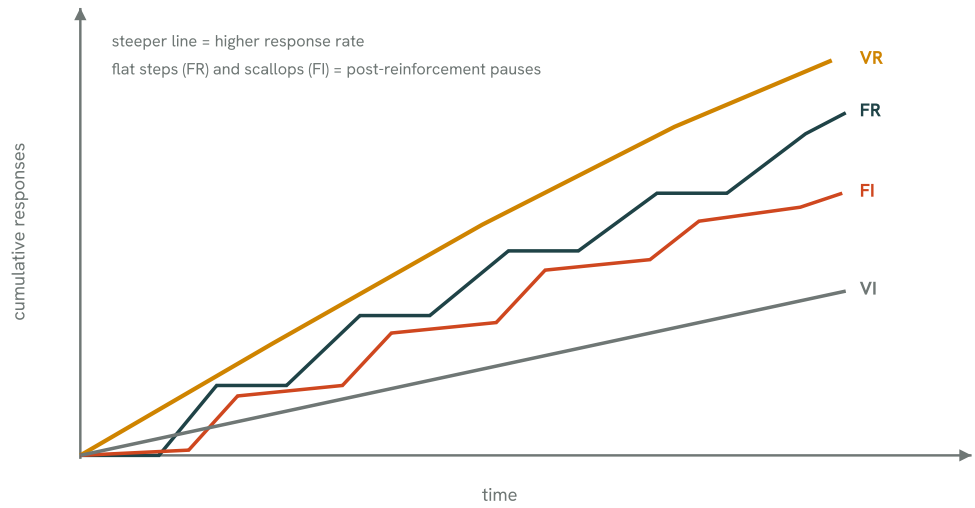


Fig 5.12 The four schedules of reinforcement as cumulative-response curves. Ratio schedules (reinforce after a number of responses) drive higher rates than interval schedules (reinforce the first response after a time). Variable schedules produce steady responding, while fixed schedules produce a pause after each reinforcement: the fixed-ratio step and the fixed-interval scallop. The variable-ratio schedule (VR) gives the highest, steadiest rate and the greatest resistance to extinction, which is why it is the schedule of gambling.

9.1 Definition: the operant and the law of consequences

A behaviour controlled by its consequences, not by an antecedent trigger. The defining contrast with Pavlovian learning is that a respondent is *elicited* and controlled by an antecedent stimulus, whereas an **operant** is *emitted* and controlled by its consequences (Kaplan & Sadock 2024). A rat is not compelled to press a lever the way it is compelled to salivate to food; it presses because pressing has been followed by a reinforcer, and if the reinforcer is withdrawn the pressing stops. Clinically this distinction is the first fork in any behavioural analysis: if a child acts out in class, the clinician asks whether the behaviour is a respondent (change its antecedents) or an operant (change its consequences) before intervening (Kaplan & Sadock 2024).

9.2 Theory one: Thorndike's law of effect (the puzzle box)

The first systematic account, from a hungry cat in a box. Edward Thorndike (1874 to 1949) placed a hungry cat in a "puzzle box" from which it could escape to food by operating a latch (Thorndike 1913, cited in Tasman Psychiatry). At first the cat unlatched the door only by accident; on being replaced it escaped progressively faster, until it operated the latch immediately. From this Thorndike derived the **law of effect**: a response followed by a satisfying consequence is strengthened (stamped in) and one followed by an annoying consequence is weakened (Kaplan & Sadock 2024). **What it fixed and what it left debated.** The law of effect fixed the absence of any mechanism for goal-directed learning, giving a lawful relation between action and outcome. What it left debated was the internal process: Thorndike's "stamping in" was a blunt strengthening metaphor with no account of what the animal actually learned, a gap the later action-outcome view had to fill.

9.3 Theory two: Skinner formalises the operant

The free operant and the experimental analysis of behaviour. In the late 1930s B. F. Skinner (Skinner 1938) enclosed a rat in a chamber (the operant chamber, popularly the "Skinner box") with a lever it was free to press repeatedly whenever it "wanted," earning a food pellet each time (Kaplan & Sadock 2024). This "free operant" arrangement, unlike Thorndike's discrete escape trials, let response *rate* be measured continuously and made behaviour a lawful function of its scheduled consequences. Skinner held that operant principles, reinforcement, punishment, extinction and stimulus control, could in principle explain virtually all human behaviour (Skinner 1938, cited in Tasman Psychiatry), and it was the specific application of these principles that became *applied behavioural analysis* and the engine of the 1950s to 1960s behaviour-therapy movement (Kaplan & Sadock 2024).

9.4 The core four-cell matrix: reinforcement versus punishment

Two questions: is a stimulus added or removed, and does the behaviour strengthen or weaken. The single most examined structure in this topic is the two-by-two matrix built from crossing *add versus remove* a stimulus with *strengthen versus weaken* the behaviour. "Positive" and "negative" here mean added and removed (like arithmetic signs), *not* pleasant and unpleasant; "reinforcement" always strengthens and "punishment" always weakens.

Positive reinforcement

An appetitive stimulus is *added* after the behaviour, strengthening it. A child praised for tidying their room tidies more (Tasman Psychiatry).

Negative reinforcement

An aversive stimulus is *removed* or avoided by the behaviour, strengthening it. A student studies to avoid failing; taking a painkiller removes pain and so is reinforced. Note it *increases* behaviour and is not punishment.

Positive punishment

An aversive stimulus is *added* after the behaviour, weakening it. A reprimand added after talking back.

Negative punishment

An appetitive stimulus is *removed* after the behaviour, weakening it. The classic form is *time-out from reinforcement* and the loss of privileges or a fine (Kaplan & Sadock 2024).

	STIMULUS ADDED (POSITIVE)	STIMULUS REMOVED (NEGATIVE)
Behaviour strengthened	Positive reinforcement (add appetitive: praise, food)	**Negative reinforcement (remove aversive: escape, avoidance)**
Behaviour weakened	Positive punishment (add aversive: reprimand, shock)	**Negative punishment (remove appetitive: time-out, fine)**

The columns are the discriminator most candidates get wrong: the sign is about adding versus removing a stimulus, never about the stimulus being nice or nasty. Negative reinforcement increases behaviour; punishment decreases it.

HOLD THIS

Positive/negative = a stimulus added or removed; reinforcement/punishment = behaviour up or down. Decode the two words independently, and never call negative reinforcement (which increases behaviour) a punishment.

COMMON TRAP

Negative reinforcement is *not* punishment. Both "negatives" involve removal, but negative reinforcement removes an *aversive* stimulus and so *increases* behaviour, whereas negative punishment removes an *appetitive* stimulus and so *decreases* it. The second trap: punishment suppresses a behaviour only temporarily and teaches no alternative, so a reprimanded child may suppress the urge to talk back yet learn no better way to communicate, or may even escalate if the scolding is the only attention (a positive reinforcer) on offer (Tasman Psychiatry).

9.5 Primary versus secondary (conditioned) reinforcers

Innately rewarding versus reward by association. A *primary reinforcer* is biologically based and rewarding without prior learning: food, water, warmth, nurturance (Tasman Psychiatry). A *secondary* or *conditioned reinforcer* has no intrinsic value and becomes reinforcing only by being paired with a primary reinforcer: money, praise, a grade, and the tokens of a token economy (Kaplan & Sadock 2024). A lollipop reinforces a child by primary means; a word of praise reinforces by conditioned means (Tasman Psychiatry). A *generalised* conditioned reinforcer such as money is one paired with many different primaries, which is why it reinforces so broadly. This is the conceptual basis of the token economy, developed in the behaviour-therapy topic.

9.6 The Premack principle

A high-probability behaviour reinforces a low-probability one. Rather than testing reinforcers by trial and error, the **Premack principle** (David Premack) predicts them from preference: if you rank a person's freely chosen activities by time spent, access to a *more-preferred* activity will reinforce a *less-preferred* one (Kaplan & Sadock 2024). For a child who prefers pinball to candy, pinball reinforces candy-eating; for one with the reverse preference, candy reinforces pinball. In everyday form this is "grandma's rule," first you eat your vegetables, then you get dessert. The refinement is that even a low-preference activity can reinforce a higher one if the person has been deprived of it below baseline (the response-deprivation account) (Kaplan & Sadock 2024).

9.7 Shaping by successive approximation, and chaining

Building a behaviour that never occurs spontaneously. **Shaping** is the operant technique of reaching a behavioural goal in stepwise fashion by selectively reinforcing closer and closer approximations to the desired behaviour (Kaplan & Sadock 2024). To teach a rat to press a high lever, you first reinforce facing it, then approaching, then touching, then pressing, raising the criterion at each step. Clinically a physician's praise for each successive step of a health-promoting change shapes a durable lifestyle change (Tasman Psychiatry). *Chaining* is the linked cousin: a complex sequence is built by joining individual responses, each response producing the discriminative stimulus for the next and the terminal reinforcer maintaining the whole chain (as in teaching a multi-step self-care routine, often taught in reverse as backward chaining).

9.8 Extinction and the extinction burst

Withhold the reinforcer and the behaviour declines, but not smoothly. *Extinction* is the decline of an operant when its reinforcer is no longer delivered (Kaplan & Sadock 2024): a tantrum maintained by parental attention fades when attention is consistently withheld. The clinically vital caveat is the *extinction burst*, a transient *increase* in the frequency, intensity and variability of the behaviour immediately after reinforcement stops, before it declines. Parents who relent during the burst inadvertently reinforce a louder tantrum on a leaner schedule. Extinction does not erase the original learning: *spontaneous recovery*, *renewal*, *reinstatement*, *rapid reacquisition* and *resurgence* (return of an old behaviour when a replacement is itself extinguished) all show the learning is suppressed and context-bound, not destroyed (Kaplan & Sadock 2024). This is exactly why exposure gains relapse and why relapse-prevention work matters.

9.9 Discriminative stimuli and stimulus control

When behaviour comes under the control of a signal. A *discriminative stimulus* (S-D) is a cue in whose presence a response is reinforced; behaviour that reliably occurs in its presence and not its absence is said to be under *stimulus control* (Kaplan & Sadock 2024). Stimulus control is learned by *discrimination*, distinguishing two similar stimuli because one signals reinforcement and the other does not: a child learns to leave class when the school bell rings but not when a telephone rings (Tasman Psychiatry). Its complement is *generalisation*, responding to stimuli resembling the trained S-D. Clinically, stimulus-control procedures are the backbone of insomnia treatment (the bed becomes a discriminative stimulus for sleep, not for lying awake) and of trigger management in addiction.

9.10 Continuous versus partial reinforcement

Every response, or only some. Under a *continuous* reinforcement schedule every target response is reinforced; this produces the fastest acquisition of a new behaviour. Under a *partial* (intermittent) schedule only some responses are reinforced, which produces slower acquisition but far greater persistence. In the natural world few actions are reinforced every time, so partial schedules are the rule (Kaplan & Sadock 2024). The best practice is therefore to acquire a new behaviour on continuous reinforcement, then thin to a partial schedule to maintain it.

9.11 The four schedules of reinforcement and their response patterns

Ratio versus interval, crossed with fixed versus variable. Partial schedules are classified on two axes: whether reinforcement depends on the *number* of responses (ratio) or on *time* elapsed (interval), and whether the requirement is *fixed* (constant) or *variable* (averages a value but varies trial to trial) (Kaplan & Sadock 2024). Ratio schedules tie reinforcement directly to work done and so drive higher response rates than interval schedules.

Fixed ratio (FR)

Every nth response is reinforced (FR-10 reinforces every 10th). High steady rate with a brief *post-reinforcement pause* after each delivery. Everyday form: piece-rate pay, one reward per fixed quota.

Variable ratio (VR)

Reinforcement after an *average* number of responses that varies unpredictably. Produces the *highest, steadiest response rate and the greatest resistance to extinction* of all four; this is the gambling / slot-

machine schedule, because the next pull might always be the payoff (Kaplan & Sadock 2024).

Fixed interval (FI)

The first response after a fixed time (say 60 seconds) is reinforced. Produces the classic *fixed-interval scallop*: responding nearly stops just after reinforcement, then accelerates as the interval's end approaches. Everyday form: cramming that intensifies as a scheduled exam nears.

Variable interval (VI)

The first response after an *average, varying* interval is reinforced. Produces a low but very steady, extinction-resistant rate. Everyday form: repeatedly checking email, since a new message becomes available at unpredictable times (Kaplan & Sadock 2024).

SCHEDULE	REINFORCED WHEN	RESPONSE PATTERN	EVERYDAY EXAMPLE
Fixed ratio (FR)	After a set number of responses	High rate, post-reinforcement pause	Piece-rate pay
Variable ratio (VR)	After an average, varying number	**Highest rate, most resistant to extinction (the gambling schedule)**	Slot machine
Fixed interval (FI)	First response after a set time	**Scalloped: pause then acceleration toward interval's end**	Cramming before a dated exam
Variable interval (VI)	First response after an average, varying time	Low but steady, extinction-resistant	Checking email for new messages

Discriminators: ratio schedules out-rate interval schedules (reinforcement tracks work); variable schedules out-persist fixed ones (unpredictability blocks the "just been reinforced" pause). Variable ratio is the peak on both counts.

RULE **Ratio out-rates, variable out-lasts, so the variable-ratio schedule wins on both: the highest, most extinction-resistant rate.** It is the gambling schedule; FI gives the scallop.

9.12 The partial-reinforcement extinction effect

Intermittently reinforced behaviour resists extinction longest. The *partial-reinforcement extinction effect* (PREE) is the paradoxical finding that a behaviour reinforced only intermittently persists *longer* when all reinforcement is withdrawn than one that had been continuously reinforced (Kaplan & Sadock 2024). It is paradoxical because the more sparsely rewarded behaviour is the more durable one. One account is that partial reinforcement trains responding *through* non-reward and frustration, so a run of unrewarded responses does not signal "extinction has begun." This is the mechanistic reason variable-ratio behaviours like gambling are so hard to extinguish, and why a tantrum a parent reinforces only occasionally (giving in "just this once") becomes especially entrenched.

TRAP The partial-reinforcement extinction effect is counter-intuitive: **intermittently reinforced behaviour resists extinction longer than continuously reinforced behaviour**, so the more sparsely rewarded habit is the more durable one.

9.13 Escape and avoidance learning; two-factor theory

Both are negative reinforcement, but avoidance is subtler. In *escape* learning the response terminates an aversive event already present (leaving a noisy room stops the noise). In *avoidance* learning the response prevents an aversive event that has not yet occurred, which raises a puzzle: how can the non-occurrence of something reinforce? Mowrer's *two-factor (two-process) theory* answers it by combining both learning types: first, Pavlovian conditioning makes a warning cue elicit fear; second, the avoidance response is negatively reinforced by the *reduction of that conditioned fear* (Kaplan & Sadock 2024). This is the standard learning model of the anxiety disorders: the obsessive-compulsive patient washes to reduce contamination anxiety, the agoraphobic stays home to escape fear of panic-associated places, and the person with bulimia vomits to reduce learned post-meal anxiety, each avoidance response reinforced by fear reduction and thereby maintained (Kaplan & Sadock 2024). Because the feared outcome is prevented, the belief that it would have happened is never disconfirmed, which is precisely why exposure with response prevention is the treatment.

> **CLINICAL ANCHOR**
>
> The negative-reinforcement trap runs through psychiatry. Compulsions, safety behaviours, avoidance in PTSD, and much substance use are maintained because the behaviour removes an aversive internal state (anxiety, craving, withdrawal), which reinforces it and blocks new learning. The therapeutic move, exposure with response prevention, deliberately breaks the negative-reinforcement contingency so the feared consequence can be disconfirmed and the fear extinguished.

9.14 Currently accepted position: reward learning as action-outcome association

From "stamping in" to a computational reward-learning account. The **currently accepted** view has moved beyond Thorndike's mechanical strengthening. The modern synthesis holds that the organism learns an *action to outcome* association (much as Pavlovian learning is stimulus to outcome), and that reinforcers act less as automatic "stampers" than as guides and motivators of goal-directed behaviour (Kaplan & Sadock 2024; Bouton 2016). A second consensus is the goal-directed versus habitual distinction: early instrumental behaviour is goal-directed and sensitive to the value of its outcome, whereas heavily overtrained behaviour becomes an outcome-insensitive *habit*, a shift central to modern models of compulsion and addiction. The quantitative law of effect (the matching law) further specifies that a behaviour's rate depends not only on its own reinforcement but on the reinforcement available for all competing behaviours, which is why enriching a young person's environment with alternative reinforcers lowers the rate of a maladaptive one (Kaplan & Sadock 2024).

9.15 Neural correlate: the dopamine reward-prediction-error system

Where reinforcement is computed in the brain. The *neural correlate* of operant reinforcement is the midbrain dopamine system. Phasic firing of dopamine neurons in the *ventral tegmental area* and *substantia nigra pars compacta*, projecting to the *ventral striatum (nucleus accumbens)* and prefrontal cortex, encodes a *reward prediction error*: dopamine rises when an outcome is better than predicted, is unchanged when it is exactly as predicted, and dips when it is worse than

predicted (Schultz 2016). This teaching signal is the biological implementation of the law of effect and explains why unpredictable schedules are so potent: a variable-ratio payoff is by design a persistent source of positive prediction error, which is the neurobiology behind gambling's grip and the dopaminergic reward pathway's central role in every substance use disorder. The goal-directed-to-habitual transition maps onto a shift from ventral (accumbens) to dorsolateral striatal control.

9.16 Worked example: an outpatient with alcohol dependence

The whole apparatus applied to one patient. A man drinks each evening. *Operant analysis:* drinking is an operant maintained by *negative reinforcement*, it removes the aversive states of anxiety and mounting withdrawal, and by *positive reinforcement*, the euphoriant and social rewards. *Discriminative stimuli:* the pub, payday and certain company are S-D cues that occasion drinking; stimulus-control work removes or re-signals them. *Schedule:* the intoxication reward arrives on a rich, near-continuous schedule, whereas the harms are delayed and intermittent, so present reinforcement dominates. *Extinction and its burst:* early abstinence brings a surge in craving and drink-seeking (an extinction burst) before decline, which must be anticipated so a lapse is not read as failure. *Shaping and Premack:* abstinence is built by reinforcing successive approximations (a dry evening, then a dry week), and higher-probability healthy activities are arranged to reinforce lower-probability recovery tasks. *Neural:* the alcohol cue drives a dopaminergic prediction-error spike in the ventral striatum, and over years control shifts toward dorsal-striatal habit, which is why willpower alone fails. The formal clinical delivery of these contingencies, contingency management and token systems, is developed in the behaviour-therapy topic.

MNEMONIC

"Positive = ADD, Negative = REMOVE; Reinforce = UP, Punish = DOWN. Schedules: VR is king."

For the matrix, decode the two words independently: the first word is whether a stimulus is added (positive) or removed (negative); the second is whether behaviour goes up (reinforcement) or down (punishment). For the schedules, remember **"Ratio out-rates, Variable out-lasts"**: ratio schedules give higher rates, variable schedules give more persistence, so *variable ratio* wins on both, the gambling schedule. For the patterns: **FI = scallop, VR = gambling.**

INDIA

Operant contingencies are culturally and economically loaded. In Indian family systems the most powerful reinforcers are frequently social and relational (parental approval, community standing) rather than material, so a behavioural plan routed through the family reinforcement network usually out-performs an individually addressed token scheme. In gambling and alcohol work, the variable-ratio structure of local betting and the ready, near-continuous availability of alcohol in many settings are the contingency realities any plan must plan around.

PEARL

The one-line arc for an examiner: Thorndike's law of effect (behaviour is selected by its consequences) was formalised by Skinner into the operant and the reinforcement-punishment matrix, elaborated into the techniques (shaping, extinction, stimulus control) and the four schedules (with variable ratio the most powerful), and is now understood as action-outcome reward learning implemented by the dopamine reward-prediction-error signal. Negative reinforcement, not punishment, is the thread that ties compulsions, avoidance and addiction together in the clinic.

GOOD TO REMEMBER

- **Operant conditioning:** behaviour changed by its consequences; the operant is emitted and controlled by consequences, unlike the elicited respondent.
- **Thorndike (1874 to 1949), law of effect (1913):** puzzle-box cats; satisfying consequences stamp a response in, annoying ones stamp it out.
- **Skinner (1938):** the free operant, operant chamber ("Skinner box"), and the experimental analysis of behaviour; founder of the reinforcement-schedule framework.
- **Positive reinforcement:** add appetitive stimulus, behaviour increases (praise, food).
- **Negative reinforcement:** remove/avoid aversive stimulus, behaviour increases (escape, avoidance); NOT punishment.
- **Positive punishment:** add aversive stimulus, behaviour decreases (reprimand, shock).
- **Negative punishment:** remove appetitive stimulus, behaviour decreases (time-out, fine).
- **Primary vs secondary reinforcer:** primary = innately rewarding (food, water); secondary/conditioned = rewarding by pairing (money, praise, tokens).
- **Premack principle (David Premack):** access to a more-preferred behaviour reinforces a less-preferred one ("grandma's rule").
- **Shaping:** reinforcing successive approximations to a target behaviour; chaining links responses into a sequence.
- **Extinction:** withholding reinforcement declines the behaviour; extinction burst = transient surge first; learning suppressed, not erased (spontaneous recovery, renewal, resurgence).
- **Discriminative stimulus / stimulus control:** a cue signalling reinforcement gains control of the behaviour; learned by discrimination, opposed by generalisation.
- **Fixed ratio (FR):** every nth response; high rate with post-reinforcement pause.
- **Variable ratio (VR):** average varying number; highest rate, most resistant to extinction; the gambling schedule.
- **Fixed interval (FI):** first response after a set time; the "scallop" (pause then acceleration).
- **Variable interval (VI):** first response after an average varying time; low but steady, extinction-resistant.
- **Continuous vs partial; PREE:** partial (intermittent) reinforcement resists extinction longer than continuous, the partial-reinforcement extinction effect.
- **Escape vs avoidance; two-factor theory (Mowrer):** Pavlovian fear plus operant fear-reduction; the learning model of anxiety disorders and compulsions.
- **Neural correlate:** dopamine reward-prediction-error signal (VTA/SNc to ventral striatum), Schultz 2016; goal-directed to habitual shift = ventral to dorsal striatum.

10 · Social learning theory (Bandura)

How behaviour is learned by watching, not only by doing. **Social learning** theory, developed by Albert Bandura at Stanford, is the bridge between the older behaviourism of Watson and

Skinner and the cognitive psychology that followed. Its central claim is that people acquire behaviour, emotions and attitudes by **observational learning**, watching a model and its consequences, without ever needing direct reinforcement of their own. Bandura integrated the principles of classical and operant conditioning with observational learning to formulate the tenets of the theory (Kaplan & Sadock 2024), and in doing so placed *cognition*, thoughts, images, beliefs and expectations, at the centre of learning. For the exam, treat this as the pivot on which twentieth-century learning theory turns: the move from **radical behaviourism**, which refused to study the unobservable mind, to the *social-cognitive* account in which expectancies mediate every learned response.

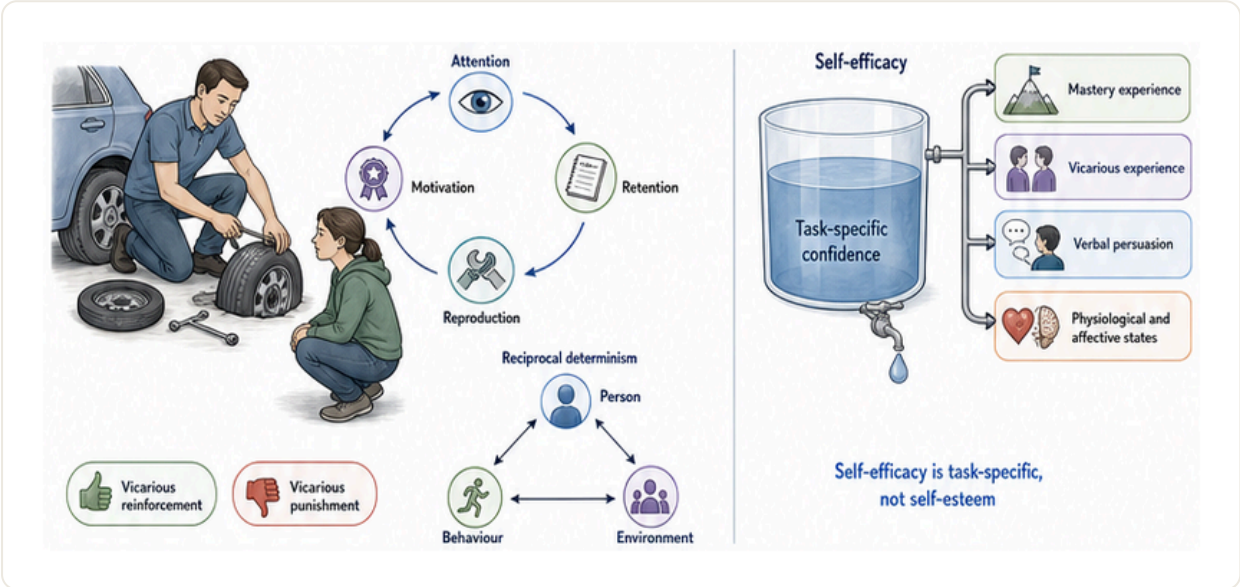


Fig 5.13 Observational learning and self-efficacy.

The clinical reach is large and directly examinable. Bandura's work is one of the three pillars of the 1960s cognitive revolution (with Beck and Ellis), it supplies the theoretical basis for modelling and participant-modelling treatments, and its later concept of **self-efficacy** underpins cognitive behaviour therapy, graded exposure and essentially every behaviour-change intervention now in use (Kaplan & Sadock 2024). Follow the standard arc: define the theory, walk the era in the order it appeared (radical behaviourism, then Rotter and Bandura's social learning, then Bandura's mature social-cognitive theory with reciprocal determinism and self-efficacy), state the currently accepted position, name its behavioural and neural correlate, and close with a worked clinical example.

10.1 What social learning theory claims

Learning through observation, mediated by cognition. Social learning theory (later renamed by Bandura himself as *social-cognitive theory*) holds that most human behaviour is learned by observing others and the consequences their behaviour brings, then reproducing or inhibiting it accordingly. Through observational learning, the process of observing the actions and reactions of others can effect a change in an individual's behaviour without that individual needing direct experience of the situation (Kaplan & Sadock 2024). The theory keeps the conditioning laws of the behaviourists but adds an indispensable cognitive layer: what is stored is not a reflex but a

symbolic *representation* of the modelled act and an *expectancy* about its likely outcome. This is why it is classed as a *social-cognitive* rather than a purely behavioural theory.

10.2 The starting point: radical behaviourism and its limit

The mind ruled out of court. The theory Bandura reacted against was **radical behaviourism**. Steeped in the tradition of Watson, radical behaviourists eschewed the study of cognition, holding that thought processes were mentalistic constructs not observable or verifiable by others and therefore outside science; directly changing behaviour was held to change the associated thoughts and feelings, so direct access to thoughts was deemed unnecessary (Kaplan & Sadock 2024). **What it left debated.** Its fatal gap was that it could not explain learning that occurs with no direct reinforcement of the learner at all, a child acquiring a whole complex behaviour merely by watching an adult, or a fear caught from a frightened parent. It also had no account of the obvious fact that the same reinforcement produces different learning in different people, because it refused to admit the mediating cognitions (expectancies, beliefs) that make the difference. Bandura's theory was built precisely to close that gap.

10.3 Rotter's social learning theory: expectancy and locus of control

The first cognitive amendment to reinforcement. Julian Rotter (1916 to 2014) offered an early version of social learning theory that first inserted cognition into the reinforcement account. Rotter proposed that human behaviour is guided not only by the actual history of reinforcement but also by plans, goals and *expectations* of success: a person performs a behaviour if they believe it is likely to lead to a valued goal (Kaplan & Sadock 2024). From this he derived **locus of control**: individuals with a history of success develop a generalised expectancy that they can control their lives (an *internal* locus of control), whereas those whose efforts have generally failed come to believe outcomes are a matter of luck or the decisions of powerful others (an *external* locus of control). **What it fixed and left open.** Rotter fixed behaviourism's silence on expectancy, showing that subjective probability of reward, not just reward history, drives behaviour. What he left for Bandura was the *mechanism of acquisition*: Rotter explained why we choose an act, but not how a novel behaviour is learned in the first place without ever performing it.

10.4 Bandura's observational learning and modelling

Acquisition without performance. Bandura's decisive addition was **modelling**: a novel behaviour can be acquired in full simply by observing a model perform it, before the observer has ever enacted or been reinforced for it. This is *observational* or *vicarious* learning, and it explains the transmission of language, skills, social conventions, fears and aggression far more economically than trial-and-error conditioning could. Bandura distinguished *acquisition* (learning the behaviour, which happens on observation) from *performance* (whether it is later enacted, which depends on expected consequences), a distinction the behaviourists could not draw. The Companion to Psychiatric Studies lists the empirically established optimum conditions for observational learning: *live modelling*, *perceived similarity* between observer and model, *seeing the model receive reinforcement*, and *familiarity* with the model (Companion to Psychiatric Studies).

10.5 The four subprocesses of observational learning

Attention, retention, reproduction, motivation. Bandura specified that observational learning proceeds through four component subprocesses, each of which must succeed for a modelled behaviour to be learned and shown. This is a classic exam list.

Attention

The observer must attend to the model and perceive the relevant features of the behaviour. Attention is raised by model salience, prestige, perceived similarity to the self, and the observer's own arousal and interest.

Retention

The observed behaviour must be encoded and stored as a symbolic (imaginal or verbal) representation in memory, so it can be recalled later in the model's absence. Rehearsal strengthens retention.

Reproduction (motor reproduction)

The observer must be physically and cognitively capable of converting the stored representation into action, comparing their own performance against the remembered model and refining it.

Motivation (motivational processes)

Even a fully acquired behaviour is performed only if the observer is motivated to do so. Motivation is supplied by anticipated consequences: direct reinforcement, *vicarious* reinforcement (seeing the model rewarded), and self-reinforcement.

10.6 Vicarious reinforcement and vicarious punishment

Consequences that fall on the model steer the observer. A cornerstone of the theory is that reinforcement need not fall on the learner. In **vicarious** reinforcement, seeing a model rewarded for a behaviour increases the observer's likelihood of performing it; in vicarious punishment, seeing a model punished decreases it. The individual thus learns not only on the basis of their own experience but also through vicarious reinforcement from the observation of others (Kaplan & Sadock 2024). This mechanism preserves the acquisition-performance distinction: watching a model be punished does not erase the observer's *learning* of the behaviour, it merely suppresses its *performance*, which reappears if the incentive changes. Vicarious reinforcement is the cognitive engine that lets the four subprocesses translate observation into action.

10.7 The Bobo doll experiments

Aggression transmitted by modelling. The empirical anchor of the theory is the Bobo doll series (Bandura, Ross and Ross 1961). Bandura produced a film of one of his students attacking an inflatable toy, a Bobo doll, and showed it to young children; when the children were subsequently given access to the doll, they copied the student's behaviour and attacked the doll (Companion to Psychiatric Studies). In a more striking extension, the experiment was repeated using a *live* clown instead of the doll (Bandura et al. 1963), and again the children copied the aggressive actions and struck the live clown after watching the film (Companion to Psychiatric Studies). The findings gave scientific legitimacy to the social learning perspective (Kaplan & Sadock 2024) by demonstrating learning of a complex behaviour, physical aggression, purely by observation, in the complete absence of any direct reinforcement of the child. Bandura's demonstration of modelling effects in the 1960s is the reason concern over depicted violence in

television, film, social media and video games is framed in observational-learning terms (Kaplan & Sadock 2024).

COMMON TRAP

Do not say the Bobo doll study proves aggression is simply "imitated." Its precise and examinable point is that a complex behaviour was *acquired by observation with no direct reinforcement of the child*, refuting the radical-behaviourist requirement that the learner be reinforced. Note also that later variants manipulated *vicarious* consequences (models rewarded, punished, or neither): children who saw the model punished showed less spontaneous aggression, yet reproduced it when later offered an incentive, proving the behaviour had been *learned* though not *performed*.

10.8 Reciprocal determinism

Person, behaviour and environment interact both ways. Bandura's mature social-cognitive theory replaced the behaviourists' one-way causal arrow (environment shapes behaviour) with **reciprocal determinism**: the person (cognitions, expectancies, self-efficacy beliefs), their behaviour, and the environment operate as three factors that continuously and mutually influence one another. The environment shapes behaviour, but behaviour also selects and alters the environment, and both are filtered through and act upon the person's cognitions. K&S illustrate the interaction directly: the same observed event, a peer being teased by a class bully, is learned differently depending on the child (an inhibited child thinks "that could happen to me" and withdraws in anxiety; a rambunctious child focuses on the bully and imitates the aggression), and the environment's response to each child's reaction then feeds back to reinforce or extinguish it (Kaplan & Sadock 2024). Reciprocal determinism is what makes the theory *interactionist* rather than environmentally deterministic.

10.9 Self-efficacy: definition and the four sources

The belief in one's own capability to execute a behaviour. Bandura's most influential single concept is **self-efficacy**: a person's belief in their capability to organise and execute the actions needed to manage a given situation or attain a goal. It is not global self-esteem but a task-specific and situation-specific judgement of "can I do this?" In the social-cognitive account of personality, the generalised sense of self-efficacy is treated as the *central individual-difference variable*: people are characterised primarily by their beliefs in their ability to control their lives, because those beliefs powerfully determine the effort they invest in adapting to their surroundings (Kaplan & Sadock 2024). Bandura held that efficacy beliefs are built from four sources, in descending order of potency.

Mastery experience (performance accomplishment)

The most powerful source: succeeding at the task oneself. Repeated personal success raises efficacy; repeated failure, especially early, lowers it. This is why graded, success-yielding exposure is the strongest efficacy-builder in therapy.

Vicarious experience (modelling)

Seeing similar others succeed ("if they can do it, so can I") raises efficacy, most strongly when the model is perceived as similar to the self. The direct clinical link to observational learning.

Verbal (social) persuasion

Being credibly encouraged or persuaded that one is capable. Weaker and more fragile than the first two, but it can raise the effort a person is willing to try.

Physiological and affective state

The person reads their own bodily and emotional arousal as information: a pounding heart and dread are interpreted as evidence of incapacity, so reducing arousal (or reappraising it) raises efficacy. Explains why calming physiology aids performance.

RULE **Mastery experience is the most powerful source of self-efficacy.** This is why graded, success-yielding exposure, not reassurance, is the strongest efficacy-builder in therapy.

10.10 Self-efficacy and self-perpetuating maladaptive behaviour

Why low efficacy is self-confirming. Low self-efficacy is not merely a symptom; in Bandura's account it is a cause that maintains disorder. Individuals who lack a strong sense of self-efficacy in social situations avoid them, and as a consequence fail to learn the social skills that would have enhanced their confidence, so self-defeating behaviours that look irrational from outside are understandable within the dynamics of learning (Kaplan & Sadock 2024). The avoidance protects the low efficacy belief from disconfirmation, a vicious cycle that maps precisely onto the maintenance model of the anxiety disorders and social phobia. Raising self-efficacy, chiefly through mastery experiences delivered as graded exposure, breaks the loop.

10.11 Currently accepted position

Social-cognitive theory as the settled synthesis. The **currently accepted** position is Bandura's mature *social-cognitive theory*: behaviour is learned through observation and direct experience, is mediated throughout by cognitive processes (symbolic representation, outcome expectancies and self-efficacy beliefs), and is co-determined by the reciprocal interaction of person, behaviour and environment. Social-cognitive approaches are among the most influential frameworks in current personality and behaviour-change research (Kaplan & Sadock 2024). All contemporary cognitive behaviour therapy protocols rest on the principles of social learning theory (Kaplan & Sadock 2024): the radical-behaviourist prohibition on studying cognition has been fully abandoned, and the "cognitive turn" Bandura, Beck and Ellis initiated in the 1960s is now orthodox. The concept has also generalised, with later theorists (for example Hazel Markus's "possible selves") extending social learning from specific behaviours to whole identities (Kaplan & Sadock 2024).

HOLD THIS

Bandura's move is acquisition without direct reinforcement: behaviour is learned by watching a model (Bobo doll), through four subprocesses and vicarious reinforcement, and organised around self-efficacy. Learning (acquisition) is distinct from doing (performance).

10.12 Behavioural and neural correlate

Where modelling lives in the brain. Behaviourally, observational learning is expressed as imitation, vicarious conditioning (acquiring a conditioned emotional response by watching another's), and the graded rise in performance and persistence that tracks rising self-efficacy. The candidate *neural correlate* of imitation and action-observation is the *mirror neuron system*, first

described in macaque premotor cortex and, in humans, mapped to a network centred on the *inferior frontal gyrus / ventral premotor cortex* and the *inferior parietal lobule*, which discharges both when an action is performed and when the same action is observed, providing a plausible substrate for learning by watching. Vicarious emotional learning (learning fear by observing another's fear) recruits the same fear circuitry as direct conditioning, notably the *amygdala*. These localisations are an active and still-debated literature (the behavioural specificity of "mirror" responses in humans remains contested), so treat them as the direction of travel rather than as fixed exam facts.

10.13 Worked clinical example: modelling and self-efficacy in a specific phobia

The theory applied to a dog phobia. Take a child with a specific phobia of dogs. *Origin (observational learning):* the fear may never have involved a bite; it can be caught by observing a frightened parent recoil from dogs (vicarious emotional learning), which is why phobias run in families. *Reciprocal determinism:* the child's fear cognition drives avoidance (behaviour), which shrinks their exposure to friendly dogs (environment), which prevents disconfirmation and entrenches the fear, each factor feeding the others. *Self-efficacy:* the child holds a low efficacy belief, "I cannot cope near a dog." *Treatment built from the theory:* Bandura's own participant modelling is the prototype, the therapist first *models* calm approach to the dog (vicarious experience), often using a peer model similar to the child to maximise perceived similarity, then guides the child through *graded mastery experiences* of approaching and touching the dog, the most potent efficacy source, while keeping arousal low so the child does not read their own racing heart as proof of danger (physiological state) and offering credible encouragement (verbal persuasion). Rising self-efficacy and repeated non-catastrophic outcomes extinguish the avoidance. This is exactly the logic of graded exposure in modern CBT, and it is drawn straight from social learning theory (Kaplan & Sadock 2024).

CLINICAL ANCHOR

Self-efficacy is the concept that ties Bandura to everyday psychiatric practice. Graded exposure works chiefly by delivering *mastery experiences*; participant modelling adds *vicarious experience*; the therapeutic relationship supplies *verbal persuasion*; and arousal-reduction skills address the *physiological state*. When an intervention "builds confidence," the mechanism you should name in an exam is a rise in task-specific self-efficacy across Bandura's four sources.

INDIA

Observational learning is culturally weighted toward high-status and familiar models. In much Indian practice, adherence and health behaviours shift most when the model is a trusted elder, senior clinician or community figure the patient perceives as similar and authoritative, satisfying Bandura's "perceived similarity," "prestige" and "familiarity" conditions at once. Peer-modelling and family-inclusive demonstrations therefore often outperform individually delivered instruction.

MNEMONIC

Subprocesses "A RRM"; efficacy sources "My Very Persuasive Physiology"

A-R-R-M = the four observational-learning subprocesses in order: *A*ttention, *R*etention, *R*eproduction, *M*otivation. **My Very Persuasive Physiology** = the four self-efficacy sources in descending potency: *M*astery experience, *V*icarious experience, verbal *P*ersuasion, *P*hysiological/affective state.

PEARL

The one-line arc for an examiner: learning theory moved from radical behaviourism (mind excluded) to Rotter's expectancy-and-locus-of-control amendment, then to Bandura's social learning, in which behaviour is acquired by observation (Bobo doll) through four subprocesses and vicarious reinforcement, governed by reciprocal determinism, and organised around self-efficacy (four sources), the whole now the "social-cognitive" theory that underpins CBT and exposure. Name that sequence and the "cognitive turn" and you have framed the topic.

GOOD TO REMEMBER

- **Albert Bandura:** founder of social learning / social-cognitive theory; integrated classical and operant conditioning with observational learning at Stanford.
- **Observational (vicarious) learning:** behaviour acquired by watching a model and its consequences, with no direct reinforcement of the learner.
- **Four subprocesses (A-R-R-M):** Attention, Retention, Reproduction (motor), Motivation.
- **Optimum conditions for observational learning:** live modelling, perceived similarity, seeing the model reinforced, familiarity with the model (Companion to Psychiatric Studies).
- **Vicarious reinforcement / punishment:** consequences falling on the model raise or suppress the observer's performance; learning persists even when performance is suppressed (acquisition vs performance).
- **Bobo doll (Bandura, Ross & Ross 1961):** children copied filmed aggression toward the inflatable doll; live-clown replication (Bandura et al. 1963). Aggression transmitted by modelling without direct reinforcement.
- **Reciprocal determinism:** person (cognition), behaviour and environment continuously and mutually interact; interactionist, not environmentally deterministic.
- **Self-efficacy:** task-specific belief in one's capability to execute a behaviour; the central individual-difference variable in social-cognitive personality theory (Kaplan & Sadock 2024).
- **Four sources of self-efficacy (descending potency):** mastery experience, vicarious experience (modelling), verbal persuasion, physiological/affective state.
- **Julian Rotter (1916 to 2014):** early social learning theory; behaviour guided by expectancy of a valued goal; internal vs external locus of control.
- **Radical behaviourism (Watson tradition):** excluded cognition as unobservable; Bandura's "cognitive turn" (with Beck and Ellis, 1960s) overturned it.
- **Currently accepted:** social-cognitive theory; all contemporary CBT protocols rest on social learning theory principles (Kaplan & Sadock 2024).
- **Neural correlate (debated):** mirror neuron system, inferior frontal gyrus / ventral premotor cortex and inferior parietal lobule for action observation; amygdala for vicarious fear learning.
- **Clinical reach:** participant modelling and graded exposure build self-efficacy chiefly via mastery experiences; underpins behaviour change generally.

11 · Learning applied to behaviour therapy, ABA and learned helplessness

The learning paradigms are not just theory; they are the therapies. Everything built in the classical and operant topics converges here: the three learning paradigms (respondent, operant, social/observational) each generated a family of clinical techniques, and one paradigm applied to a natural experiment generated a whole model of depression. This is the topic that ties the behavioural-science paper to the clinical papers. The examiner wants you to be able to walk from a learning principle to the named therapy it produced, and back again: from **reciprocal inhibition** to **systematic desensitisation**, from operant reinforcement to the **token economy** and **applied behaviour analysis**, from Pavlovian-plus-operant fear to **exposure** and **flooding**, and from uncontrollable aversive events to **learned helplessness** as a model of depression.

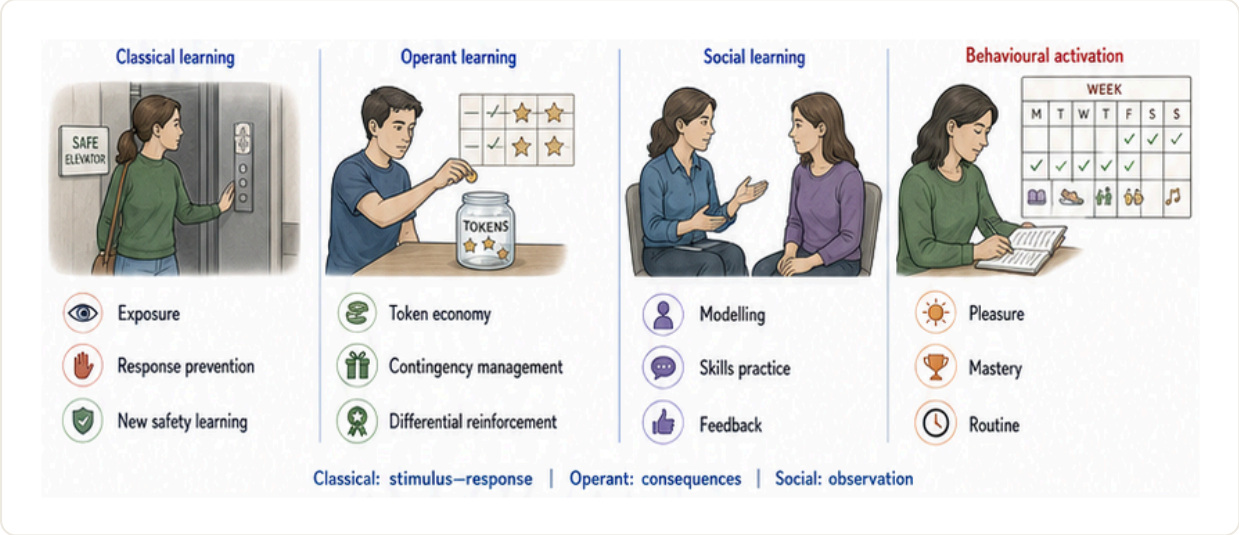


Fig 5.14 Learning mechanisms in behaviour therapy.

Behaviour therapy is defined as the systematic application of principles derived from learning theory to the modification of maladaptive behaviour (Kaplan & Sadock 2024). The field arose in the 1950s, in three centres almost at once, out of dissatisfaction with the length and unfalsifiability of psychoanalysis: the United States (Skinner and the operant tradition), South Africa (Wolpe), and the United Kingdom (Eysenck and Rachman) (Kaplan & Sadock 2024; Tasman Psychiatry). The standard way to organise the many techniques is by their parent paradigm, which is exactly how this topic is built, followed by the learned-helplessness thread and its attributional reformulation.

11.1 Definition and the three-wave frame

Behaviour therapy as applied learning theory, developing in three waves. Behaviour therapy treats maladaptive behaviour as learned, and therefore as unlearnable by the same principles, without any requirement to uncover unconscious conflict (Kaplan & Sadock 2024). The historical scaffold examiners like is the three-wave model (Kaplan & Sadock 2024). The *first wave* (1950s to 1960s) was pure classical-and-operant behaviour therapy: systematic desensitisation, exposure, aversion, token economies. The *second wave* (1970s onward) added cognition, growing out of Bandura's social learning theory into cognitive behaviour therapy (Beck, Ellis); it is the dominant system worldwide today. The *third wave* (from the 1990s) added acceptance, mindfulness and

values (DBT, ACT), and emerged in part from Jacobson's finding that behavioural activation alone matched full CBT for depression. This topic covers the behavioural (first-wave) engine and its direct descendants.

11.2 From classical conditioning: reciprocal inhibition and systematic desensitisation (Wolpe 1958)

The first named behaviour therapy, built on counterconditioning. Joseph Wolpe, a South African psychiatrist frustrated by psychoanalysis, published *Psychotherapy by Reciprocal Inhibition* (Wolpe 1958). **Reciprocal inhibition** is the principle that two physiologically antagonistic states cannot be held at once: if a response incompatible with anxiety (deep relaxation) is evoked in the presence of an anxiety-provoking stimulus, the bond between that stimulus and anxiety is weakened (Companion to Psychiatric Studies; Kaplan & Sadock 2024). **Systematic desensitisation** operationalises this in three components (Kaplan & Sadock 2024): (1) training in a competing response, usually progressive deep muscle relaxation; (2) construction of an *anxiety hierarchy*, a graded list of feared situations rated by subjective units of distress (SUDS) from least to most frightening; and (3) graded pairing, in which the relaxed patient imagines each hierarchy item in ascending order, moving up only when the current item no longer evokes anxiety. **What it fixed and what it left debated.** It fixed the slowness and indirectness of insight therapy for phobias, giving a rapid, replicable, testable method. What it left debated was its *mechanism*: Wolpe attributed the effect to counterconditioning (reciprocal inhibition), but later work suggested the relaxation and the hierarchy may be inessential and that plain habituation and extinction through exposure do most of the work, a debate the exposure therapies settled.

11.3 From classical conditioning: exposure, flooding and implosion

Confront the fear directly and let the anxiety extinguish. **Exposure** therapy rests on the premise that fear, acquired by associative learning, is eliminated by systematic contact with the feared object, event or situation until the conditioned anxiety habituates and extinguishes (Kaplan & Sadock 2024). It can be graded (as in in-vivo desensitisation) or intensive. In **flooding**, the patient is exposed immediately to the feared stimulus at full strength, without relaxation, and stays until anxiety peaks and falls; the imaginal, catastrophically-vivid variant is *implosion (implosive therapy)* (Kaplan & Sadock 2024). Exposure is almost always paired with *response prevention*, blocking the escape and avoidance and other anxiety-reducing rituals so that the feared consequence can be disconfirmed; exposure and response prevention (ERP) is the treatment of choice for obsessive-compulsive disorder (Kaplan & Sadock 2024). Distinguish *within-session* extinction (anxiety falling during one exposure) from *between-session* extinction (peak anxiety and time-to-settle both falling across sessions); the second predicts durable gain. **What it fixed.** Exposure fixed the mechanistic ambiguity of desensitisation by showing the graded hierarchy and relaxation are helpful but not necessary: extinction through contact is the active ingredient, and this is the currently accepted account of how anxiety-focused behaviour therapy works.

11.4 From classical conditioning: aversion therapy and cue exposure

Two opposite uses of the conditioned stimulus. **Aversion** therapy pairs an unwanted appetitive behaviour with an unpleasant stimulus so that the behaviour itself comes to elicit discomfort. Historically it used a subthreshold electric shock or an emetic such as apomorphine paired with alcohol, and the covert form, *covert sensitisation*, pairs the imagined behaviour with an imagined aversive scene. Its use has narrowed sharply on both efficacy and ethical grounds, but it remains an examinable technique (in alcohol dependence, some paraphilias historically). *Cue exposure* is the mirror-image application in addiction: the patient is repeatedly exposed to drug- or alcohol-associated cues while consumption is prevented, so the conditioned craving response to those cues extinguishes (Stahl, Substance Use). Both are classical-conditioning techniques; aversion builds a new conditioned aversion, cue exposure extinguishes an existing conditioned craving.

GOOD TO REMEMBER

- **Reciprocal inhibition (Wolpe 1958):** relaxation, an anxiety-antagonistic state, weakens the stimulus-anxiety bond; the basis of systematic desensitisation.
- **Systematic desensitisation:** relaxation training + graded anxiety hierarchy (SUDS) + graded imaginal/in-vivo pairing; classical-conditioning (counterconditioning) technique.
- **Exposure:** systematic contact with the feared stimulus until anxiety habituates and extinguishes; graded or intensive.
- **Flooding / implosion:** immediate full-strength exposure without relaxation; implosion is its imaginal variant; usually with response prevention (ERP for OCD).
- **Aversion therapy:** pairs an unwanted behaviour with an aversive stimulus (shock, apomorphine); covert sensitisation is the imaginal form.
- **Cue exposure:** extinguishes conditioned craving by exposing to drug cues while blocking use (addiction).

TECHNIQUE	PARENT PARADIGM	MECHANISM	SIGNATURE USE
Systematic desensitisation	Classical	**Reciprocal inhibition / counterconditioning + graded hierarchy**	Specific phobia
Exposure / flooding / implosion	Classical	**Habituation and extinction of conditioned fear (with response prevention)**	OCD, phobias, PTSD
Aversion / covert sensitisation	Classical	Conditioning a new aversion to the behaviour	Alcohol dependence, some paraphilias
Cue exposure	Classical	Extinction of conditioned craving	Substance use disorders
Token economy	Operant	Secondary (conditioned) reinforcement	Chronic inpatient wards
Contingency management	Operant	**Positive reinforcement of a verified target (abstinence)**	Substance use disorders

TECHNIQUE	PARENT PARADIGM	MECHANISM	SIGNATURE USE
Shaping / differential reinforcement	Operant	Reinforcing successive approximations / other behaviour (DRO)	Autism, intellectual disability
Time-out / response cost	Operant	Negative punishment (removing an appetitive stimulus)	Child behaviour programmes
Modelling / skills training	Social learning	**Observational learning (Bandura)**	Social skills, assertiveness
Behavioural activation	Operant / social	Restoring response-contingent positive reinforcement	Depression

The whole of behaviour therapy sorted by its parent learning paradigm. The discriminator columns are the mechanism: classical techniques act on stimulus-response bonds (counterconditioning, extinction), operant techniques act on consequences (reinforcement, punishment), social-learning techniques act by observation.

RULE **Name a behaviour therapy by its parent paradigm and its mechanism.** Classical acts on stimulus-response bonds (desensitisation, exposure); operant acts on consequences (token economy, contingency management, ABA); social learning acts by observation (modelling, skills training).

11.5 From operant conditioning: the token economy

A whole-ward contingency system built on secondary reinforcers. The **token economy** is a structured programme in which patients earn tokens (a generalised secondary reinforcer) for performing specified target behaviours, later exchanging them for backup reinforcers such as privileges or goods (Kaplan & Sadock 2024; Companion to Psychiatric Studies). Its logic is pure operant: the token has no intrinsic value but, by pairing with many backup rewards, becomes a generalised conditioned reinforcer that can be delivered immediately and precisely. Ted Ayllon and Nathan Azrin established the first comprehensive token economy at Anna State Hospital, Illinois, producing marked improvements in the targeted behaviour of chronic inpatients with severe mental illness (Kaplan & Sadock 2024). The historical antecedent examiners cite is Alexander Maconochie's early-19th-century points system for prisoners at Norfolk Island (Kaplan & Sadock 2024). Token economies flourished on chronic wards and in residential and school settings, though their use has declined with deinstitutionalisation.

11.6 From operant conditioning: contingency management, shaping and differential reinforcement

Reinforcing verified target behaviour, one approximation at a time. *Contingency management* is the systematic delivery of a positive reinforcer (a voucher, prize or privilege) contingent on an objectively verified target behaviour, most classically a clean urine drug screen in substance use disorder treatment (Kaplan & Sadock 2024; Stahl, Substance Use); it is among the most robustly evidenced psychosocial treatments in addiction. *Shaping* reaches a behaviour that never occurs spontaneously by reinforcing successive approximations to it, the operant backbone of teaching self-care and language in intellectual disability. *Differential reinforcement* reduces an unwanted behaviour not by punishing it but by reinforcing an alternative: *differential reinforcement of other*

behaviour (DRO) reinforces the absence of the problem behaviour, and *differential reinforcement of an incompatible behaviour* (DRI) reinforces a response that cannot co-occur with it (Tasman Psychiatry; Kaplan & Sadock 2024). These are the constructive alternatives to punishment across child and developmental work.

11.7 From operant conditioning: time-out and response cost (the punishment-side techniques)

Reducing behaviour by removing an appetitive stimulus. Both are forms of *negative punishment*. *Time-out* (time-out from positive reinforcement) removes the person from the reinforcing environment for a brief period contingent on the problem behaviour, so the behaviour no longer accesses reinforcement (Kaplan & Sadock 2024). *Response cost* removes a specified quantity of an already-held reinforcer (tokens, points, privileges) contingent on the behaviour, and is often built into a token economy. Because punishment suppresses without teaching an alternative, best practice pairs these with a differential-reinforcement procedure that builds the desired behaviour at the same time.

11.8 Applied behaviour analysis (ABA): the systematic clinical application of operant principles

Functional analysis, the ABC chain, and its use in autism and intellectual disability. **Applied behaviour analysis** (**ABA**) is the systematic application of operant learning principles to socially significant behaviour, and it is the umbrella under which shaping, differential reinforcement, chaining and the rest are clinically deployed (New Oxford Textbook of Psychiatry). Its engine is the *functional analysis*: rather than treat a behaviour as a fixed trait, ABA analyses the *ABC chain*, the **antecedent**, the **behaviour**, and the **consequence** that maintains it (Kaplan & Sadock 2024, "the ABCs of therapy"). A functional analysis typically resolves a challenging behaviour into one of a small set of maintaining functions: escape or avoidance of a demand, attention-seeking, tangible access to a wanted item or activity, and automatic or sensory reinforcement (Oxford Handbook of DBT). Once the function is known, the treatment follows from it: an escape-maintained behaviour is treated differently from an attention-maintained one. ABA is the best-evidenced psychosocial intervention for the core deficits and challenging behaviours of autism spectrum disorder and intellectual disability, where it is used to build communication, self-care and social skills and to reduce self-injury and aggression (New Oxford Textbook of Psychiatry). The child-psychiatry detail of autism and intellectual-disability management is developed in Paper III (child).

11.9 From social learning: modelling, skills training and behavioural activation

Learning by observation, and re-engaging with reinforcing activity. Albert Bandura's social learning theory holds that behaviour is acquired not only by direct conditioning but by *observational learning*, watching a model perform a behaviour and experience its consequences (Kaplan & Sadock 2024). Its clinical arm is *modelling* and *social skills training*: the therapist demonstrates a target behaviour (assertiveness, a social response), the patient rehearses it with feedback and reinforcement, and it is generalised to real settings; participant modelling, in which the patient performs the feared action alongside the model, is a potent phobia treatment. *Behavioural activation* (BA) is the depression-specific technique that treats low mood as, in part, a state of reduced response-contingent positive reinforcement (drawing on Lewinsohn's

reinforcement model of depression); it systematically schedules and grades pleasant and mastery activities to restore that reinforcement (Kaplan & Sadock 2024). BA is examinable because Jacobson's component analysis and Dimidjian and colleagues' 2006 trial showed BA alone matched full CBT and antidepressant medication for severe depression, which helped launch the third wave.

11.10 Learned helplessness: Seligman's shuttle-box experiments

Uncontrollable aversive events produce passivity. **Learned helplessness** is the paradigm through which learning theory generated a model of depression. Working with dogs, Martin **Seligman** and colleagues exposed animals to inescapable electric shock; when later placed in a shuttle-box where a simple response (jumping a barrier) would let them escape, these animals failed to learn to escape and passively endured the shock, whereas animals given escapable shock, or none, learned readily (Seligman 1975; Kaplan & Sadock 2024; Tasman Psychiatry). Seligman argued the crucial variable was not the shock but its *uncontrollability*: the animals had learned that outcomes were independent of their responses, and this learned expectation of uncontrollability generalised into motivational, cognitive and emotional deficits (reduced initiation of action, failure to learn that responding now works, and blunted affect). He proposed **learned helplessness**, defined as the belief that it is futile to initiate personal action to reverse aversive circumstances, as an experiential analogue of human depression (Kaplan & Sadock 2024).

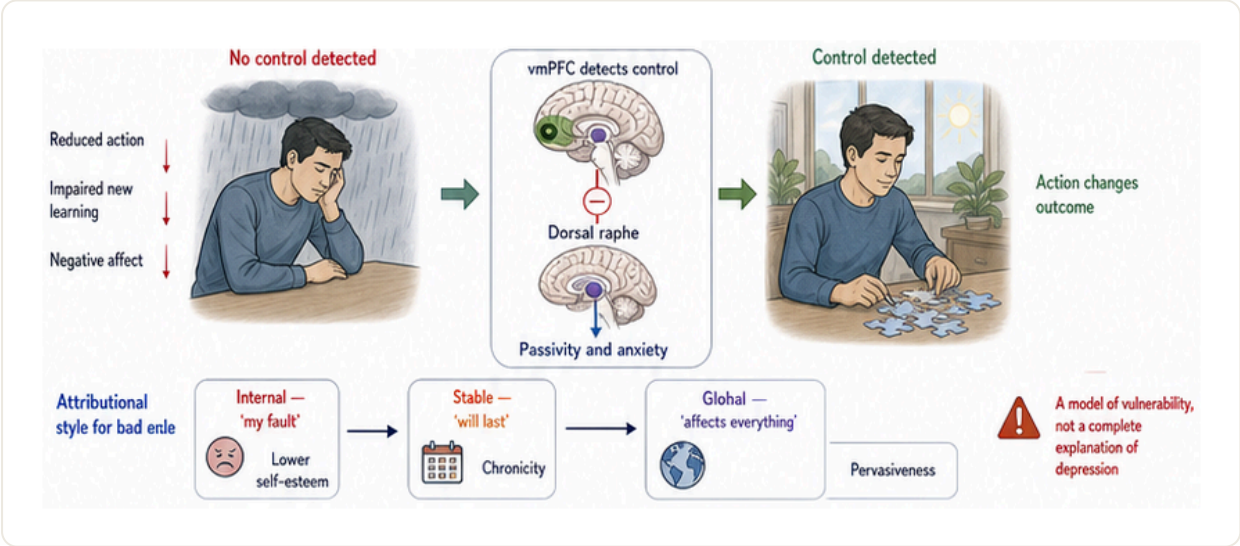


Fig 5.15 Learned helplessness, control and explanatory style.

11.11 The attributional reformulation (Abramson, Seligman and Teasdale 1978)

What fixed the original model: it is not helplessness itself but how you explain it. The original animal model could not explain why, faced with the same uncontrollable event, some people become depressed and others do not, nor why human depression involves self-blame. The *attributional (cognitive) reformulation* (Abramson, Seligman & Teasdale 1978) fixed this by inserting a cognitive step: what matters is the *causal attribution* a person makes for the uncontrollable event, their characteristic *attributional (explanatory) style* (Tasman Psychiatry). The depressogenic style attributes bad events along three dimensions: *internal* ("it is my fault") rather

than external, *stable* ("it will last forever") rather than unstable, and *global* ("it will affect everything") rather than specific (Tasman Psychiatry; Kaplan & Sadock 2024). Internal attributions explain the loss of self-esteem, stable ones the chronicity, and global ones the pervasiveness of depressive symptoms. This was later extended into the *hopelessness theory* of depression (Abramson, Metalsky & Alloy 1989), in which a stable and global attributional style, plus a negative event, generates hopelessness, a proximal sufficient cause of a hopelessness subtype of depression. This reformulation is what made learned helplessness a genuinely cognitive model and the bridge to Beck's cognitive theory.

HOLD THIS

The depressogenic attributional style for bad events is internal, stable and global (I See Grief). Internal drives low self-esteem, stable drives chronicity, global drives pervasiveness; for positive events the depressive style is the reverse.

11.12 Currently accepted position and the neural correlate

From learned helplessness to learned passivity, with a mapped circuit. The **currently accepted** position, argued by Maier and Seligman on the paradigm's fiftieth anniversary, actually inverts the original interpretation: passivity in the face of prolonged aversive events is the animal's *default, unlearned* response, and what is genuinely *learned* is the *detection of control*, which then inhibits that default passivity. In other words, the organism does not learn to be helpless; it fails to learn that it has control. The *neural correlate* is now well specified in this reformulation: prolonged uncontrollable stress activates the *dorsal raphe nucleus* serotonergic system, driving passivity and anxiety, while the *ventromedial prefrontal cortex* detects the presence of behavioural control and, when control is present, inhibits the dorsal raphe response (Maier & Seligman 2016). The broader neurobiology of learned helplessness implicates the same stress systems central to depression, the hypothalamic-pituitary-adrenal axis and forebrain serotonergic and dopaminergic circuits sensitised by early-life and chronic stress (Tasman Psychiatry). This dovetails with the wider mood-disorder correlates developed in the mood disorders notes.

11.13 Learned helplessness as a model of depression

Why the paradigm earns its place in psychiatry. Learned helplessness sits alongside Beck's cognitive model and Lewinsohn's reinforcement model as one of the three great learning-and-cognition models of depression (Kaplan & Sadock 2024). Its explanatory yield is real: it accounts for the passivity, motivational deficit and low hostility seen in some depressed patients; the reformulated version accounts for the self-blame, chronicity and pervasiveness through the internal-stable-global attributional triad; and it makes a testable therapeutic prediction, that changing expectations of uncontrollability and modifying attributional style should relieve depression, which is precisely what cognitive therapy sets out to do (Kaplan & Sadock 2024). Its role reaches beyond depression to a general disposition relevant to post-traumatic stress disorder, chronic pain and states of social powerlessness (Kaplan & Sadock 2024). The standard caveat is that the leap from animal analogue and self-report inventory to clinical depression must be made

cautiously, and that recent work implicates genetic vulnerability in how readily helpless behaviour is learned (Kaplan & Sadock 2024).

11.14 Worked example: a patient with panic disorder and agoraphobia

The learning-to-therapy chain applied to one presentation. A woman develops panic attacks and begins avoiding buses and crowded markets. *Classical arm:* the market has become a conditioned stimulus for panic; the behavioural analysis identifies the antecedent cue (crowds), the behaviour (fleeing), and the consequence (immediate anxiety relief) that negatively reinforces the avoidance. *The therapy that follows:* a graded anxiety hierarchy is built (from imagining a quiet shop to standing in a crowded market at peak hour, rated by SUDS), and either systematic desensitisation (relaxation paired with each step) or, more efficiently, graded in-vivo exposure with response prevention is used, so she stays in each situation until anxiety habituates and the catastrophic prediction is disconfirmed. *Operant arm:* her partner's reassurance and permission to leave were positively reinforcing the avoidance, so a contingency is arranged to reinforce staying, not fleeing. *Social-learning arm:* the therapist models entering the feared setting first (participant modelling). *Learned-helplessness arm:* if she has come to believe her panic is uncontrollable and to attribute it internally, stably and globally ("I am broken, this will never change, it ruins everything"), the cognitive work targets exactly that attributional style, restoring a sense of control, which is the learned-helplessness reformulation put to clinical use.

CLINICAL ANCHOR

When you name a behaviour therapy in an exam or on a ward round, say which paradigm it comes from and what it does mechanistically. "Systematic desensitisation, a classical-conditioning technique working by reciprocal inhibition and graded exposure." "Contingency management, an operant technique reinforcing verified abstinence." "Behavioural activation, restoring response-contingent positive reinforcement in depression." The examiner is testing whether you can move between the principle and the technique, not whether you can list therapies.

COMMON TRAP

Do not confuse the two intensive exposures. *Flooding* is real-life or imaginal full-strength exposure; *implosion* is specifically the imaginal, deliberately-exaggerated form. And systematic desensitisation is *graded* and paired with relaxation (counterconditioning), whereas flooding is *ungraded* and deliberately without relaxation (extinction). A second trap: in the attributional reformulation the depressogenic style is internal-stable-global for *negative* events; for positive events the depressive style is the reverse (external-unstable-specific), a symmetry examiners like to probe.

MNEMONIC

"I See Grief" for the depressogenic attributional style: Internal, Stable, Global.

The three attributional dimensions that make learned helplessness depressogenic for bad events are **I**nternal (my fault), **S**table (permanent), **G**lobal (affects everything): I-S-G, "I See Grief". Internal drives low self-esteem, Stable drives chronicity, Global drives pervasiveness. For the techniques, sort by paradigm: classical = desensitisation/exposure/aversion/cue; operant = token economy/contingency management/ABA/time-out; social = modelling/skills/behavioural activation.

INDIA

ABA and structured behavioural programmes for autism and intellectual disability are resource-intensive and unevenly available across Indian settings, so parent-mediated behavioural training, which teaches caregivers to run the antecedent-behaviour-consequence analysis and deliver reinforcement at home, is often the pragmatic backbone rather than clinic-delivered one-to-one ABA. In addiction work, contingency management fits Indian de-addiction settings well because its reinforcers can be modest and locally meaningful, and cue exposure maps onto the culturally specific drinking and substance cues a plan must address.

PEARL

The one-line arc for an examiner: the three learning paradigms each became a therapy family, classical conditioning gave systematic desensitisation (Wolpe, reciprocal inhibition), exposure and flooding, aversion and cue exposure; operant conditioning gave the token economy (Ayllon and Azrin), contingency management, shaping and differential reinforcement, and applied behaviour analysis with its functional analysis of the antecedent-behaviour-consequence chain for autism and intellectual disability; and social learning gave modelling, skills training and behavioural activation. Learned helplessness (Seligman) turned uncontrollable aversive events into a model of depression, and its attributional reformulation (Abramson, Seligman and Teasdale 1978, internal-stable-global) made it cognitive and the bridge to CBT.

GOOD TO REMEMBER

- **Behaviour therapy:** systematic application of learning theory to modify maladaptive behaviour; arose 1950s (Skinner, Wolpe, Eysenck/Rachman); three-wave model (behavioural, cognitive, acceptance-based).
- **Wolpe (1958), *Psychotherapy by Reciprocal Inhibition*:** reciprocal inhibition (relaxation inhibits anxiety) underlies systematic desensitisation.
- **Systematic desensitisation:** relaxation + graded anxiety hierarchy (SUDS) + graded pairing; classical/counterconditioning; for specific phobia.
- **Exposure:** contact with the feared stimulus until anxiety habituates/extinguishes; within-session vs between-session extinction.
- **Flooding / implosion:** immediate full-strength exposure without relaxation; implosion = imaginal exaggerated form; with response prevention (ERP for OCD).
- **Aversion therapy:** pair unwanted behaviour with aversive stimulus (apomorphine, shock); covert sensitisation = imaginal.
- **Cue exposure:** extinguishes conditioned craving in addiction.
- **Token economy (Ayllon & Azrin, Anna State Hospital):** operant; tokens as generalised secondary reinforcers exchanged for backups; antecedent = Maconochie.
- **Contingency management:** operant; positive reinforcement of verified target (clean urine screen) in substance use disorder.
- **Shaping / differential reinforcement:** reinforce successive approximations / reinforce other (DRO) or incompatible (DRI) behaviour.
- **Time-out / response cost:** negative punishment (removing an appetitive stimulus).
- **Applied behaviour analysis (ABA):** systematic operant application; functional analysis of the ABC (antecedent-behaviour-consequence) chain; four functions (escape/avoidance, attention, tangible, sensory); best-evidenced for autism and intellectual disability (Paper III child).
- **Modelling / skills training (Bandura):** social-learning technique via observational learning; participant modelling for phobias.
- **Behavioural activation (Jacobson; Dimidjian 2006):** restores response-contingent positive reinforcement in depression (Lewinsohn roots).
- **Learned helplessness (Seligman 1975):** inescapable shock in dogs, shuttle-box; uncontrollability produces passivity; belief that action is futile; a model of depression.
- **Attributional reformulation (Abramson, Seligman & Teasdale 1978):** depressogenic explanatory style for bad events = internal, stable, global; extended to hopelessness theory (Abramson, Metalsky & Alloy 1989).
- **Currently accepted (Maier & Seligman 2016):** passivity is the default; control-detection is what is learned; neural correlate = ventromedial prefrontal cortex detecting control inhibits the dorsal raphe serotonergic passivity response.

Personality and psychodynamic theory

12 · Meyer, Rank and the wider psychodynamic map

The depth-psychology map, and the two figures these notes owns. Classical **depth psychology** radiates from three primary schools: Sigmund Freud's **psychoanalysis**, Alfred Adler's individual psychology, and Carl Jung's analytical psychology. All three, together with their apparatus (the **topographic model** of conscious, preconscious and unconscious; the **structural model** of id, ego and **superego**; and the great defections of Adler and Jung) are taught in full on the General and Developmental Psychology notes and are only named and cross-referenced here.

What these notes adds is the pair of Paper-1 scientists who sit at the edges of that map and are examinable in their own right: Adolf Meyer, whose **psychobiology** is the American holistic-formulation tradition that anticipated the modern biopsychosocial model, and Otto Rank, the analyst whose **birth trauma** and **will therapy** broke from Freud and seeded humanistic and existential practice.



Fig 5.16 Meyer and Rank: two exits from Freud.

The exam framing is precise. Freud, Adler and Jung are General and Developmental Psychology items; do not re-teach them here. Meyer and Rank are the two names these notes must deliver, each as a short evolution-of-ideas: what each figure took from the psychoanalytic mainstream, what he replaced, and what survives in contemporary practice. Meyer feeds directly into formulation and nosology; Rank feeds into the humanistic and existential therapies. The neo-Freudian relationalists (Horney, Sullivan, Fromm) are named at the end only as a bridge into the object-relations and interpersonal topic developed next.

12.1 The three primary schools: named, and referred to the General and Developmental Psychology notes

Freud, Adler, Jung, taught in full elsewhere. The organising spine of depth psychology is three schools, each with its own founder, its own account of the unconscious, and its own therapeutic aim.

Psychoanalysis (Freud)

The parent school. Its models of mind are the **topographic model** (conscious, preconscious, unconscious) and the later **structural model** (id, ego, **superego**); its engine is intrapsychic conflict, drive and defence, with the Oedipus complex central. Taught in full on **the General and Developmental Psychology notes**.

Individual psychology (Adler)

The first major defection. Replaces libido as prime mover with striving for superiority to compensate for inferiority; emphasises social interest, the family constellation and the unified goal-directed self. Cross-referenced to **the General and Developmental Psychology notes**.

Analytical psychology (Jung)

The second defection. Adds the collective unconscious, archetypes, the persona and shadow, individuation, and the introversion-extraversion typology. Cross-referenced to **the General and Developmental Psychology notes**.

Everything below is the delta these notes add: two Paper-1 scientists whom the General and Developmental Psychology notes does not cover.

TRAP Do not re-teach Freud, Adler and Jung here: they are cross-referenced only. The two examinable figures in this topic are **Meyer (psychobiology) and Rank (birth trauma)**.

12.2 Adolf Meyer: the man and the idea of psychobiology

The whole organism reacting to its life. Adolf Meyer (1866 to 1950), Swiss-born and Baltimore-based, was the dominant figure in early twentieth-century American psychiatry, directing the Henry Phipps Psychiatric Clinic at Johns Hopkins (New Oxford Textbook of Psychiatry). His system, **psychobiology**, treated the person as a single biological unit, maintaining internal and external equilibrium while coping with new situations, and understood mental disorder not as a discrete brain lesion nor as a purely intrapsychic drama but as a maladaptive *reaction of the whole organism* to its life circumstances (The Psychotherapy Guidebook). Meyer was influenced by Hughlings Jackson's levels of nervous integration and by American pragmatism (James, Dewey), giving the system a concrete, optimistic, anti-dogmatic character that deliberately avoided the metapsychological speculation of the European schools.

12.3 Meyer's ergasiology: reaction-types instead of one-word diagnoses

Ergasia: behaviour as work of the organism. Dissatisfied with the reductive one-word diagnoses of Kraepelinian nosology, Meyer classified disorders as *reaction-types*, patterned maladaptive responses of the person to circumstance rather than fixed disease entities. In the 1920s he coined *ergasia* (from Greek *ergon*, work) for behaviour and mental activity as a whole, and its plural *ergasias* for specific behavioural units, the vocabulary now labelled **ergasiology**. Organic brain reactions were "anergasia", toxic psychoses "dysergasia", and so on (The Psychotherapy Guidebook). The idiosyncratic ergasia terms were never adopted into formal nomenclature, but the underlying *reaction* concept was: it entered American classification directly, so that DSM-I (1952), strongly shaped by Meyer's views, described conditions as "reactions" (for example schizophrenic reaction, manic-depressive reaction) rather than as diseases (Shorter Oxford Textbook of Psychiatry).

12.4 Meyer's method: the life chart, distributive analysis and habit training

Plot the life, then re-train the habits. Meyer's clinical signature is the **life chart**: the psychiatrist plots the patient's life on a single time-line from birth to the present, penciling in major life events alongside the onset and worsening of illness, so that recurrent associations between circumstance and symptom become visible (Kaplan & Sadock 2024). The biographical data gathered this way were then worked through by *distributive analysis* (the patient examines the components of the problem and their relative weight) and *distributive synthesis* (reconstructing healthier patterns), with therapy proceeding as *habit training*, the modification of unhealthy adaptations through guidance, re-education and direction, engaging the healthier part

of the patient's own ego. Meyer held this approach especially valuable for psychotic patients, and he was an early architect of the mental-hygiene and community-care movements alongside Clifford Beers (The Psychotherapy Guidebook).

CLINICAL ANCHOR

Meyer's life chart is the direct ancestor of the timeline every trainee draws in a formulation: the longitudinal plotting of stressors, episodes and treatments to expose temporal patterns. His reaction-type view is the seed of the modern *biopsychosocial* formulation, illness read as the whole person's maladaptive reaction to biological, psychological and social forces rather than as an isolated diagnosis. When you write "onset followed the loss of employment and coincided with sleep disruption", you are doing Meyerian psychobiology.

12.5 Otto Rank: the birth trauma

Separation from the mother as the root of anxiety. Otto Rank (1884 to 1939), one of Freud's closest early collaborators, made his decisive move in *The Trauma of Birth* (1924). He took Freud's own passing idea that the violent physical separation of birth is the prototype of anxiety and made it the *central* source, arguing that all later anxiety re-enacts the primal **birth trauma** (Kaplan & Sadock 2024; Wolberg). Two opposed strivings follow from it: an impulse to return to the womb and restore prenatal security (expressed as dependent, clinging attachment), and an impulse for rebirth and independence (expressed as the will to separate and individuate). Rank named the two poles of this conflict the *life fear* (the dread that asserting one's separateness and creativity will isolate one from others) and the *death fear* (the dread of losing one's individuality by being absorbed into another). This relocation of the origin of anxiety from the Oedipal, father-centred conflict to the *pre-Oedipal*, mother-centred separation is Rank's core contribution and the point on which he parted from Freud.

12.6 Rank's will therapy and his influence downstream

Mobilise the will in the present relationship. Rank's therapeutic system, set out in *Will Therapy* (1936), abandoned the archaeological search for buried content and made the therapeutic *relationship in the present* the curative agent (Wolberg). Therapy is patient-centred and active: the analyst mobilises the patient's constructive "creative will impulse" toward self-direction and self-realisation, and studies the patient's reactions to the inevitable *separation* at the end of treatment as the working-through of the birth-derived conflict between union and autonomy. Insight and unconscious content are secondary to the corrective relational experience. With Ferenczi and Stekel, Rank thereby pioneered short-term, flexible, active psychotherapy. His influence runs forward on two lines: Carl Rogers absorbed Rank's philosophy of self-realisation and the patient-centred stance into humanistic *client-centred therapy*, and Rank's emphasis on will, separation, isolation and the confrontation with individuality prefigured the *existential* therapies (Wolberg). His functional-casework legacy also shaped American social work through Jessie Taft and Virginia Robinson.

COMMON TRAP

Do not attribute the concept of the "birth trauma" to Freud, and do not confuse Rank's *will therapy* with Adler's will-to-power or with the later existentialists' terms. Rank is Paper-1 examinable as a distinct figure: birth trauma (1924), will therapy (1936), pre-Oedipal focus, break from Freud, influence on humanistic and existential therapy. Also keep Rank's *birth trauma* (a psychodynamic construct about separation anxiety) separate from Stanislav Grof's later "birth matrices" and from any obstetric use of the phrase.

12.7 Meyer versus Rank: two ways off the Freudian main line

Same era, opposite exits. Both men worked at the edge of psychoanalysis in the same decades, but they left it in opposite directions: Meyer outward toward biology, society and pragmatic formulation, Rank inward toward the pre-Oedipal relationship and the will. The table fixes the discriminators.

FEATURE	ADOLF MEYER (PSYCHOBIOLOGY)	OTTO RANK (WILL THERAPY)
Core construct	**Mental illness as a maladaptive *reaction* of the whole organism**	**Anxiety rooted in the *birth trauma*; life fear versus death fear**
Break point from Freud	Rejected metapsychology for holistic, pragmatic biography; not a pupil-defector but a parallel American tradition	Moved the origin of anxiety from Oedipal to *pre-Oedipal* separation; formal break from Freud
Signature method	The *life chart*, distributive analysis and synthesis, habit training	Active, patient-centred *will therapy*; the present relationship and its ending are curative
Unit of classification	Reaction-types; the *ergasia* vocabulary (ergasiology)	Personality as normal, neurotic, or creative-artist types
Enduring influence	American nosology (DSM-I "reactions"); the biopsychosocial formulation; community psychiatry	Rogerian client-centred therapy; existential therapy; short-term dynamic therapy; functional social work

The two discriminator rows are the core construct (organism-level reaction versus birth-trauma separation anxiety) and the enduring influence (formulation and nosology versus humanistic and existential therapy).

12.8 Currently accepted position and its correlate

Meyer survives as method, Rank as lineage. Neither man's system is practised intact, but each is metabolised into current thinking. The **currently accepted** descendant of Meyer's psychobiology is the *biopsychosocial* model (Engel, 1977) and the longitudinal case formulation, both routine in contemporary training; Meyer's specific ergasia nomenclature is obsolete, but the "reaction/adjustment" logic persists in categories such as adjustment disorder and in the whole-person emphasis of formulation. Rank's system likewise survives not as a standalone therapy but as an acknowledged root of the humanistic and existential traditions and of brief dynamic therapy. The *neural correlate* is meaningful chiefly for the underlying constructs rather than the schools: separation-related distress, Rank's territory, maps onto a well-characterised separation-

distress circuitry involving the *amygdala*, *anterior cingulate cortex* and periaqueductal grey and the oxytocin and endogenous-opioid attachment systems (a neurobiology developed with the attachment material in the General and Developmental Psychology notes), while Meyer's stressor-to-illness reaction is the same stress-response neurobiology (HPA axis, amygdala, hippocampus, prefrontal cortex) that his life chart set out to make visible clinically.

HOLD THIS

Meyer survives as method (the biopsychosocial formulation and the DSM-I "reactions"); Rank survives as lineage (root of humanistic, existential and brief dynamic therapy). Neither system is practised intact today.

12.9 Worked example: one patient, read through both lenses

A first manic episode after migration and job loss. Take a young adult presenting with a first manic episode some months after moving city for work and then losing the job. *Through Meyer:* draw the life chart, the migration, the isolation, the sleep disruption and the job loss plotted against symptom onset, so the episode is formulated as the whole organism's maladaptive reaction to a cluster of stressors on a biological diathesis, and the plan targets habit re-training (sleep, routine, re-employment) alongside medication, the biopsychosocial formulation in action. *Through Rank:* the same migration is a concrete *separation*, reviving the birth-derived tension between the pull toward dependent security (returning home, clinging) and the push toward independent individuation (the reason for leaving), and the "life fear" of standing alone is live material; a Rankian-descended, relationship-focused brief therapy would work with the patient's will and with the meaning of separation rather than excavate childhood content. The two readings are complementary, not rival: Meyer organises the formulation, Rank supplies one lens on its psychological content.

PEARL

The fastest way to hold these two apart in the exam: *Meyer = the chart* (biography plotted, whole-organism reactions, feeds nosology and formulation), *Rank = the birth* (birth trauma, pre-Oedipal separation, will therapy, feeds humanistic and existential therapy). Freud, Adler and Jung are on **the General and Developmental Psychology notes**; if a Paper-1 stem names Meyer or Rank, it is testing exactly the deltas above.

GOOD TO REMEMBER

- **Three primary schools (the General and Developmental Psychology notes):** psychoanalysis (Freud), individual psychology (Adler), analytical psychology (Jung), named here, taught in full on the General and Developmental Psychology notes.
- **Topographic model:** conscious, preconscious, unconscious (Freud, the General and Developmental Psychology notes).
- **Structural model:** id, ego, superego (Freud, the General and Developmental Psychology notes).
- **Adolf Meyer (1866 to 1950):** founder of psychobiology; person as a biological unit; illness as a maladaptive reaction of the whole organism.
- **Ergasiology / ergasia:** Meyer's reaction-type vocabulary (anergasia, dysergasia); never entered formal nomenclature.
- **Life chart:** Meyer's biographical time-line of life events against illness onset; ancestor of the modern formulation timeline.
- **Distributive analysis and synthesis; habit training:** Meyer's therapeutic method.
- **Meyer's nosological legacy:** shaped DSM-I (1952) "reaction" terminology; precursor of the biopsychosocial model and community psychiatry.
- **Otto Rank (1884 to 1939):** Freud collaborator who broke away; pre-Oedipal, mother-centred focus.
- **Birth trauma (The Trauma of Birth, 1924):** Rank's relocation of the root of anxiety to the primal separation at birth; life fear versus death fear.
- **Will therapy (Will Therapy, 1936):** Rank's active, patient-centred, present-relationship therapy; mobilises the creative will; separation at termination is curative.
- **Rank's influence:** Rogerian client-centred (humanistic) therapy, existential therapy, short-term dynamic therapy, functional social work.
- **Neo-Freudian bridge:** Horney, Sullivan, Fromm, the relational/interpersonal turn developed in the object-relations topic next.

13 · Defence mechanisms and the Vaillant hierarchy

A **defence mechanism** is an automatic, unconscious mental process the ego uses to protect against the anxiety generated by intrapsychic conflict, unacceptable impulses, and external stressors (Kaplan & Sadock 2024). The concept is Freudian in origin but was first catalogued and systematised by **Anna Freud** in *The Ego and the Mechanisms of Defence* (1936), which moved the defences from scattered clinical observations into a coherent list. The examiner's favoured organising frame, and the one that carries the most marks, is **George Vaillant**'s arrangement of the defences into a maturity **hierarchy**: from the most pathological (psychotic) up through immature and neurotic to the most adaptive (mature). The same American spelling, defense mechanism, appears throughout the US texts and the DSM.

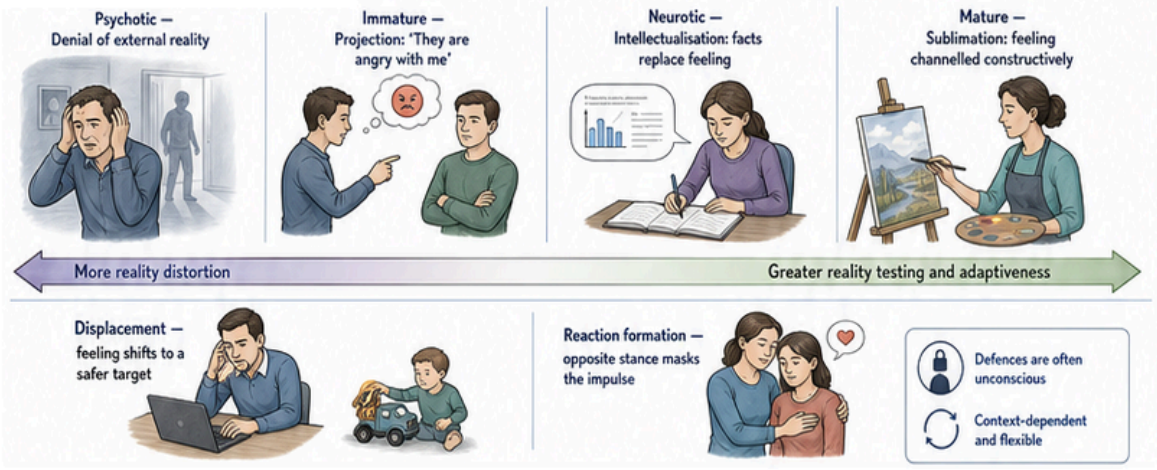


Fig 5.17 Defence mechanisms in action.

Why it matters. Defences are not inherently pathological. They are part of normal development and everyone uses the whole range, but the *habitual predominant level* a person deploys under stress is diagnostically and prognostically informative. The immature cluster (splitting, projective identification) anchors the borderline and other severe personality disorders, while the mature cluster predicts good long-term outcome. Learn the four tiers, one crisp definition and one clinical example each, and the disorder anchors, and this topic is essentially closed.

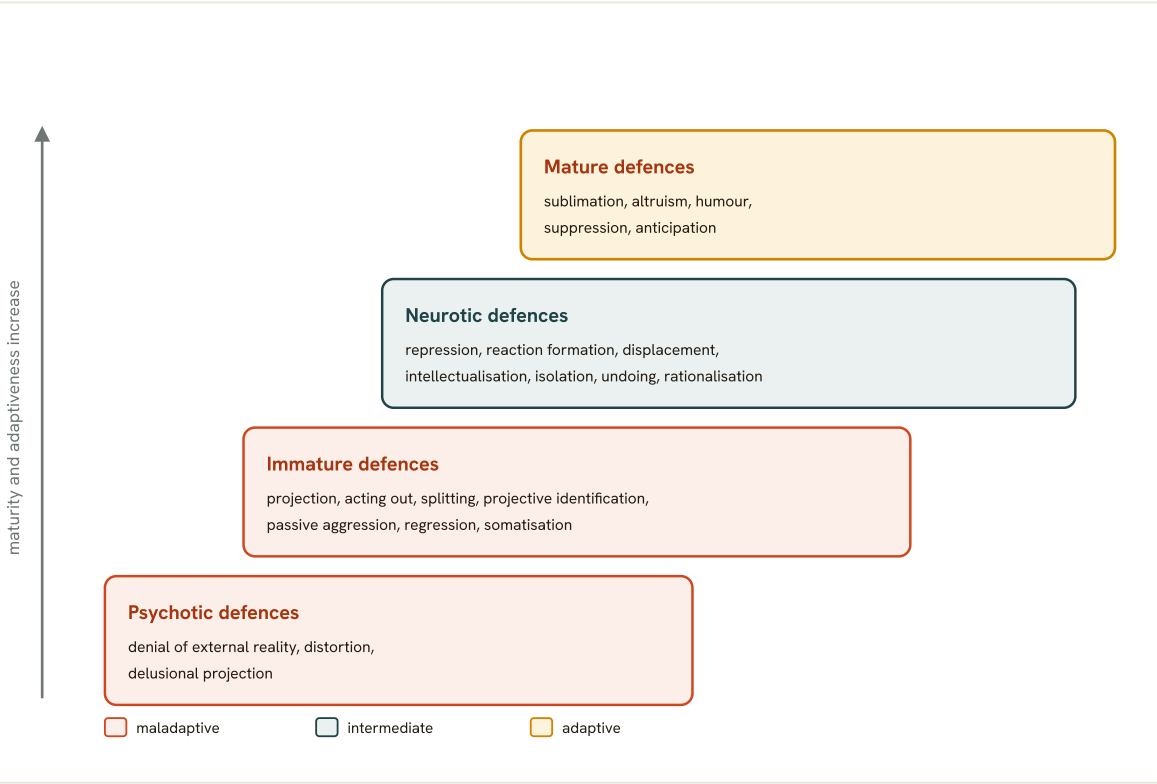


Fig 5.18 Vaillant's hierarchy of defence mechanisms, arranged from the least to the most adaptive. Psychotic defences deny or remake external reality; immature defences externalise conflict onto others; neurotic defences keep the conflict internal and out of awareness; mature defences channel it into something useful or tolerable. The same person uses defences from several levels, but the habitual level predicts functioning and outcome, a finding from Vaillant's long Grant Study cohort. Splitting and projective identification at the immature level are the exam's signature borderline defences.

13.1 Definition and the three founding ideas

The core definition. Defence mechanisms are automatic, unconscious psychological processes, both cognitive and emotional, that protect against anxiety arising from internal conflict or external threat (Kaplan & Sadock 2024). Three features are exam-worthy: they operate *outside awareness* (this separates a defence from a conscious coping strategy), they *distort or exclude* some aspect of internal or external reality to reduce unpleasure, and they change the relationship between the self and the object (Vaillant & Vaillant 1998). Anna Freud's 1936 monograph is the systematising text; her father Sigmund Freud had described repression as the foundational defence, and Melanie Klein later elaborated the earliest, most primitive defences (splitting, projective identification, projection) as characteristic of the paranoid-schizoid position of infancy.

13.2 The evolution of the classification, and the currently accepted frame

From a flat list to a maturity gradient. Anna Freud (1936) gave a flat catalogue of about ten defences with no ordering. The advance that the exam rewards is **Vaillant**'s reconceptualisation of the defences as a developmental *hierarchy of affect regulators*: more sophisticated, more effective defensive strategies emerge across adolescence and adulthood, and a person's defensive level can be scored empirically (Vaillant 1993, *The Wisdom of the Ego*). This fixed the previous scheme's silence on adaptiveness: it tells you which defences are healthy and which are pathological, and it made defence a *measurable* variable in longitudinal research rather than a purely interpretive one. The **currently accepted** operationalisation is Vaillant's four-tier model (psychotic, immature, neurotic, mature), whose adaptiveness ranking DSM-IV carried forward in the more finely graded seven-level *Defensive Functioning Scale* in its appendix. Its *neural correlate* is not a single structure: the automaticity of defence maps onto implicit procedural memory systems that deal with unpleasant affect outside awareness (Gabbard), and the regulation of affect that defences perform is subserved by prefrontal (especially ventromedial and dorsolateral) modulation of limbic structures, notably the amygdala. Mature suppression, for example, recruits deliberate prefrontal control over amygdala-driven affect, whereas psychotic-level denial reflects a failure of reality-testing networks. Name the systems, not a single locus.

HOLD THIS

Vaillant ranks the defences by maturity: psychotic, immature, neurotic, mature. Everyone uses the whole range; the habitual predominant level under stress is what is diagnostic and prognostic, and mature defences predicted better outcomes in the Grant Study.

CLINICAL ANCHOR

Defensive level is part of the psychodynamic formulation and of the mental state's assessment of insight and coping. On the ward, a patient who idealises the morning nurse and vilifies the evening nurse (splitting) signals a borderline-level organisation; a patient who channels grief over a terminal diagnosis into meticulous advance-care planning (anticipation) signals mature functioning and a better prognosis.

13.3 Level 1: Psychotic defences

Psychotic level. These are the most primitive defences, marked by a frank break with reality-testing. They are normal in early childhood and in dreams, but in an adult they signify psychosis. The three classic **psychotic defense** mechanisms:

Denial (of external reality)

Refusal to accept an intolerable external fact, abolishing its very perception. Example: a man with an obvious hemiplegia after a stroke insists nothing is wrong with his arm (anosognosia).

Distortion

Grossly reshaping external reality to fit inner need, including wish-fulfilling delusions and hallucinations. Example: a patient reworks a hostile world into a grandiose belief that he is a chosen prophet.

Delusional projection

Externalising one's own unacceptable impulses as frank persecutory delusions. Example: a patient's own aggressive impulses are experienced as a neighbour's plot to poison him.

13.4 Level 2: Immature defences

Immature level. Common in adolescence, in severe depression, and centrally in the personality disorders. Reality-testing is intact, but the defences are socially undesirable and often externalise distress onto others. This tier includes the Kleinian primitive defences.

Projection

Attributing one's own unacceptable feelings or impulses to another person. Example: a man who resents his wife accuses her of hating him. Core defence of paranoid personality disorder.

Acting out

Discharging an unconscious wish or conflict directly through action rather than reflection, to avoid feeling it. Example: a bereaved adolescent starts fights instead of grieving.

Splitting

Keeping contradictory images of self and others (all-good vs all-bad) rigidly apart because they cannot be integrated. Example: idealising the ward team on Monday and condemning them as cruel on Tuesday. The primary defence of borderline personality disorder (Kaplan & Sadock 2024).

Projective identification

Projecting a part of the self into another, then unconsciously pressuring that person to actually feel or enact it, so the projection is confirmed. Example: a patient projects rage into the therapist and behaves so provocatively that the therapist genuinely becomes angry. Hallmark of borderline organisation; strong driver of countertransference.

Passive aggression

Expressing hostility indirectly through non-compliance, procrastination, or inefficiency. Example: an angry trainee agrees to a task then quietly never completes it.

Regression

Retreating to an earlier developmental level of functioning under stress. Example: a hospitalised adult becomes clingy and demands to be fed.

Somatisation

Converting intrapsychic conflict into bodily symptoms and preoccupation. Example: unexpressed marital distress presents as recurrent unexplained abdominal pain.

Schizoid fantasy

Retreating into an inner world of imagination to resolve conflict and avoid intimacy. Example: a lonely person substitutes an elaborate fantasy life for real relationships (schizoid personality).

13.5 Level 3: Neurotic defences

Neurotic level. Common in everyone under stress and prominent in the neurotic disorders (anxiety, obsessive-compulsive, dissociative, and conversion presentations). They alter the internal experience of a conflict rather than distorting external reality; they are largely private and cause the person, not others, the difficulty.

Repression

The foundational neurotic defence: unconsciously barring an unacceptable idea or feeling from awareness. Example: a woman has no memory of a childhood assault. Distinguish from conscious suppression (mature).

Reaction formation

Transforming an unacceptable impulse into its exact opposite. Example: a person with unconscious hostility becomes exaggeratedly solicitous. Generates obsessive-compulsive personality traits.

Displacement

Redirecting an affect from its true object onto a safer substitute. Example: a man berated by his boss goes home and shouts at his child. Underlies phobia formation in psychodynamic theory.

Intellectualisation

Managing a threatening feeling by engaging with it only in abstract, theoretical terms. Example: a newly diagnosed patient discusses cancer statistics at length but shows no emotion.

Isolation of affect

Separating an idea from the feeling attached to it, so the idea stays in consciousness stripped of emotion. Example: an OCD patient recounts an aggressive intrusive thought flatly, with no distress.

Undoing

Performing an act (often ritualistic) that magically cancels or atones for an unacceptable thought or impulse. Example: a compulsion to wash repeatedly to undo a feared harm. Generates OCD compulsions.

Rationalisation

Offering a plausible, reassuring, but false reason for behaviour whose true motive is unacceptable. Example: a rejected candidate decides the job was beneath him.

Dissociation

A temporary drastic modification of one's sense of identity or consciousness to avoid emotional distress. Example: a person derealises during an assault and later has amnesia for it.

13.6 Level 4: Mature defences

Mature level. The most adaptive tier, characteristic of healthy adults. Mature defences integrate conflicting motives, optimise gratification, and are experienced by others as virtues. They are the

residues that become stable, partly conscious coping styles and mature character traits (Kaplan & Sadock 2024). The five classic **mature defense** mechanisms:

Sublimation

Channelling an unacceptable impulse into a socially valued activity, keeping the aim's energy while altering its object. Example: aggressive drive redirected into competitive surgery or contact sport.

Altruism

Meeting one's own needs vicariously through constructive service to others. Example: a bereaved parent founds a support charity.

Humour

Expressing a distressing feeling openly without discomfort to self or others, giving perspective without denial. Example: a patient jokes gently about his own illness to ease a tense consultation.

Suppression

The conscious or semiconscious decision to postpone attention to a conflict or impulse. Example: a doctor deliberately sets aside personal worry to finish a night shift, then returns to it. The one deliberate defence; contrast with unconscious repression.

Anticipation

Realistic planning for future inner discomfort, rehearsing the affect in advance. Example: rehearsing likely feelings before a difficult conversation, so the emotion is manageable when it arrives.

13.7 Vaillant's Grant Study: the outcome data

The empirical payoff. Vaillant's evidence base was the **Grant Study**, the roughly 60-year prospective longitudinal follow-up of an initially healthy cohort of Harvard undergraduates (Vaillant 1995), part of the Harvard Study of Adult Development. Rating each man's habitual defensive style, Vaillant found that predominant use of *mature* defences (sublimation, altruism, humour, suppression, anticipation) predicted better outcomes across the board: mental and physical health, career and income success, marital stability, and life satisfaction. Predominant *immature* defences predicted the reverse. Two exam-relevant conclusions follow: defensive maturity is not fixed but can advance across the lifespan, and it is one of the stronger psychosocial predictors of successful ageing, independent of the childhood social class the men started from.

13.8 Disorder anchors: which defence flags which condition

The high-yield associations. Examiners test defences most often through their disorder pairings. The table collects the ones that recur in questions.

DEFENCE	VAILLANT LEVEL	CLASSIC DISORDER ASSOCIATION
Splitting	Immature	**Borderline personality disorder (primary defence)**
Projective identification	Immature	**Borderline organisation; drives countertransference**
Projection	Immature	**Paranoid personality disorder; paranoid states**
Schizoid fantasy	Immature	Schizoid personality disorder
Isolation of affect, undoing	Neurotic	**Obsessive-compulsive disorder (compulsions)**
Reaction formation	Neurotic	Obsessive-compulsive personality traits
Displacement	Neurotic	**Phobia formation**
Repression, dissociation	Neurotic	Dissociative and conversion disorders
Denial, distortion, delusional projection	Psychotic	**Psychotic disorders; acute mania (denial)**

The pairings that generate single-best-answer questions: splitting to borderline, projection to paranoid, isolation and undoing to OCD, displacement to phobia.

RULE **Only psychotic-level defences abolish reality-testing.** If a stem preserves reality-testing, the answer is never denial of external reality, distortion or delusional projection.

COMMON TRAP

Do not confuse **suppression** with **repression**. Suppression is *conscious and deliberate* (a mature defence, the only one that is intentional); repression is *unconscious* (a neurotic defence). A stem describing a person who "decided to put the worry out of mind until the exam was over" is suppression, not repression. Likewise, **projection** (immature: attributing your feeling to another) is not **projective identification** (immature: making the other actually feel it).

PEARL

Reality-testing is the fault line between the top and bottom of the ladder. Only the *psychotic* defences abolish reality-testing (denial of external reality, distortion, delusional projection). Every immature, neurotic, and mature defence leaves reality-testing intact and distorts only the internal experience. If a stem preserves reality-testing, the answer is never a psychotic-level defence.

MNEMONIC

Some Adults Have Sensible Anticipation

The five **mature** defences: **S**ublimation, **A**ltruism, **H**umour, **S**uppression, **A**nticipation. These are the ones the Grant Study tied to good outcome, so if a question asks for the "healthiest" defence in a list, pick from this five.

INDIA

Indian teaching frames the defences through their psychodynamic disorder models: isolation of affect, undoing, and displacement generating OCD symptoms; projection generating paranoid presentations; splitting as the borderline defence. For theory-paper answers, pair each defence with its disorder model rather than listing defences in isolation.

GOOD TO REMEMBER

- **Defence mechanism:** automatic unconscious ego process that reduces anxiety from conflict or external threat (Kaplan & Sadock 2024).
- **Anna Freud (1936):** systematised the defences in *The Ego and the Mechanisms of Defence*.
- **George Vaillant (1993):** arranged defences into a four-tier maturity hierarchy of affect regulators; basis of DSM-IV Defensive Functioning Scale.
- **Psychotic defences:** denial of external reality, distortion, delusional projection (reality-testing lost).
- **Immature defences:** projection, acting out, splitting, projective identification, passive aggression, regression, somatisation, schizoid fantasy.
- **Neurotic defences:** repression, reaction formation, displacement, intellectualisation, isolation of affect, undoing, rationalisation, dissociation.
- **Mature defences:** sublimation, altruism, humour, suppression, anticipation (SAHSA).
- **Splitting and projective identification:** primary defences of borderline personality disorder.
- **Projection:** defence of paranoid personality disorder / paranoid states.
- **Isolation of affect and undoing:** defences behind OCD compulsions; displacement behind phobia.
- **Suppression vs repression:** suppression is conscious and mature; repression is unconscious and neurotic.
- **Grant Study (Vaillant 1995):** ~60-year Harvard cohort; predominant mature defences predicted better health, relationships, and successful ageing.

14 · Object relations and the neo-Freudians

The relational turn in psychoanalysis, and the school Paper 1 tests most. After Freud, one large branch of psychoanalysis stopped asking "how does the drive discharge?" and started asking "whose face is the drive reaching for?". That shift is **object relations** theory: the mind is built not out of drives seeking pleasure but out of internalised relationships, the residues of early experience with caregivers laid down as **internal objects** that then govern how the person loves, hates and perceives others for life. Alongside it a looser group, the **neo-Freudian** analysts, kept Freud's method but replaced his biological drive with culture, interpersonal reality and social forces. This topic is high-yield: examiners pair a theorist with a signature concept (Klein and the positions, Winnicott and the transitional object, Fairbairn and object-seeking libido, Kohut and the selfobject, Kernberg and levels of organisation) and they trace the line from these ideas into the borderline-personality therapies now used in the clinic.

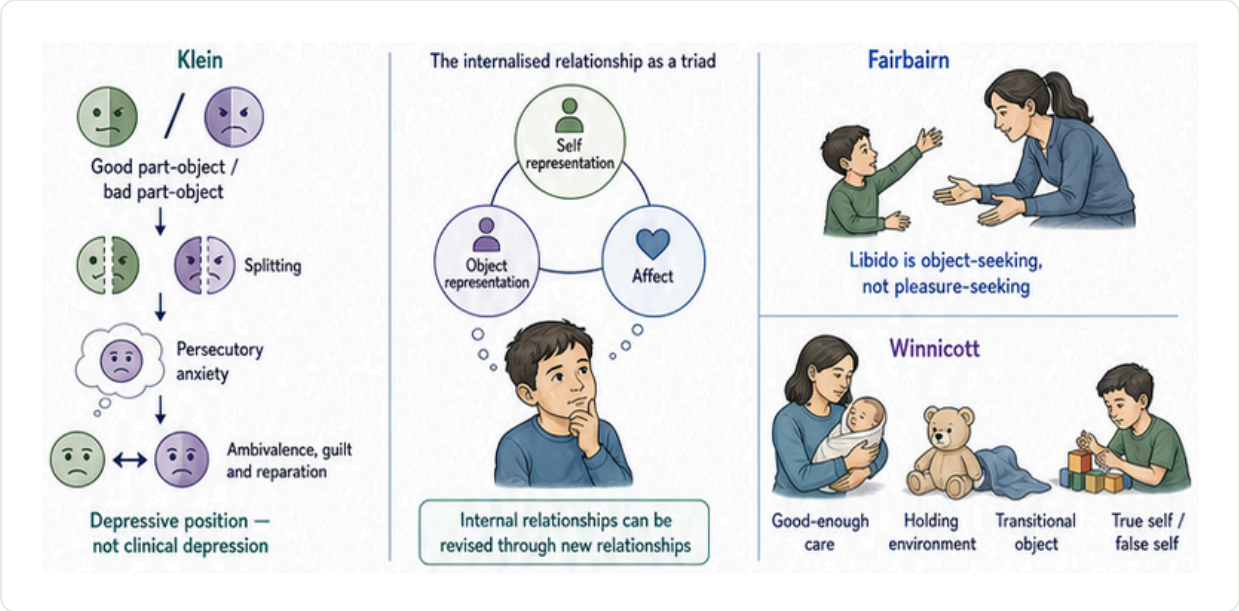


Fig 5.19 Object relations: the internal relational world.

The exam framing follows a clean lineage. Melanie Klein opens the object-relations school by turning Freud's drives inward into a world of good and bad internal objects; the British Independent school (Fairbairn, Winnicott, Balint) makes relationship, not drive, the prime mover; Kohut and Kernberg carry the school into the modern understanding of narcissism and borderline pathology; and Horney, Sullivan and Fromm run in parallel as the socio-cultural neo-Freudians. Mahler (separation-individuation), Adler and Jung belong to the General and Developmental Psychology notes and are only cross-referenced here. Structure below is the standard evolution-of-theories spine: definition, then each theorist in the order the ideas appeared and what each fixed from the last, then the currently accepted synthesis, its neural correlate, and a worked clinical example.

14.1 What "object relations" means

The object is a person, held inside the mind. In psychoanalytic usage the *object* is the target of a drive or a relationship, in practice a person or part of a person (Freud's original term). Object relations theory holds that the infant internalises early relationships as **internal objects**, mental representations of self and other bound together by an affect, and that these internalised self-object-affect units, not the vicissitudes of libido, are the fundamental structures of personality and psychopathology (Kaplan & Sadock 2024). The clinical corollary is that neurosis and character pathology are disturbances in the internal object world, and that the treatment relationship works by offering a new relational experience that can revise those internal objects.

14.2 Melanie Klein: the two positions and the internal object world

Klein turns the drives inward into a world of good and bad objects. Melanie Klein founded the object-relations tradition by taking Freud's late instinct theory, above all the death instinct, and relocating the action into the infant's earliest months (Kaplan & Sadock 2024). Driven to expel intolerable destructive impulses, the infant projects them outward, so the first relationships are with *part-objects*, the gratifying *good breast* and the depriving, persecutory *bad breast*, not yet

combined into a whole mother. Klein described two developmental configurations she called *positions* (recurring modes of experience, not one-off stages).

Paranoid-schizoid position

The earliest mode (roughly the first months). The object is split into an all-good and an all-bad part-object; the dominant anxiety is *persecutory* (fear that the bad object will attack and annihilate the self); the dominant defence is **splitting** together with projection and idealisation. "Schizoid" names the splitting; "paranoid" names the persecutory dread.

Depressive position

The later mode (from around weaning, but revisited lifelong). The infant recognises that the good and bad breast are one whole mother, and that its own aggression has been aimed at the very object it loves and needs. The anxiety shifts from persecution to *guilt and concern*; the developmental work is mourning, reparation and tolerating ambivalence. Reaching and holding the depressive position is, for Klein, the hallmark of psychic maturity.

Two further Kleinian concepts are examinable in their own right. **Projective identification** (elaborated by Klein and extended by Wilfred Bion) is a process in which the subject splits off a part of the self, projects it into another person, and then unconsciously pressures that person to feel and behave in line with the projection, so it is at once a defence, a primitive communication and an interpersonal manoeuvre (Kaplan & Sadock 2024). Bion added the *container-contained* metaphor: the mother (or analyst) absorbs, detoxifies and returns the projected distress in tolerable form for re-internalisation. Klein is regularly criticised for reading all aggression as the death instinct and for dating complex structures such as the superego implausibly early, but her achievement (the internal object world, the two positions, splitting, projective identification) is the foundation of the whole school.

TRAP Klein's **depressive position is a developmental achievement** (whole-object relating, guilt, reparation), not clinical depression.

14.3 Ronald Fairbairn: libido is object-seeking, not pleasure-seeking

The single sentence that defines the school. Ronald Fairbairn made the decisive theoretical break: he held that *libido is object-seeking, not pleasure-seeking* (Kaplan & Sadock 2024). For Freud the infant seeks tension-reducing gratification and the object is merely the means; for Fairbairn the infant seeks the object (the relationship) from the start, and pleasure is the signpost to the object, not the goal. He recast the ego, in Freud a superficial servant of the id, as the core of the psyche, an authentic self that is object-relating from birth. Working chiefly with schizoid patients, he argued their central problem was not controlling dangerous impulses but having an ego capable of relating to objects at all. To manage unsatisfying early relationships the ego *splits* internally, giving Fairbairn's **endopsychic structure**: a central ego relating to an ideal object, a libidinal ego tied to an exciting (tantalising) object, and an anti-libidinal ego (the internal saboteur) tied to a rejecting object. This tripartite internal world of self-and-object pairs is Fairbairn's signature and a direct ancestor of Kernberg's later model.

HOLD THIS

Fairbairn's one line defines the whole school: libido is object-seeking, not pleasure-seeking. The infant seeks the relationship from the start; pleasure is the signpost to the object, not the goal.

14.4 Donald Winnicott: good-enough mothering, the transitional object, the true and false self

The paediatrician-analyst of the Independent school. Donald Winnicott, a paediatrician before he was an analyst and the best-known figure of the British *Independent* (Middle) group, grounded development in the earliest mother-infant relationship (Kaplan & Sadock 2024). His concepts are a cluster examiners love.

Good-enough mother

The mother need not be perfect, only **good-enough**: reliably responsive at first, then failing the infant in small, graduated, tolerable ways so that the child moves from absolute dependence to relative dependence and learns to tolerate frustration. Perfect attunement would in fact impede growth.

Holding environment

The physical and emotional "holding" the mother provides, later a metaphor for the safe, reliable containment the analyst provides in therapy.

Primary maternal preoccupation

The heightened, almost illness-like state of identification with the baby that lets the mother sense and meet its needs in the earliest weeks.

Transitional object

The child's first "not-me" possession (the blanket, the teddy) that stands in for the mother and occupies an intermediate *transitional* space that is neither wholly inner fantasy nor wholly outer reality. It is the developmental bridge from subjective omnipotence to objective reality; Winnicott saw this same intermediate realm of illusion surviving in adult creativity, play, art and religious experience (these are the **transitional** phenomena).

True self and false self

From authentic spontaneous gestures met by good-enough care grows the *true self*. When care is impinging or the child must comply with the mother's needs, a compliant *false self* is built as a protective shell; such patients present as neither neurotic nor psychotic but as subtly unreal, disengaged and compliant.

14.5 The British Independent school and Balint

The middle group that made relationship primary. The *British Independent* (or Middle) group, which formed to sit between Anna Freud's ego-psychological Freudians and the Kleinians during the wartime "Controversial Discussions", is the home of Fairbairn, Winnicott and Michael Balint. Balint's contribution is the **basic fault**: a level of pre-verbal, two-person early damage below the reach of ordinary verbal interpretation, where the therapeutic task is empathic recognition rather than interpretation, and he distinguished benign from malignant regression in treatment (Kaplan & Sadock 2024). The common thread of the Independents is that relationship with the object, not drive discharge, is the engine of development, and that the earliest failures are pre-Oedipal and require a relational, not purely interpretive, cure.

14.6 Heinz Kohut: self psychology and the selfobject

The self, not the drive, at the centre. Heinz Kohut founded **self psychology** in the United States after finding classical drive theory unhelpful with narcissistic patients (Kaplan & Sadock 2024). His organising unit is the **selfobject**: another person experienced not as a separate individual but as a part of, and in the service of, the self, providing functions the self cannot yet perform alone. The infant needs selfobject responses across development, and Kohut named three selfobject transferences that reveal these needs in treatment: *mirroring* (the need to be admired and confirmed, met originally by the gleam in the mother's eye and reflecting the child's *grandiose self*), *idealising* (the need to merge with a calm, strong, idealised figure, the *idealised parental imago*), and *twinship*/alter-ego (the need for likeness and belonging). Normal narcissism matures through gradual, non-traumatic disappointments (*optimal frustration* and *transmuting internalisation*) into healthy self-esteem, ambitions and ideals. Pathological narcissism reflects failed **empathic** mirroring and a self left prone to fragmentation, and the treatment is above all empathic, restoring the arrested developmental need rather than interpreting a conflict.

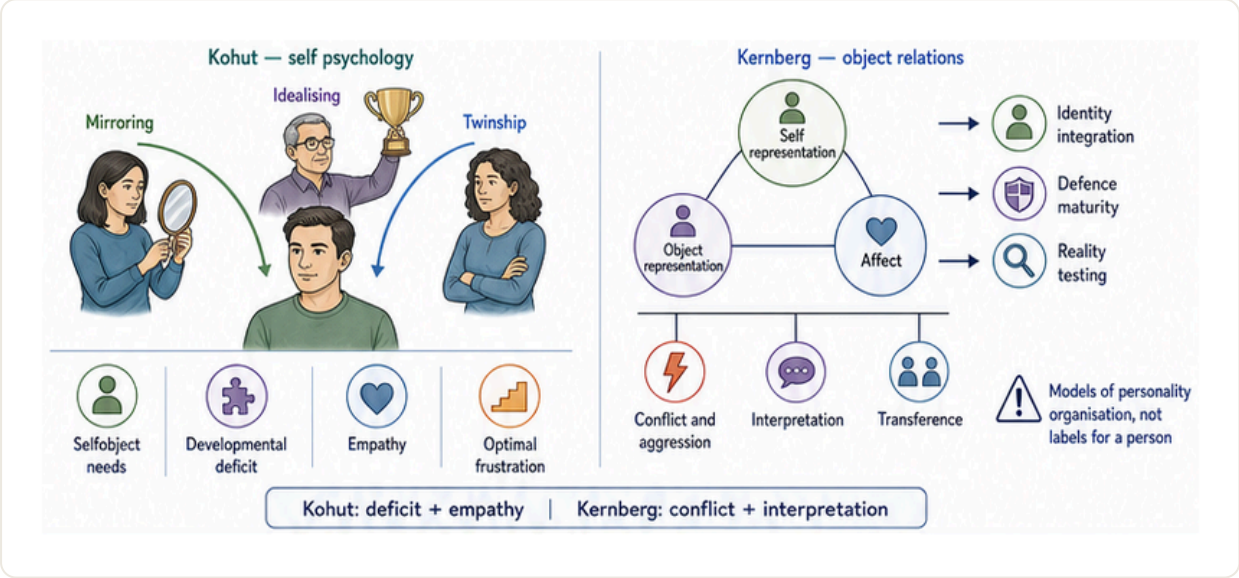


Fig 5.20 Kohut and Kernberg: two models of narcissism.

14.7 Otto Kernberg: the object-relations model of borderline organisation

Drive and object relations, fused, staged by severity. Otto Kernberg integrated ego psychology with object relations and, unlike Kohut, kept libido and aggression inside the model (Kaplan & Sadock 2024). For Kernberg the building blocks of the psyche are *self-representation, object-representation and the affect linking them*, laid down under highly activated early affect states; excess constitutional aggression is central to severe pathology. His most examined contribution is the classification of personality by **levels of personality organisation**, defined by three variables: identity integration, the maturity of defences, and reality testing.

LEVEL	IDENTITY	PREDOMINANT DEFENCES	REALITY TESTING
Neurotic organisation	Integrated (stable sense of self and others)	**Repression-based (repression, reaction formation, intellectualisation)**	Intact
Borderline organisation	**Identity diffusion (contradictory, unintegrated self and object images)**	**Splitting-based (splitting, projective identification, denial, idealisation/devaluation, omnipotence)**	Grossly intact but fragile under stress
Psychotic organisation	Identity diffusion	Splitting-based, more primitive	**Lost**

The two discriminators that place a patient are identity (integrated versus diffuse) and reality testing (intact in neurotic and borderline, lost in psychotic); splitting versus repression separates borderline from neurotic. This is Kernberg's structural interview in one grid.

Borderline *personality organisation* is a broad structural level (identity diffusion + splitting defences + preserved reality testing) that is wider than the DSM/ICD borderline personality *disorder* category and houses much of severe personality pathology. This model is the theoretical engine of transference-focused psychotherapy (below).

14.8 Kohut versus Kernberg on narcissism

The single most-tested contrast in the topic. Both wrote the modern account of narcissism, and they disagree at the root.

FEATURE	KOHUT (SELF PSYCHOLOGY)	KERNBERG (OBJECT RELATIONS)
Status of drive theory	**Discards drive theory; deficit model**	**Retains libido and aggression; conflict model**
Nature of the grandiose self	A fixation of a *normal* archaic infantile self, arrested by empathic failure	A *pathological* structure fusing real self, ideal self and ideal object, saturated with aggression
Core problem	**Developmental *deficit* from failed empathy**	**Defensive structure against oral *aggression* and envy**
Stance in treatment	Empathic, provides missing self-object experience	Interpretive and confrontational; interprets aggression and defences in the transference

Deficit-and-empathy (Kohut) versus conflict-aggression-and-interpretation (Kernberg) is the discriminator line; if a stem contrasts two narcissism theorists, it is testing exactly this.

RULE **On narcissism, Kohut is deficit plus empathy; Kernberg is conflict, aggression and interpretation.** They are opposites, not variants, and a stem contrasting two narcissism theorists is testing exactly this.

14.9 The neo-Freudians: Horney, Sullivan, Fromm

Keep the method, swap the drive for culture and relationships. The **neo-Freudian** analysts accepted Freud's clinical method but replaced his biological instinct theory with social, cultural

and interpersonal determinants.

Karen Horney

Horney located neurosis in disturbed early relationships producing **basic anxiety**, the child's feeling of isolation and helplessness in a potentially hostile world. The child defends against it with one of three *neurotic trends* (interpersonal orientations): *moving toward people* (compliance, seeking love), *moving against people* (aggression, seeking mastery), and *moving away from people* (detachment, seeking self-sufficiency). She is also the first major critic of Freud's *penis envy*, arguing it was a cultural artefact of women's subordinate social position rather than an anatomical inevitability, and she countered it with the notion of male *womb envy*. Her later "tyranny of the should" and the idealised self prefigure cognitive therapy.

Harry Stack Sullivan

Sullivan founded *interpersonal theory*: personality is "the relatively enduring pattern of recurrent interpersonal situations", not an intrapsychic apparatus, so it cannot even be studied apart from relationships. Anxiety originates interpersonally, transmitted from mother to infant, and the self-system develops to avoid it, sorting experience into the *good-me*, *bad-me* and (dissociated, anxiety-laden) *not-me*. He described the *parataxic distortion* (perceiving a present person through the template of a past relationship, an interpersonal reading of transference) and stressed the therapist as a *participant observer*.

Erich Fromm

Fromm, the social and humanistic analyst, sited the person within society and history. In *Escape from Freedom* he argued that modern freedom brings isolation, so people flee it through authoritarianism, destructiveness or automaton conformity. He described non-productive character orientations (receptive, exploitative, hoarding, marketing) versus the healthy *productive* orientation, and set human *existential needs* (relatedness, transcendence, rootedness, identity, a frame of orientation) at the centre of character.

14.10 Currently accepted position

Metabolised, not practised intact. No single one of these systems is used whole today, but the **currently accepted** position is that object relations is the dominant relational framework in contemporary psychodynamic practice, converging with attachment theory (the General and Developmental Psychology notes) and with mentalisation research into a single account: personality is organised around internalised relationships (internal working models / internal objects), and both develop through the caregiver's empathic responsiveness. The practical descendants are two manualised, evidence-based therapies for borderline personality: *transference-focused psychotherapy* (Kernberg and colleagues), which uses the here-and-now transference to integrate split self and object representations, and *mentalisation-based treatment* (Bateman and Fonagy), which grows the capacity to read mental states in self and other, itself rooted in attachment and object-relations thinking (cross-referenced with the personality-disorder and psychotherapy topics). Klein's splitting, Winnicott's holding and Kohut's empathic stance are now common technical vocabulary across the psychodynamic field.

14.11 Neural correlate

Where the internal object world lives, tentatively, in the brain. These are psychological constructs, so any *neural correlate* is a mapping onto systems rather than a discovery within the theories, and it should be held loosely. The *neurobiology* most relevant is the social-cognition and attachment circuitry: representing self and other and reading their mental states engages the *medial prefrontal cortex*, *temporoparietal junction* and *posterior superior temporal sulcus* (the mentalising network that underwrites Fonagy's reflective function). The affect that binds each internal object is carried by the *amygdala* and *anterior cingulate cortex*, and the attachment and selfobject-seeking pull rests on the *oxytocin* and endogenous-opioid systems and mesolimbic reward pathways. Splitting and identity diffusion in borderline organisation track onto impaired prefrontal (especially ventromedial and dorsolateral) regulation of an over-reactive amygdala, the same amygdala-prefrontal imbalance described in the borderline-personality neurobiology. The claim is only that internalised-relationship constructs plausibly ride on the brain's social-cognitive, affective and attachment systems, not that Klein or Kohut localised anything.

14.12 Worked example: one patient through the school

A young woman with unstable relationships and self-harm. Take a patient who idealises a new partner one week and vilifies them the next, cannot say who she is when alone, and cuts herself after feeling abandoned. *Klein:* she is operating largely in the paranoid-schizoid position, splitting each person into all-good and all-bad and using projective identification, drawing others into the very rage she fears. *Winnicott:* a history of impinging, non-attuned early care fostered a false-self compliance masking an unmet true self, and the therapeutic frame must first provide reliable holding. *Kohut:* she seeks selfobjects to steady a fragile self and fragments when mirroring fails, so an empathic stance is primary. *Kernberg:* she shows borderline personality organisation, identity diffusion plus splitting defences with intact reality testing, and transference-focused work would name the alternating idealised and persecutory object relations as they appear with the therapist to integrate them. *Fonagy:* her deficit is mentalising under attachment stress, the explicit target of mentalisation-based treatment. Each lens reads the same clinical picture; together they are the object-relations account of borderline pathology and its treatment.

CLINICAL ANCHOR

Splitting is the concept that unites the school with the ward. The patient who divides the team into all-good and all-bad staff, and the borderline patient who idealises then devalues the same clinician, is displaying Klein's paranoid-schizoid splitting operationalised in Kernberg's borderline organisation. Recognising it (and not taking a side in the split) is the practical yield of this entire topic.

COMMON TRAP

Do not confuse the paired opposites. Klein's *depressive position* is a developmental achievement (whole-object relating, guilt, reparation), not clinical depression. Kohut is *deficit + empathy*; Kernberg is *conflict + aggression + interpretation*, they are opposites on narcissism, not variants. Fairbairn's line is "libido is object-seeking, not pleasure-seeking" (do not swap it onto Winnicott). And keep the neo-Freudians (Horney, Sullivan, Fromm), who replace the drive with culture and interpersonal reality, separate from the object-relations analysts (Klein, Fairbairn, Winnicott), who keep an internal-world focus.

MNEMONIC

"Kids Fear Weird Bosses; Kohut Knows Kids"

The object-relations line in order, then the two moderns: **K**lein (positions, splitting), **F**airbairn (object-seeking libido, endopsychic structure), **W**innicott (good-enough, transitional object, true/false self), **B**alint (basic fault); then **Kohut** (selfobject, mirroring) and **K**ernberg (levels of organisation). For Horney's three trends: "toward, against, away".

GOOD TO REMEMBER

- **Object relations:** mind built from internalised relationships (internal objects), not drive discharge; object = a person or part-person.
- **Melanie Klein:** founder of the school; part-objects (good/bad breast); death-instinct basis.
- **Paranoid-schizoid position:** earliest mode; splitting + persecutory anxiety; all-good vs all-bad part-objects.
- **Depressive position:** whole-object relating; guilt, concern, mourning, reparation; a maturational achievement, not clinical depression.
- **Projective identification:** Klein (extended by Bion); split-off part projected into another who is pressured to enact it; Bion's container-contained.
- **Ronald Fairbairn:** "libido is object-seeking, not pleasure-seeking"; endopsychic structure (central ego / libidinal ego + exciting object / anti-libidinal ego (internal saboteur) + rejecting object); schizoid focus.
- **Donald Winnicott:** good-enough mother; holding environment; primary maternal preoccupation; transitional object and transitional phenomena; true self and false self.
- **Michael Balint:** the basic fault (pre-verbal two-person deficit); benign vs malignant regression.
- **British Independent (Middle) school:** Fairbairn, Winnicott, Balint; relationship over drive; pre-Oedipal focus.
- **Heinz Kohut:** self psychology; the selfobject; mirroring, idealising and twinship transferences; grandiose self and idealised parental imago; optimal frustration and transmuting internalisation; empathy central; discards drive theory (deficit model).
- **Otto Kernberg:** integrates object relations with drive theory (conflict model); self-representation + object-representation + affect; levels of personality organisation (neurotic / borderline / psychotic) defined by identity, defences (repression vs splitting), reality testing; borderline personality organisation; engine of transference-focused psychotherapy.
- **Kohut vs Kernberg:** deficit + empathy vs conflict + aggression + interpretation; normal-archaic vs pathological grandiose self.
- **Karen Horney:** basic anxiety; three neurotic trends (moving toward, against, away from people); critique of penis envy (cultural, not anatomical); womb envy.
- **Harry Stack Sullivan:** interpersonal theory; personality as recurrent interpersonal situations; good-me / bad-me / not-me; parataxic distortion; participant observer.
- **Erich Fromm:** social/humanistic psychoanalysis; Escape from Freedom; character orientations (receptive, exploitative, hoarding, marketing, productive); existential needs.
- **Clinical reach:** transference-focused psychotherapy (Kernberg) and mentalisation-based treatment (Bateman and Fonagy) for borderline personality; converges with attachment theory (the General and Developmental Psychology notes).

15 · Personality theories: trait, type, humanistic and positive psychology

The century-long argument about what a person *is*, told as a sequence of theories each fixing the last one's blind spot. **Personality** is the enduring, characteristic pattern of thinking, feeling and behaving that distinguishes one individual from another and shows consistency across time and situations. The exam does not want a single definition; it wants the four grand traditions and how they answer the same question differently: the **psychodynamic** tradition (personality as the outcome of unconscious conflict and defence, covered under Freud, Jung, Adler on the General and Developmental Psychology notes), the **trait** tradition (personality as a profile of measurable stable dimensions), the **humanistic** tradition (personality as the striving of a whole self toward growth), and the **social-cognitive** tradition (personality as learned expectancies and constructs

interacting with situations). Before all four sat the ancient **type theories**, which sorted people into discrete boxes rather than placing them on continua (Kaplan & Sadock 2024; Companion to Psychiatric Studies).

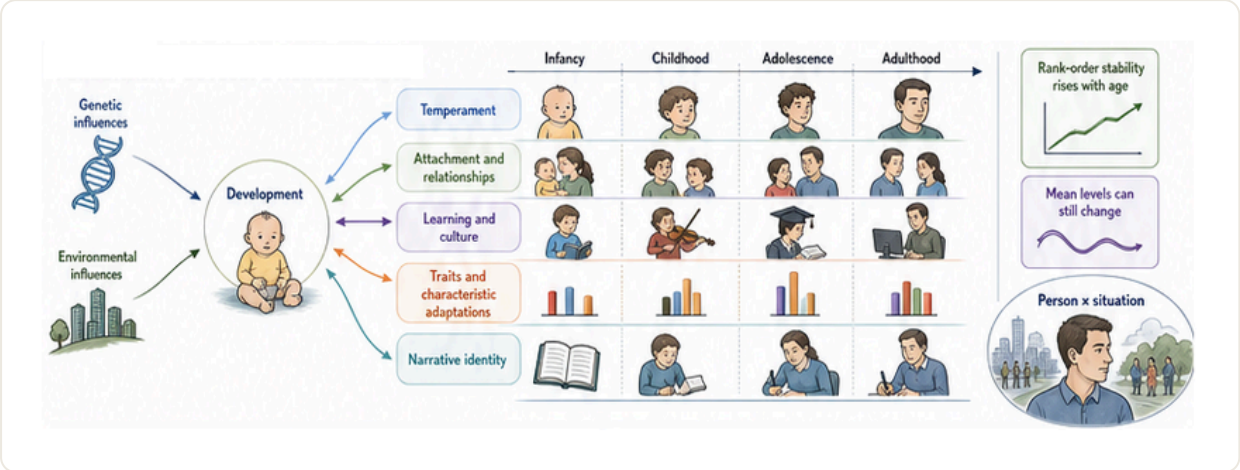


Fig 5.21 Personality develops across levels.

Structure your answer as an evolution. Type theories gave way to the trait tradition when Allport, Eysenck and Cattell showed that people are better described by where they fall on continuous dimensions than by which box they occupy; the trait tradition converged, via the lexical hypothesis and factor analysis, on the **Big Five** or five-factor model, which is the currently accepted descriptive consensus; the humanistic tradition (Rogers, Maslow, and the existential strand of May and Frankl) rose as a "third force" reacting against both the determinism of psychoanalysis and the mechanism of behaviourism; Kelly's personal construct theory bridged into social cognition; the person-situation debate raised by Mischel was resolved into interactionism; and behavioural genetics and the neuroscience of traits supplied the biological correlate. Positive psychology (Seligman, Csikszentmihalyi) is the newest layer, routed here from the General and Developmental Psychology notes, studying what makes life worth living rather than what makes it go wrong (Kaplan & Sadock 2024).

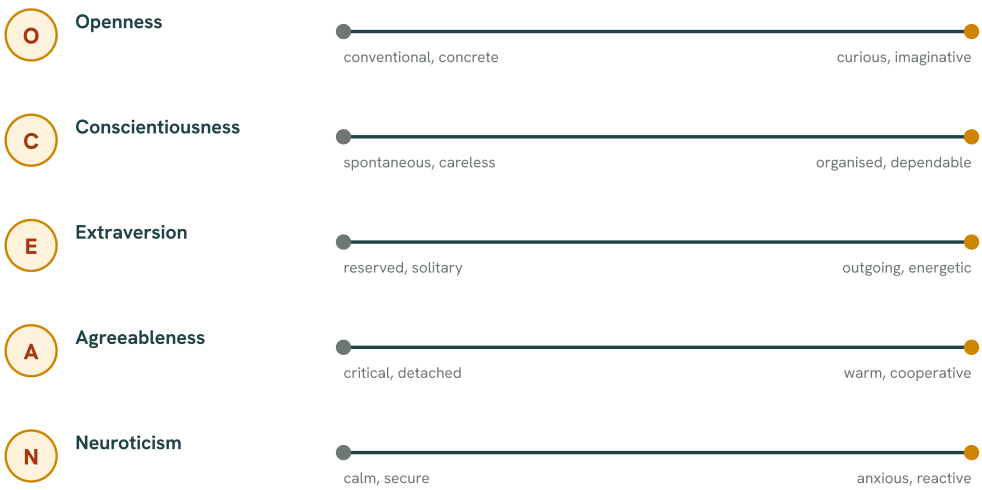


Fig 5.22 The five-factor model (OCEAN), the current descriptive consensus in trait theory. Each factor is a continuous dimension, not a type: a person sits somewhere along all five at once. The poles shown are the extremes; most people cluster near the middle. The model is robust across cultures and languages and is measured by the NEO-PI-R. Neuroticism is the factor most tied to psychopathology, and low conscientiousness and low agreeableness track with externalising problems.

	Psychodynamic	Trait	Type	Humanistic	Social-cognitive
unit	unconscious conflict	stable dimensions	discrete categories	the self, growth	person x situation
human nature	driven, determined	consistent traits	born a type	free, self-actualising	agentic, learning
assessed by	projectives, free association	NEO-PI, 16PF, EPQ	typologies	self-report, Q-sort	behavioural, self-efficacy
key figures	Freud, Klein	Allport, Eysenck	Sheldon, Kretschmer	Rogers, Maslow	Bandura, Mischel

Fig 5.23 The five traditions of personality theory compared. Each answers the same questions differently: what the basic unit of personality is, whether the person is determined or free, how personality is measured, and who its founders are. The trait tradition (now the Big Five) describes personality; the psychodynamic explains its unconscious roots; the type tradition sorts people into kinds; the humanistic centres the self and growth; the social-cognitive puts behaviour at the meeting of person and situation.

15.1 Type theories: the ancient precursor

Sorting people into boxes. A **type theory** proposes a small number of discrete, qualitatively distinct categories into which every person falls; you are one type or another, not more or less of a dimension. The oldest is the humoral scheme of **Hippocrates** and later **Galen**, which linked four bodily humours to four temperaments: blood to the *sanguine* (cheerful, sociable), black bile to the *melancholic* (gloomy, anxious), yellow bile to the *choleric* (irritable, driven), and phlegm to the *phlegmatic* (calm, slow). The word "temperament" preserves this idea of a mixture (Latin *temperare*, to mix). Two twentieth-century constitutional type theories are examinable:

Kretschmer correlated body build with temperament and psychosis-proneness (the lean *asthenic/leptosomic* build with schizoid/schizophrenic tendency, the rounded *pyknic* build with cyclothymic/manic-depressive tendency, plus the *athletic* and *dysplastic* types), and **Sheldon** restated this as three **somatotypes**, the soft rounded *endomorph* (viscerotonic, sociable, comfort-loving), the muscular *mesomorph* (somatotonic, assertive, energetic), and the thin fragile *ectomorph* (cerebrotonic, restrained, introverted). The fatal weakness of every type theory, and the reason the trait tradition replaced it, is that real people do not fall into clean boxes; the correlations were weak and the categories forced continuous variation into false dichotomies (Kaplan & Sadock 2024).

TRAP Type theories are **categories** (you are a type); trait theories are **dimensions** (you have a score on a continuum). The whole point of the trait tradition was to replace the former with the latter.

15.2 Allport: the founding of the trait tradition

What Allport fixed: continua instead of boxes, and the individual restored. Gordon **Allport** (his classic monograph appeared in 1937) is credited with making personality a scientific discipline and with defining the **trait** as a generalised, enduring neuropsychic disposition to render many stimuli functionally equivalent and to initiate consistent forms of behaviour (Kaplan & Sadock 2024). His enduring exam-content is a three-tier hierarchy of traits by how pervasive they are in a life:

Cardinal trait

A single dominant disposition so ruling that almost every act can be traced to it; rare, and it can lend its bearer's name to a quality (Machiavellian, narcissistic). Most people have none.

Central traits

The five to ten general characteristics that describe a person's core and would head a good reference letter (honest, anxious, sociable); the building blocks of personality.

Secondary traits

Situation-specific, peripheral dispositions and preferences (a dislike of crowds, a food preference) shown only in particular contexts and not central to the person.

Allport's second lasting contribution is the **idiographic** versus **nomothetic** distinction. The nomothetic approach studies universal dimensions on which everyone can be ranked and compared (the strategy of Eysenck, Cattell and the Big Five); the idiographic approach studies the unique organisation of the single individual, insisting that the pattern of one person cannot be fully captured by scores on group-derived dimensions. Allport championed the idiographic view while conceding the value of both, and the tension he named still runs through the field (Companion to Psychiatric Studies).

15.3 Eysenck: the biologically grounded trait model

What Eysenck fixed: few dimensions, each with a physiological cause. Hans **Eysenck** insisted that a good trait theory must be parsimonious and biologically anchored, and used factor analysis to reduce personality to a small number of higher-order dimensions with a causal substrate

(Eysenck & Eysenck 1975; Shorter Oxford Textbook of Psychiatry). His **PEN model** has three superfactors:

Extraversion to introversion (E)

Sociability, liveliness and stimulation-seeking versus quiet reserve. Eysenck's causal claim: introverts have *higher* baseline cortical arousal (an ascending reticular activating system set higher), so they seek less external stimulation; extraverts are chronically under-aroused and seek stimulation to compensate.

Neuroticism to stability (N)

Emotional lability, anxiety and reactivity versus calm and even-temperedness, grounded in the reactivity of the limbic/autonomic (visceral brain) system.

Psychoticism (P)

A dimension of tough-mindedness, aggression, impulsivity, coldness and non-conformity (not psychosis itself), added later and the weakest of the three empirically.

What Eysenck left debated: three dimensions proved too few. Many robust traits (notably conscientiousness and agreeableness) do not reduce cleanly to E, N and P, and the arousal theory of extraversion has only partial empirical support. His enduring win is the idea that traits are dimensions with a neurobiology, which the modern field kept (Kaplan & Sadock 2024).

15.4 Cattell: the factor-analytic 16PF

What Cattell fixed: let the data, not the theorist, decide the number of traits. Raymond **Cattell** took the opposite tack to Eysenck's parsimony. Starting from the thousands of trait words in the dictionary (the lexical raw material) and from behavioural and questionnaire data, he applied factor analysis to distil the many observable **surface traits** (clusters of correlated behaviour) down to the smaller set of underlying **source traits** that generate them. He arrived at sixteen source-trait factors and built the **16PF** (Sixteen Personality Factor Questionnaire) to measure them (Companion to Psychiatric Studies). What Cattell left debated was granularity: sixteen factors were too many to be stable and several were intercorrelated, so higher-order analysis of his own factors kept collapsing them into a handful of broad dimensions. That collapse pointed straight at five, and the field's centre of gravity shifted from sixteen to five.

> **PEARL**
>
> Read Eysenck and Cattell as two answers to one question, "how many traits?" Eysenck went top-down and biological and said three; Cattell went bottom-up and statistical and said sixteen. The Big Five sits between them and is where higher-order factoring of Cattell's sixteen and expansion of Eysenck's three both converge. That convergence, from opposite methods, is why the five-factor solution is so trusted.

15.5 The lexical hypothesis and the Big Five (five-factor model)

The currently accepted descriptive consensus. The **lexical hypothesis** holds that the personality differences most important in human affairs have become encoded as single words in every natural language, so factor-analysing the trait lexicon should reveal the true basic dimensions. Independent lexical and questionnaire programmes across the 1980s and 1990s

repeatedly recovered the same five broad orthogonal factors, the **Big Five** or **five-factor** model, remembered by the acronym **OCEAN** (Kaplan & Sadock 2024; Tasman Psychiatry).

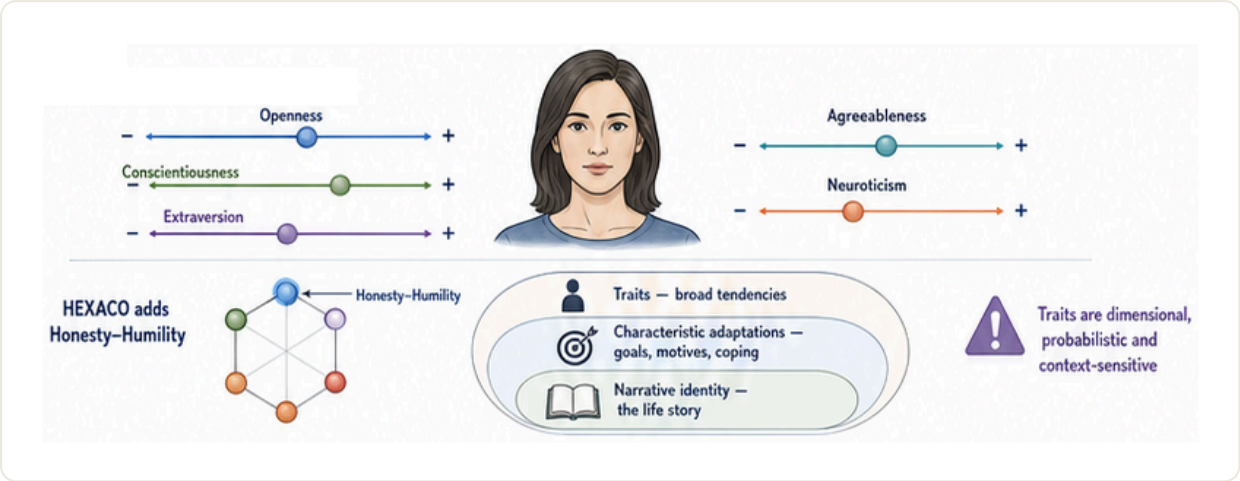


Fig 5.24 Dimensional trait structure.

FACTOR (OCEAN)	HIGH POLE	LOW POLE / CONTRAST
O: **Openness to experience**	Imaginative, curious, unconventional, aesthetically sensitive, open to ideas and feelings	**Closedness: practical, conventional, prefers routine and the familiar**
C: **Conscientiousness**	Organised, dependable, self-disciplined, goal-directed, deliberate	**Impulsivity: careless, disorderly, spontaneous, undisciplined**
E: **Extraversion**	Sociable, assertive, energetic, positive-emotion-prone, stimulation-seeking	**Introversion and detachment: reserved, quiet, solitary**
A: **Agreeableness**	Trusting, cooperative, warm, altruistic, compliant	**Antagonism: suspicious, competitive, callous, oppositional**
N: **Neuroticism**	Anxious, moody, emotionally reactive, prone to negative affect	**Emotional stability: calm, even-tempered, resilient**

The discriminator that makes the five-factor model examinable: each factor is a bipolar continuum, not a type, and the five are broadly independent, so a person is a *profile* of five scores. Costa and McCrae's NEO-PI further divides each domain into six narrower facets (thirty facets in all).

HOLD THIS

The Big Five (OCEAN) is the currently accepted descriptive consensus, measured by the NEO-PI. Eysenck (three, PEN) and Cattell (sixteen, 16PF) converge on it from opposite methods; neuroticism is the factor most tied to psychopathology.

Costa and McCrae's NEO-PI. The standard instrument for the five-factor model is the **NEO-PI** (originally the NEO Personality Inventory, later NEO-PI-R, and the brief NEO-FFI), developed by Paul Costa and Robert McCrae, which scores the five domains and their thirty facets and carries strong evidence of reliability, cross-cultural replicability and temporal stability across the adult lifespan (Kaplan & Sadock 2024; Companion to Psychiatric Studies; Tasman Psychiatry). Its clinical footprint is direct: the DSM-5 Section III alternative model of personality disorders

reframes pathology as maladaptive variants of five domains (negative affectivity, detachment, antagonism, disinhibition, psychoticism) that map onto the maladaptive poles of the five-factor model, high neuroticism, low extraversion, low agreeableness, low conscientiousness, and high openness respectively (Kaplan & Sadock 2024).

15.6 The humanistic tradition: Rogers and the self

The "third force" reacting against determinism. The **humanistic** psychologists rejected both the psychoanalytic view of the person as driven by unconscious conflict and the behaviourist view of the person as a bundle of conditioned responses, and put in their place a person who is fundamentally growth-oriented, free and striving toward fulfilment. Carl **Rogers** built the most complete humanistic personality theory, his *self theory* (Wolberg, Technique of Psychotherapy; Kaplan & Sadock 2024). Its core constructs:

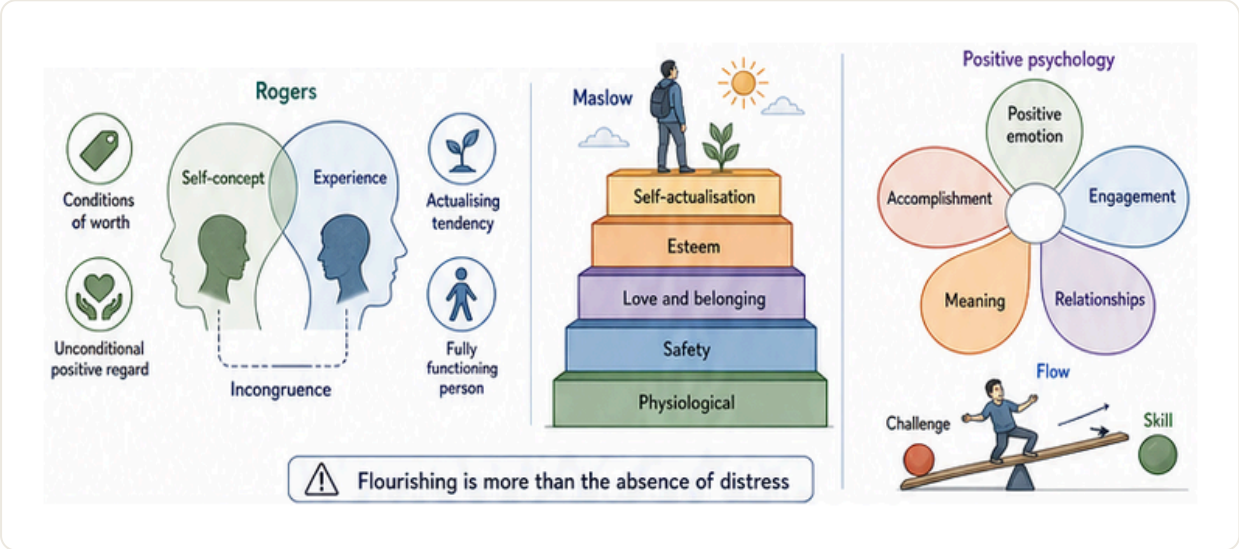


Fig 5.25 Humanistic and positive psychology.

Self-concept

The organised, consistent set of perceptions and beliefs a person holds about themselves; the "real self". Rogers also posits an "ideal self", the person one wishes to be.

Congruence and incongruence

The degree of match between self-concept and actual experience (and between real and ideal self). High congruence underlies psychological health; incongruence, the gap between them, generates anxiety and defensiveness.

Conditions of worth

Internalised standards, learned from others' conditional acceptance, that make self-regard contingent on meeting demands; the developmental source of incongruence.

Unconditional positive regard

Acceptance and valuing of a person without conditions attached. Received in childhood it builds congruence; supplied by the therapist it is the healing condition of client-centred therapy.

Fully functioning person

Rogers' endpoint of healthy development: someone open to experience, living existentially in the present, trusting their own organismic valuing, free and creative.

Driving all of it is a single motivational assumption, the **actualising tendency**, an innate push of every organism toward maintenance, growth and the realisation of its potential. Personality, for Rogers, is what happens to that tendency under the conditions of worth a life imposes (Kaplan & Sadock 2024).

15.7 Maslow and the existential strand

Self-actualisation as a personality endpoint. Abraham **Maslow**, the other pillar of humanism, is examined here for his **hierarchy of needs** (physiological, safety, love and belonging, esteem, and at the summit **self-actualisation**, the realisation of one's full potential) and for his study of self-actualised people as the model of the healthy personality, marked by accurate perception of reality, autonomy, spontaneity, deep relationships, peak experiences and a problem-centred rather than self-centred focus. Where the trait theorists describe the average person, Maslow described the flourishing one, and made growth, not the reduction of tension, the organising motive of personality (Kaplan & Sadock 2024).

The **existential** strand is humanism's darker, European cousin, concerned with freedom, responsibility, meaning and the confrontation with death, isolation and meaninglessness. Rollo **May** brought existential thought into American psychology, framing anxiety as the normal accompaniment of freedom and the awareness of non-being, and distinguishing normal from neurotic anxiety. Viktor **Frankl**, a psychiatrist and Holocaust survivor, founded logotherapy on the "will to meaning", the thesis that the primary human drive is to find meaning, and that meaning can be found even in unavoidable suffering; his *Man's Search for Meaning* is the movement's touchstone. The existentialists fixed a gap in Rogers and Maslow by taking seriously the tragic givens of existence that a purely growth-optimistic humanism underplayed (Kaplan & Sadock 2024).

15.8 Kelly's personal construct theory: the social-cognitive bridge

The person as scientist. George Kelly's **personal construct** theory casts each person as an intuitive scientist who construes the world through a personal repertoire of bipolar dimensions (constructs such as kind-cruel, safe-dangerous) and uses them to anticipate events; behaviour follows from the anticipations these constructs generate, and psychological problems arise when a person's construct system fits the world poorly and resists revision. Because it locates personality in learned cognitive structures interacting with situations rather than in fixed traits or unconscious drives, it forms the bridge from the humanistic tradition into the social-cognitive one (Bandura's reciprocal determinism and self-efficacy, Rotter's locus of control, Mischel's cognitive-affective processing), which is developed under the learning-theory topics (Kaplan & Sadock 2024).

15.9 Currently accepted: the Big Five and the resolution of the person-situation debate

The consensus and the crisis it survived. The **currently accepted** descriptive framework for normal personality is the Big Five / five-factor model: five broad, replicable, cross-culturally recovered dimensions that subsume the earlier trait models and now anchor the dimensional reframing of personality disorder in DSM-5 Section III and ICD-11 (Kaplan & Sadock 2024). It

reached this status only after surviving the **person-situation debate**. In 1968 Walter **Mischel** observed that trait scores predict behaviour in any single situation only modestly (the "personality coefficient" ceiling of roughly 0.30) and argued that situations, not traits, drive behaviour. The debate was resolved into **interactionism**: traits predict behaviour well when it is *aggregated* across many situations (a person high in conscientiousness is reliably more conscientious on average), while situations determine the specific act; person and situation interact, and Mischel's own later cognitive-affective processing system (CAPS) model captured the stable *if-then* behavioural signatures that reconcile cross-situational variability with genuine personality consistency.

15.10 The behavioural-genetic and neural correlate of traits

Where the dimensions live in the biology. Twin and adoption studies converge on a **heritability** of the major personality traits of roughly 40 to 50 per cent (often quoted as the 40 to 60 per cent band across studies and traits), with the remaining variance dominated by the *nonshared* environment and shared-family environment contributing little; large genome-wide association studies have so far failed to pin the heritability to reliable common variants, the classic missing-heritability picture (Tasman Psychiatry; Kaplan & Sadock 2024). For the **neural correlate**, two frameworks are examinable. Jeffrey **Gray**'s reinforcement-sensitivity theory reinterprets Eysenck's axes as two motivational systems: a behavioural inhibition system (BIS, septo-hippocampal and amygdalar, sensitive to punishment and novelty, underlying anxiety and mapping toward high neuroticism/introversion) and a behavioural activation system (BAS, mesolimbic dopaminergic, sensitive to reward, underlying impulsivity and mapping toward extraversion). Colin **DeYoung**'s cybernetic/personality-neuroscience programme links each Big Five domain to systems: extraversion to dopaminergic reward circuitry, neuroticism to the amygdala and threat/defensive systems, conscientiousness to lateral prefrontal cortex, openness to dopaminergic cognitive-exploration circuits, and agreeableness to social-cognition and theory-of-mind networks. The through-line is that traits are moderately heritable dimensions with identifiable neurotransmitter and circuit substrates, exactly the biological grounding Eysenck first demanded (Kaplan & Sadock 2024).

40-50%	~0.30	5
HERITABILITY OF MAJOR TRAITS	MISCHEL'S PERSONALITY COEFFICIENT CEILING	FACTORS (OCEAN), 30 FACETS

CLINICAL ANCHOR

A worked example that ties the traditions together. A reserved, meticulous, easily-worried patient can be read at every level: a *type* theorist would once have called him a melancholic or an ectomorph; the *trait* reading is low extraversion, high conscientiousness, high neuroticism on the NEO-PI; Eysenck would flag high N and high introvert arousal; Gray would locate an overactive behavioural inhibition system; the *humanistic* reading asks what conditions of worth made his self-worth contingent on flawless performance and where his self-concept is incongruent with his experience; Kelly would map the rigid bipolar constructs (perfect-worthless) through which he anticipates evaluation. None is wrong; each tradition answers a different clinical question, and a good formulation uses more than one.

15.11 Positive psychology (delta): Seligman, PERMA, strengths and flow

The science of what goes right, routed here from the General and Developmental Psychology notes. **Positive psychology**, launched as a formal programme by Martin **Seligman** during his 1998 American Psychological Association presidency, studies positive emotions, positive traits and enabling institutions, the conditions under which people and communities flourish, as a deliberate counterweight to psychology's traditional focus on disorder. It sits naturally beside the humanistic tradition (both centre growth and the healthy person) but insists on empirical measurement (Kaplan & Sadock 2024).

PERMA

Seligman's five-element model of well-being: **P**ositive emotion, **E**ngagement, **R**elationships (positive), **M**eaning, and **A**ccomplishment. Well-being is the flourishing that comes of building all five, not merely the absence of distress.

Character strengths and virtues

Peterson and Seligman's classification (the deliberate "un-DSM") of 24 measurable character strengths grouped under six universal virtues (wisdom, courage, humanity, justice, temperance, transcendence), assessed by the VIA Inventory of Strengths.

Flow

Mihaly **Csikszentmihalyi**'s state of complete absorption in an intrinsically rewarding activity, in which challenge and skill are well matched and self-consciousness and the sense of time drop away; the experiential core of engagement.

Authentic happiness / well-being theory

Seligman's earlier "authentic happiness" scheme (pleasant, engaged and meaningful lives) which he later broadened into the multi-element well-being theory captured by PERMA.

COMMON TRAP

Do not confuse the neighbouring frameworks. Type theories are *categories* (you are a type); trait theories are *dimensions* (you have a score on a continuum), and the whole point of the trait tradition was to replace the former with the latter. Eysenck (three factors, PEN) is not Cattell (sixteen factors, 16PF), and neither is the Big Five (five factors, NEO-PI), though all three are trait/nomothetic models. Maslow's self-actualisation is the *top of a need hierarchy*; Rogers' fully functioning person is the *outcome of unconditional positive regard and congruence*, the two are humanistic cousins but not the same construct. And positive psychology (Seligman, an empirical programme with instruments) is not the same as humanism (Rogers/Maslow, a mid-century philosophical movement), even though they share the growth agenda.

INDIA

The five-factor structure replicates in Indian samples but is not culturally exhaustive: indigenous work has argued for additional or reweighted dimensions, and constructs such as the trigunas of Samkhya (sattva, rajas, tamas) have been operationalised into scales as an emic model of personality. For the exam, know that the Big Five is the accepted *universal* descriptive framework while accepting that lexical studies in different languages recover locally salient factors on top of it.

MNEMONIC

OCEAN and PERMA

The Big Five is **OCEAN**: **O**penness, **C**onscientiousness, **E**xtraversion, **A**greeableness, **N**euroticism. Positive-psychology well-being is **PERMA**: **P**ositive emotion, **E**ngagement, **R**elationships, **M**eaning, **A**ccomplishment. For the traditions in order, remember "Boxes, then Dimensions, then Selves, then Scientists": type theories (boxes), trait theories (dimensions), humanism (the self), social-cognitive/constructs (the person as scientist).

GOOD TO REMEMBER

- **Personality:** enduring characteristic pattern of thought, feeling and behaviour, consistent across time and situations.
- **Four grand traditions:** psychodynamic (unconscious conflict), trait (measurable dimensions), humanistic (the striving whole self), social-cognitive (learned expectancies and constructs); type theories are the ancient precursor.
- **Type theories:** Hippocrates/Galen four humours and temperaments (sanguine, melancholic, choleric, phlegmatic); Kretschmer (asthenic-schizoid, pyknic-cyclothymic, athletic); Sheldon somatotypes (endomorph-viscerotonic, mesomorph-somatotonic, ectomorph-cerebrotonic).
- **Allport:** cardinal, central and secondary traits; the idiographic (unique individual) versus nomothetic (universal dimensions) distinction; founder of trait psychology.
- **Eysenck:** biologically grounded PEN model, extraversion-introversion (introverts higher cortical arousal), neuroticism (limbic reactivity), psychoticism; three superfactors.
- **Cattell:** factor-analytic model, surface traits versus source traits, sixteen source factors measured by the 16PF.
- **Big Five / five-factor model (OCEAN):** Openness, Conscientiousness, Extraversion, Agreeableness, Neuroticism; the currently accepted descriptive consensus, measured by Costa and McCrae's NEO-PI (five domains, thirty facets).
- **Rogers (self theory):** self-concept, real versus ideal self, congruence-incongruence, conditions of worth, unconditional positive regard, the fully functioning person, actualising tendency.
- **Maslow:** hierarchy of needs topped by self-actualisation as the healthy-personality endpoint.
- **Existential strand:** May (anxiety as accompaniment of freedom and non-being) and Frankl (logotherapy, the will to meaning).
- **Kelly:** personal construct theory, the person as intuitive scientist; the bridge into social cognition.
- **Person-situation debate:** Mischel (1968) challenged trait predictiveness (the ~0.30 personality coefficient); resolved into interactionism (traits predict aggregated behaviour, situations predict the specific act).
- **Heritability of traits:** roughly 40 to 60 per cent, remainder mostly nonshared environment; GWAS missing-heritability picture.
- **Neuroscience of traits:** Gray's BIS/BAS (septo-hippocampal/amygdalar punishment system; mesolimbic-dopaminergic reward system); DeYoung's personality neuroscience (extraversion-dopamine reward, neuroticism-amygdala threat, conscientiousness-prefrontal, openness-dopaminergic exploration, agreeableness-social cognition).
- **Positive psychology (Seligman, 1998):** PERMA (positive emotion, engagement, relationships, meaning, accomplishment); character strengths and virtues (24 strengths, 6 virtues, VIA inventory); flow (Csikszentmihalyi); well-being theory.

Special topics

16 · Psychology of rape

The **psychology of rape** is a named Paper-1 essay topic, and it is examined as a piece of applied social and forensic psychology rather than as a description of an offence. It sits on these notes because it draws together attribution, aggression, attitudes and the psychology of the survivor. The register throughout is clinical and sober: this is doctor-facing revision, the material concerns both the person who offends and the person who is harmed, and it is written without case detail or sensationalism.

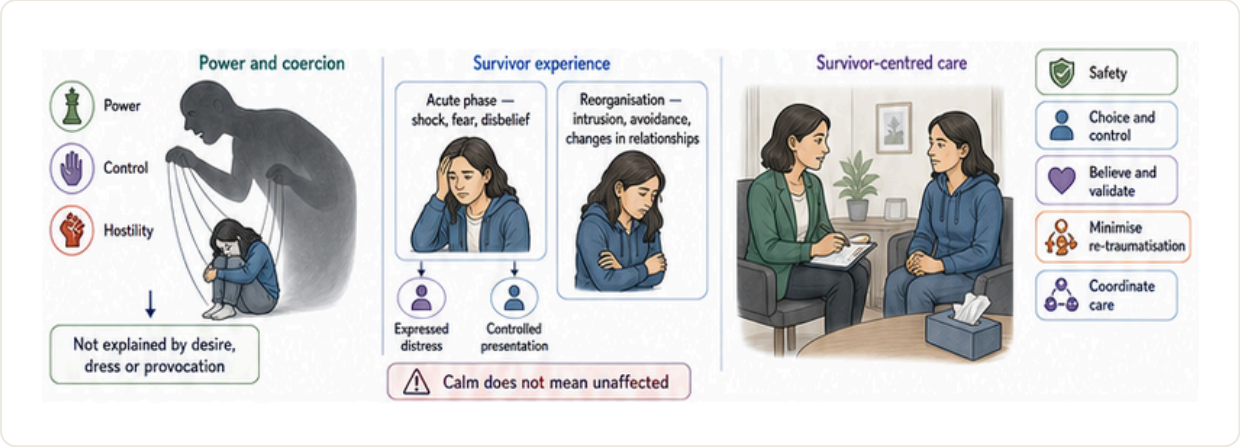


Fig 5.26 Sexual violence: power, trauma and survivor-centred care.

Two bodies of theory are examined. The first is the psychology of the offender, where the central shift over the last half century has been away from the idea that **rape** is driven by sexual desire and toward understanding it as an act of power and aggression expressed through sex. The second is the psychology of the survivor of **sexual assault**, where the key construct is the patterned psychiatric response first described as the rape trauma syndrome. The clinician also needs the framework for a trauma-informed response and an outline of the Indian medico-legal setting.

16.1 The reframing: power and aggression, not lust

The foundational idea, from Nicholas Groth's clinical work with offenders (Men Who Rape, 1979), is that rape is the sexual expression of power and anger, not primarily the aggressive expression of sexuality. Sexuality is the medium; power, control and hostility are the motives. This reframing matters clinically and forensically because it predicts that rape is poorly explained by sexual deprivation or provocation, and it displaces the rape myths that treat the act as a misunderstanding about sex. It also aligns the offence with the general aggression literature of these notes rather than with the paraphilias, although a minority of offenders do have a paraphilic (sexual sadism) or antisocial profile.

RULE **Rape is the sexual expression of power and anger, not primarily lust (Groth).** Sexuality is the medium; power, control and hostility are the motives, which is why the act is poorly explained by sexual deprivation or provocation.

16.2 Offender typologies

Groth (1979) himself described *three* patterns by the motive that predominates: **anger rape**, **power rape** and **sadistic rape**. The four-type scheme below is the later investigative elaboration associated with Hazelwood and the FBI, which splits Groth's power category into reassurance and assertive subtypes (a split Knight's typology also uses) and his anger category into retaliatory and excitation subtypes. Cite the three when asked for Groth and the four when asked for the investigative typology. Either way it is a clinical heuristic, not a diagnosis, and most real offenders are heterogeneous, so the caveats matter as much as the categories.

TYPE	PREDOMINANT MOTIVE	CHARACTER
Power-reassurance	**Restoring a fragile sense of masculine adequacy**	The least overtly aggressive; scripted, seeks reassurance; the commonest type
Power-assertive	**Asserting dominance and entitlement**	Uses force to control; sees the act as a right, not a fantasy
Anger-retaliatory	**Punishing and degrading, revenge on women**	Impulsive, high gratuitous violence, brief and brutal
Anger-excitation (sadistic)	**Eroticised suffering**	The rarest and most dangerous; planned, ritualised; overlaps sexual sadism and psychopathy

The four investigative offender types (Hazelwood and the FBI, elaborating Groth's three) by predominant motive; power types outnumber anger types, and the sadistic type is rare but carries the greatest risk.

16.3 Risk factors and the limits of prediction

The best-supported model of the propensity to sexual aggression is Malamuth's confluence model, which locates risk at the meeting of two paths: hostile masculinity (adversarial, controlling attitudes toward women, hostility, and a need to dominate) and an impersonal, non-intimate orientation to sex. Attitudinal factors (acceptance of rape myths, hostility) and situational disinhibitors (alcohol, peer norms) raise risk. The clinically honest point for the exam is that prediction at the level of the individual is weak: these are group-level associations, and no profile identifies an offender with useful accuracy.

TRAP Groth's typologies and the confluence-model risk factors are **group-level associations, not an individual-prediction tool**; no profile identifies an offender with useful accuracy.

16.4 Rape myths and their harm

Rape myths are false but widely held beliefs about rape, offenders and survivors that serve to deny, minimise or justify sexual aggression: that survivors provoke it by dress or conduct, that only strangers commit it, that a real rape leaves visible injury, that a delayed or calm disclosure means it did not happen. Rape myth acceptance is measurable and predicts victim-blaming attitudes. Its harm is concrete: it suppresses disclosure, colours the medical and legal response, and inflicts the second injury of not being believed. Recognising these myths is part of a competent clinical stance.

16.5 The survivor: the rape trauma syndrome

Ann Burgess and Lynda Holmstrom described the rape trauma syndrome in 1974 as the patterned psychological response to sexual assault, in two phases. The acute or disorganisation phase (days to weeks) brings shock, fear, disbelief, and either an expressed style (overt distress) or a controlled style (a composed, flat presentation that can be misread as unaffected). The reorganisation phase (months and longer) brings the intrusive and avoidant symptoms, phobias, sexual difficulties, and changes to lifestyle and relationships. In modern terms this maps onto acute stress and post-traumatic stress disorder, with high rates of comorbid depression, sexual dysfunction and substance use; suicidality must be assessed.

HOLD THIS

The rape trauma syndrome (Burgess and Holmstrom 1974) runs in two phases: acute or disorganisation, then reorganisation. The acute phase can present as an expressed (overt distress) or a controlled (composed, flat) style, and a calm presentation must not be misread as unaffected.

16.6 Secondary victimisation and a trauma-informed response

Secondary victimisation, the second injury, is the further harm done by the responses of services, family and the legal process: disbelief, blame, intrusive questioning, and loss of control over the process. The clinical antidote is a trauma-informed response whose principles are safety first, restoring choice and control to the survivor, believing and validating, minimising re-traumatisation during examination, and coordinating the medical, psychological and forensic tasks so the survivor is not made to repeat the account needlessly.

16.7 The Indian medico-legal frame

INDIA

In India the clinical care of a survivor of sexual assault is governed by consent, the guidance that treatment is not conditional on reporting to police, and the post-2013 reforms that discredited and moved away from the so called two-finger test as unscientific and degrading. Offences against minors are dealt with under the Protection of Children from Sexual Offences (POCSO) Act. The statutory detail belongs to the the forensic psychiatry chapter and is cross-referenced there; what belongs here is the clinical stance: examine with consent, document carefully, treat injuries and prophylaxis, and provide trauma-informed psychological care.

GOOD TO REMEMBER

- **Reframing (Groth 1979):** rape is power and anger expressed through sex, not lust.
- **Offender types:** Groth's own three are anger, power and sadistic rape; the investigative four (Hazelwood/FBI) are power-reassurance (commonest), power-assertive, anger-retaliatory and anger-excitation or sadistic (rarest, most dangerous).
- **Risk (Malamuth confluence model):** hostile masculinity plus impersonal sex; individual prediction is weak.
- **Rape myths:** false beliefs that deny or justify assault; raise victim-blaming, suppress disclosure.
- **Rape trauma syndrome (Burgess and Holmstrom 1974):** acute or disorganisation phase (expressed or controlled style) then reorganisation phase; maps onto ASD and PTSD with depression and sexual dysfunction.
- **Second injury:** secondary victimisation by services and the process; countered by a trauma-informed response.
- **India:** consent-based care, care not conditional on reporting, the two-finger test abandoned (2013), POCSO for minors.

17 · The Indian therapy relationship: guru-chela and expressed emotion

Two constructs from the Paper-1 syllabus carry a distinct Indian weight, and both concern the relationships around the patient rather than the patient alone. The first is the **guru-chela** relationship, an Indian model of the therapeutic bond. The second is **expressed emotion**, the

measurable emotional atmosphere of the family, whose Indian findings are part of why outcomes for serious mental illness have been better in the developing world.

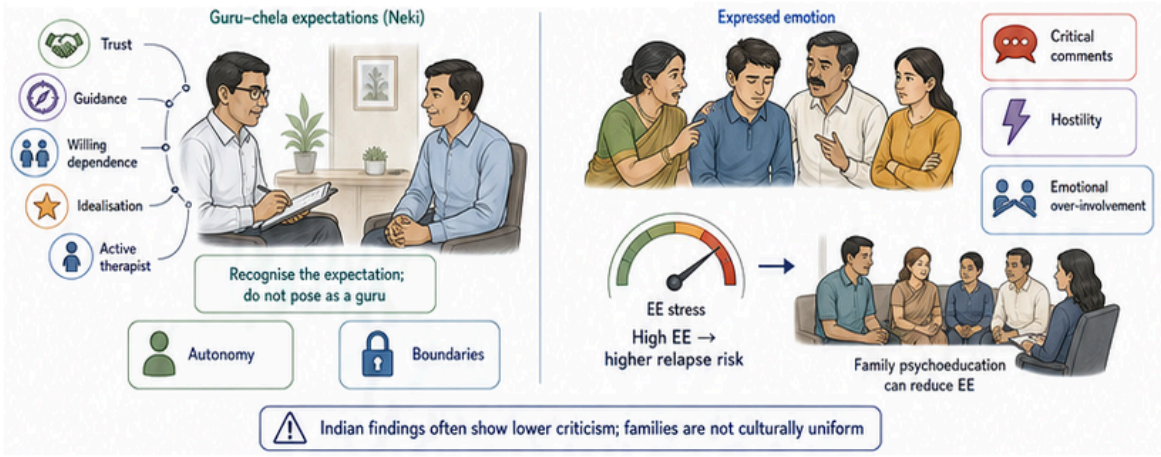


Fig 5.27 Indian therapy relationship and expressed emotion.

17.1 The guru-chela relationship (Neki)

J. S. Neki, in a classic pair of papers (Guru-Chela relationship: the possibility of a therapeutic paradigm, American Journal of Orthopsychiatry, 1973), argued that the Western contractual, autonomy-valuing therapeutic alliance is a poor cultural fit for many Indian patients, and that the indigenous guru-shishya (guru-chela) ideal offers a better paradigm. In that ideal the disciple approaches the teacher with trust, reverence and a willing dependence; the guru accepts responsibility for the disciple's growth, offers guidance and a model to identify with, and the bond is warm, hierarchical and personal rather than contractual and time-limited.

17.2 Why it matters for practice

The guru-chela frame reframes several things the Western model treats as problems. Dependence, which the autonomy-valuing model tends to pathologise, is here a legitimate and even therapeutic stage; idealisation of the therapist is expected rather than interpreted away at once; and the therapist is permitted to be more active, directive and personally invested. Neki's point is not that the therapist should pose as a guru, but that Indian patients often enter treatment with guru-chela expectations, and that understanding this improves engagement and the handling of transference and dependence. Its risks are the risks of any hierarchical bond: fostering excessive dependence, and blurring boundaries if the therapist accepts the idealisation uncritically.

RULE **In the guru-chela paradigm (Neki), dependence and idealisation are legitimate therapeutic stages, not pathology to interpret away.** The point is not to pose as a guru but to recognise the expectations Indian patients often bring.

17.3 Expressed emotion: the construct

Expressed emotion is a measure of the emotional climate a relative shows toward a patient, developed by George Brown and Michael Rutter and assessed through the Camberwell Family

Interview. It has three key components: critical comments (the count of critical remarks), hostility (generalised rejection of the person, not just their behaviour), and emotional over-involvement (over-protective, self-sacrificing, dramatic concern). A household is rated high in expressed emotion if a relative exceeds threshold on criticism or hostility, or shows marked over-involvement.

HOLD THIS

Expressed emotion (Brown and Rutter; Camberwell Family Interview) has three components: critical comments, hostility and emotional over-involvement. Indian families tend to show lower expressed emotion, part of the better outcome of schizophrenia in the developing world.

17.4 Expressed emotion and relapse

The robust finding, replicated across many samples, is that patients with schizophrenia who return to a high expressed emotion household relapse at markedly higher rates than those returning to a low expressed emotion household (Vaughn and Leff), and the effect extends to mood disorders and other conditions. The mechanism is understood as a chronic stressor acting on a vulnerable individual, a family-level instance of the diathesis-stress model. The practical payoff is that family psychoeducation which lowers expressed emotion reduces relapse: Leff and colleagues (1982) showed a controlled social intervention in families cut the relapse rate, which is why lowering expressed emotion is a target of family work.

RULE **High expressed emotion predicts relapse; lowering it (through family psychoeducation) reduces relapse.** It acts as a chronic stressor on a vulnerable individual, a family-level instance of diathesis-stress.

17.5 Expressed emotion in India

INDIA

The cross-cultural expressed emotion research, including the WHO Determinants of Outcome study and Indian work by Wig, Leff and colleagues in Chandigarh, found that Indian families tend to show lower expressed emotion than Western families, with fewer critical comments and less over-involvement. This lower family criticism is one of the cultural factors invoked to explain the better course and outcome of schizophrenia reported in the developing world (cross-ref the cross-cultural outcome material). It is a clean example of a social variable, the family's emotional tone, shaping the course of a biological illness.

GOOD TO REMEMBER

- **Guru-chela (Neki 1973):** an Indian therapeutic paradigm of trust, reverence and willing dependence on the therapist-as-guru, against the Western contractual, autonomy-valuing alliance.
- **Clinical use:** dependence and idealisation are legitimate stages, the therapist is more active; the risk is over-dependence and boundary blurring.
- **Expressed emotion (Brown and Rutter; Camberwell Family Interview):** critical comments, hostility, emotional over-involvement.
- **High expressed emotion predicts relapse** in schizophrenia (Vaughn and Leff) and mood disorders; a family-level diathesis-stress effect.
- **Family psychoeducation** that lowers expressed emotion reduces relapse (Leff et al 1982).
- **India:** Indian families tend to show lower expressed emotion (Wig, Leff), part of the better outcome of schizophrenia in the developing world.

Discriminate

18 · Discriminate: the paradigms side by side

The examinable skill of these notes is discrimination: not reciting one theory, but telling it apart from its neighbours. Three comparisons carry most of the marks. The first tells the learning paradigms apart, the second tells the personality models apart, and the third tells the social-thinking biases apart. Read each table down the discriminator column, the shaded cell, because that is where the distinguishing feature sits.

18.1 The learning paradigms: classical, operant and social learning

The three paradigms are often confused because all three are about learning, but they differ in what is associated, what the learner does, and the therapy each produces. The move across them is also historical, from a passive organism forming stimulus associations to an active, cognitive one learning by watching.

FEATURE	CLASSICAL (PAVLOV)	OPERANT (SKINNER)	SOCIAL LEARNING (BANDURA)
What is learned	**A stimulus predicts a stimulus (CS predicts US)**	**A behaviour predicts a consequence**	**A behaviour and its outcome, by watching a model**
Key relationship	CS paired with US, before the response	Reinforcement or punishment, after the response	Vicarious reinforcement of the model
The learner	Passive, reflexive (involuntary responses)	Active, emitting behaviour (voluntary responses)	Cognitive: attends, retains, expects
Signature study	Salivating dogs; Little Albert	The Skinner box; schedules of reinforcement	The Bobo doll
Therapy it yields	Systematic desensitisation, exposure, aversion	Token economy, contingency management, ABA	Modelling, skills training, self-efficacy work

Classical learns what predicts what before a reflex; operant learns what a voluntary action earns; social learning learns by watching a model, with cognition in the middle.

HOLD THIS

Classical is a stimulus predicting a stimulus before an involuntary reflex; operant is a voluntary behaviour shaped by its consequence; social learning is behaviour acquired by watching a model. The learner moves from passive to active to cognitive across the three.

18.2 The personality models: five traditions

The five traditions answer the same questions differently: what the basic unit of personality is, whether the person is determined or free, how personality is measured, and what the main criticism is. Type theories sort people into kinds; trait theories place them on continuous dimensions; the psychodynamic explains the unconscious roots; the humanistic centres the self and growth; the social-cognitive puts behaviour at the meeting of person and situation.

TRADITION	UNIT OF ANALYSIS	ASSESSED BY	MAIN CRITICISM
Psychodynamic	**Unconscious conflict and drives**	Projective tests, free association	Hard to test, over-interprets
Trait	**Stable dimensions (the Big Five)**	Questionnaires (NEO-PI, 16PF, EPQ)	Describes rather than explains
Type	**Discrete categories or kinds**	Typologies, body build	Loses individual variation
Humanistic	**The self, growth, meaning**	Self-report, Q-sort	Vague, optimistic, hard to measure
Social-cognitive	**Person interacting with situation**	Behavioural measures, self-efficacy scales	Underweights emotion and biology

The five personality traditions compared on their unit of analysis, their assessment method and their main criticism; the trait tradition, now the Big Five, is the descriptive consensus.

18.3 The social-thinking biases

Four social-cognitive phenomena from these notes are easily confused because each describes a distortion in how people think about themselves and others. The one-line signature tells them apart.

BIAS	SIGNATURE
Fundamental attribution error	**Over-attributing others' behaviour to disposition, underrating the situation**
Self-serving bias	**Taking credit for success (internal), blaming the situation for failure (external)**
Cognitive dissonance	**Changing an attitude to resolve the tension of inconsistent cognitions**
Group polarisation	**A group's average view becoming more extreme after discussion**

Four social-thinking distortions distinguished by their signatures; the first two are attribution biases, the third an attitude-change process, the fourth a group effect.

COMMON TRAP

The high-yield mix-ups: classical conditioning is before the reflex and involuntary, operant is after a voluntary act; negative reinforcement strengthens behaviour (it removes something aversive) and must not be called punishment, which weakens it; Eysenck's model is a few broad biologically grounded dimensions (PEN) while Cattell's is sixteen factors (16PF); and in object relations, Klein is the paranoid-schizoid and depressive positions while Kohut is self psychology and the selfobject.

Apply and consolidate

19 · Apply: four psychology vignettes

Four short worked vignettes turn this theory into the reasoning the exam actually rewards. Each gives a brief presentation, then the psychological reasoning, then the read. The tool changes each time, so that the discriminator carries the answer.

RULE **In an applied vignette, name the process, not the personality.** Identify the domain and its mechanism (a bias, a conditioning contingency, a Big Five profile, a group effect), and the discriminator carries the mark.

19.1 An attribution read

CLINICAL ANCHOR

Case: a vignette in attribution. A final-year student fails an examination and tells you the paper was unfair and the examiners had it in for him, while explaining that his distinctions in earlier years were down to his own ability. Reasoning: the failure is attributed to external, unstable, uncontrollable causes and the successes to internal, stable ones. This asymmetry, taking credit for success and externalising failure, is the self-serving bias. His readiness to see the examiners' intent rather than the situation is the fundamental attribution error turned on others. The read: a self-serving attributional style, which protects self-esteem but, if rigid, blocks the learning that a more balanced, effort-based attribution would allow.

19.2 A learning and behaviour-therapy plan

CLINICAL ANCHOR

Case: a vignette in conditioning. A woman develops an intense fear of lifts after being trapped in one during a power cut; she now avoids lifts entirely and her world is shrinking. Reasoning: the trapping (an aversive unconditioned stimulus) was paired with the lift (now a conditioned stimulus), so the lift alone evokes a conditioned fear response, classical conditioning; the avoidance is then maintained by operant negative reinforcement, because escaping the lift removes the anxiety and so is reinforced. The read: a specific phobia by conditioning. The matching treatment follows the paradigm: graded exposure or systematic desensitisation to extinguish the conditioned fear, and blocking the avoidance so the negative reinforcement cycle cannot maintain it.

19.3 A personality-model read

CLINICAL ANCHOR

Case: a vignette in personality. A colleague is described as anxious and easily stressed, meticulous and dutiful, reserved in company, and quick to imagine worst cases. Reasoning on the Big Five: high neuroticism, high conscientiousness, low extraversion, with average openness and agreeableness. A trait clinician stops there and predicts behaviour from the profile. A psychodynamic clinician asks what unconscious conflict the meticulousness defends against (obsessional defences against anxiety). A humanistic clinician asks whether the person is living in line with their own values or an introjected standard, and where the conditions of worth lie. The read: the same person, formulated three ways, showing how the tradition you choose determines the questions you ask.

19.4 A group-influence read

CLINICAL ANCHOR

Case: a vignette in social influence. A junior doctor on a ward round privately doubts a senior's plan but says nothing, and later, in an unanimous team, finds the group settling on a riskier plan than any member would have chosen alone. Reasoning: the silence in the face of an authority is obedience and normative conformity; the unanimous team suppressing dissent and drifting to a more extreme, poorly examined decision is groupthink and group polarisation. The read: name the processes rather than the personalities, and note the antidotes, inviting dissent, a devil's advocate, and anonymous input, that break the pressure toward uniformity.

HOLD THIS

The same case reads differently in each tradition, and the exam rewards saying which lens you are using. A trait reading, a psychodynamic reading and a humanistic reading of one person ask different questions; none is wrong.

20 · Consolidate: mnemonic, retrieval and synthesis

This chapter closes with three consolidation devices: a master mnemonic that chains the whole of it, a set of answer-free retrieval prompts to test yourself against, and a synthesis map to redraw from memory. Use them actively; reading them is not the same as recalling them.

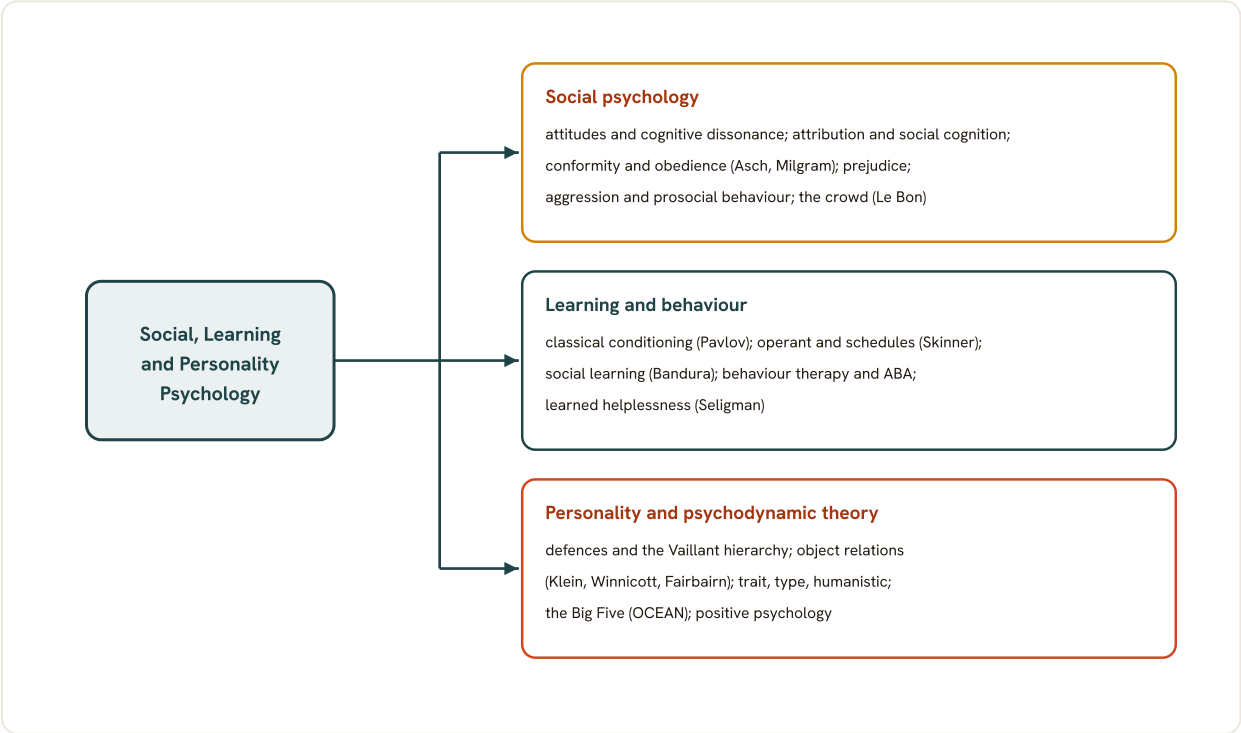


Fig 5.28 The whole synthesis map. Redraw it from memory as a recall check: the three domains branch from the centre, and under each you should be able to reconstruct its topics and their key figures. If a branch comes back thin, that is the section to revisit. Social psychology is how people are moved by others; learning and behaviour is how conduct is shaped and reshaped; personality is how the whole person is theorised.

20.1 The master mnemonic

MNEMONIC

Walk three lands: SOCIAL, LEARNING, PERSONALITY

This chapter is three lands, S, L, P (Social, Learning, Personality). In the SOCIAL land, six phenomena in the line **"Any Argument Gets People Awfully Cross"**: **A**ttitudes (and cognitive dissonance), **A**ttribution (and its biases), **G**roup dynamics (conformity, obedience), **P**rejudice, **A**ggression (and prosocial behaviour), **C**rowd. In the LEARNING land, **"Clever Owls Study Behaviour"**: **C**lassical conditioning, **O**perant conditioning (and schedules), **S**ocial learning (Bandura), **B**ehaviour therapy (with ABA and learned helplessness). In the PERSONALITY land, **"Defend Our Persons"**: **D**efences (the Vaillant hierarchy), **O**bject relations (and the neo-Freudians), **P**ersonality theories (trait, type, humanistic, positive). Two Paper-1 extras hang off the map: the named schools Meyer and Rank, and the two clinical relationships, the psychology of rape and the Indian pair guru-chela and expressed emotion.

HOLD THIS

The whole chapter is three lands: Social, Learning, Personality (SLP). Social psychology is how people are moved by others, learning is how conduct is shaped and reshaped, personality is how the whole person is theorised.

20.2 Retrieval practice

RETRIEVAL PRACTICE, COVER THE ANSWERS

Use active recall: cover the answers you know from this material and try to produce each of these from memory before checking back. This is retrieval practice, and it is worth more than rereading.

1. State Festinger's cognitive dissonance theory and the counter-intuitive result of the induced-compliance study.
2. Name Kelley's three covariation criteria and two attribution biases.
3. Distinguish normative from informational influence, and name the Asch, Milgram and Zimbardo studies.
4. Give Allport's four conditions for the contact hypothesis to reduce prejudice.
5. Contrast the frustration-aggression hypothesis with the social-learning account of aggression.
6. Put the four crowd theories in order from Le Bon to the social identity model.
7. Define the unconditioned and conditioned stimulus and response, and describe extinction and spontaneous recovery.
8. Draw the reinforcement-versus-punishment matrix and name the four schedules with their response patterns.
9. List Bandura's four subprocesses of observational learning and the four sources of self-efficacy.
10. Match three behaviour-therapy techniques to their parent learning paradigm, and state the learned-helplessness reformulation.
11. Name the four levels of Vaillant's defence hierarchy with one mechanism each.
12. Distinguish Klein, Winnicott and Fairbairn in one line each.
13. Give Eysenck's PEN dimensions, Cattell's model and the five factors of OCEAN.
14. State what positive psychology added, and what PERMA stands for.
15. Explain the guru-chela paradigm and the three components of expressed emotion.

20.3 The synthesis map

Finally, redraw the whole synthesis map from memory. Start from the title at the centre, branch to the three domains, and under each branch reconstruct its topics and their key figures: the social phenomena and their theorists, the learning paradigms and the therapies they yield, and the personality strands ending in the Big Five. If a branch comes back thin when you redraw it, that is the section to revisit. The map is not decoration; rebuilding it from memory is the last and best retrieval check for this material.

Previously asked

Real long-essay (25-mark) and short-note (10-mark) questions from the social, learning and personality-psychology territory, most-recent year shown.

LONG ESSAYS (25 MARKS)

Q Discuss the theories of learning and the various types of learning, classical conditioning, and its applied aspect. MUHS 2017

- Discuss defence mechanisms. Discuss their relevance in mental illness. MUHS 2015
- Describe the role of genetic, biological and psychological factors in the development of personality. MUHS 2018
- Describe the basic principles and clinical application of behaviour therapy. MUHS 2012
- Describe the clinical assessment of personality. MUHS 2013
- Discuss the risk factors for aggression. Describe the investigation and management of an aggressive patient. MUHS 2015

SHORT NOTES (10 MARKS)

- Attitudes. MUHS 2017
- Operant conditioning. MUHS 2017
- Humanistic theories in personality. MUHS 2018
- Etiology of aggression. MUHS 2018
- Psychology of aggression and its clinical implications. MUHS 2019

This territory is examined reliably: learning and conditioning with its applied aspect (behaviour therapy), defence mechanisms, the theories of personality and the clinical assessment of personality, and the psychology of aggression recur as both essays and short notes. Prepare each so you can give the core theory, the named figures and one clinical link in a few lines. The acute evaluation and management of the aggressive or violent patient is developed on the the emergency psychiatry chapter; personality and intelligence testing (MMPI, Rorschach, the Wechsler scales) is taken up on the Psychometry, Assessment and Descriptive Psychopathology notes; and Freud's models, Adler and Jung are covered in full on the General and Developmental Psychology notes. The psychology of rape, the guru-chela therapeutic relationship and expressed emotion are named in the Paper 1 syllabus and are covered here.

Quick review

The whole picture in one table	
THE THREE DOMAINS	After the General and Developmental Psychology notes's general functions and developmental theorists, this material covers the social person (moved by others), the learned person (behaviour shaped by consequence and models) and the theorised person (personality). Freud's models, Adler and Jung are on the General and Developmental Psychology notes; the psychological tests are on the Psychometry, Assessment and Descriptive Psychopathology notes.
ATTITUDES AND DISSONANCE	Attitude as affect, behaviour and cognition; the attitude-behaviour gap. Change: the Yale persuasion approach, Festinger's cognitive dissonance (inconsistent cognitions drive change; induced compliance, effort justification), Bem's self-perception, and the elaboration likelihood model (central versus peripheral route). Currently accepted: dual-process persuasion.
ATTRIBUTION AND SOCIAL COGNITION	Heider's naive psychology, Jones-Davis correspondent inference, Kelley's covariation (consensus, distinctiveness, consistency), Weiner's dimensions (locus, stability, controllability). The biases: fundamental attribution error, actor-observer asymmetry, self-serving bias, just-world, false consensus. Culture shifts the default (individualist versus collectivist).
GROUP DYNAMICS	Sherif norm formation; Asch conformity (normative versus informational); Milgram obedience (agentic state, situational factors); Zimbardo roles (with the modern critique). Group decisions: polarisation, groupthink (Janis), social facilitation (Zajonc), social loafing, minority influence (Moscovici).
PREJUDICE	Stereotype (cognition), prejudice (affect), discrimination (behaviour). Allport; the authoritarian personality; realistic conflict (Robbers Cave); social identity theory (Tajfel, minimal groups, in-group favouritism). Reduction: the contact hypothesis and its conditions (equal status, common goals, cooperation, institutional support).
AGGRESSION AND PROSOCIAL	Aggression: instinct and ethology, the frustration-aggression hypothesis (Dollard-Miller, Berkowitz), social learning (Bandura, Bobo doll), biological substrates. Prosocial: the bystander effect and diffusion of responsibility (Latane and Darley), empathy-altruism (Batson) versus social exchange and reciprocity (Trivers), kin selection.
CROWD AND MOB	Le Bon (contagion, suggestibility, the group mind) to deindividuation (anonymity, reduced self-awareness) to emergent-norm theory (Turner and Killian) to the social identity model of crowds (Reicher: crowds act on a shared identity, not mindless contagion). Relevance: mass hysteria, panic, riots.

The whole picture in one table	
CLASSICAL CONDITIONING	Pavlov: US, UR, CS, CR; acquisition, extinction, spontaneous recovery, generalisation, discrimination, higher-order. Watson's Little Albert (conditioned fear). Rescorla-Wagner (learning as prediction and surprise; blocking); preparedness and taste aversion (Garcia). Clinical: phobia, conditioned nausea, cue reactivity.
OPERANT CONDITIONING	Thorndike's law of effect to Skinner: the reinforcement-versus-punishment matrix (positive and negative each), primary and secondary reinforcers, Premack; shaping, chaining, extinction burst, stimulus control. The four schedules: fixed and variable, ratio and interval; variable ratio gives the highest, most extinction-resistant rate.
SOCIAL LEARNING	Bandura: observational learning and modelling (attention, retention, reproduction, motivation), vicarious reinforcement, the Bobo doll. Reciprocal determinism (person, behaviour, environment). Self-efficacy and its four sources (mastery, vicarious, persuasion, physiological state). The cognitive turn away from radical behaviourism.
BEHAVIOUR THERAPY, ABA, LEARNED HELPLESSNESS	From classical conditioning: systematic desensitisation (Wolpe), exposure and flooding, aversion. From operant: token economy, contingency management, applied behaviour analysis (functional analysis, ABC). Seligman's learned helplessness (uncontrollable aversive events, the attributional reformulation) as a model of depression.
MEYER, RANK AND THE MAP	The three depth-psychology schools (Freud psychoanalysis, Adler individual psychology, Jung analytical psychology) are on the General and Developmental Psychology notes. these notes add the two Paper-1-named figures: Adolf Meyer's psychobiology (the reaction-type view, the life chart, his influence on formulation) and Otto Rank (birth trauma, will therapy, the break from Freud).
DEFENCES AND VAILLANT	The full catalogue by Vaillant's maturity levels: psychotic (denial of reality, distortion, delusional projection), immature (projection, acting out, splitting, projective identification, passive aggression, regression), neurotic (repression, reaction formation, displacement, intellectualisation, isolation, undoing), mature (sublimation, altruism, humour, suppression, anticipation).
OBJECT RELATIONS AND NEO-FREUDIANS	Klein (paranoid-schizoid and depressive positions, projective identification), Winnicott (good-enough mother, transitional object, holding, true and false self), Fairbairn (libido is object-seeking); Kernberg (levels of personality organisation) and Kohut (self psychology, the selfobject). Neo-Freudians: Horney, Sullivan, Fromm.
PERSONALITY THEORIES	Type theories (humours, Sheldon, Kretschmer) to trait (Allport; Eysenck PEN; Cattell 16PF) to the Big Five consensus (OCEAN, NEO-PI) to humanistic (Rogers self theory, unconditional positive regard; Maslow; existential) to Kelly's constructs. The

The whole picture in one table	
	person-situation debate resolves into interactionism. Then positive psychology (Seligman, PERMA, character strengths, flow).
PSYCHOLOGY OF RAPE	Rape as an act of power and aggression more than sexuality (Groth); offender typologies (with their caveats) and the limits of prediction; rape myths and their harm. Survivor side: the rape trauma syndrome (Burgess and Holmstrom), PTSD and sequelae, the second injury of secondary victimisation, and trauma-informed care. The Indian medico-legal frame is on the forensic psychiatry chapter.
GURU-CHELA AND EXPRESSED EMOTION	Neki's guru-chela model: an Indian, culturally rooted therapeutic relationship built on guidance, dependence and idealisation, contrasted with the Western contractual alliance. Expressed emotion (Brown and Rutter; the Camberwell Family Interview): critical comments, hostility and over-involvement predict relapse; Indian families tend to show lower expressed emotion.
DISCRIMINATE AND APPLY	Tell the learning paradigms apart (classical versus operant versus social learning), the personality models apart (psychodynamic, trait, type, humanistic, social-cognitive), and the social biases apart (fundamental attribution error, self-serving, dissonance, group polarisation). Apply by reading an attribution, choosing a behaviour-therapy technique, placing a person on the Big Five, and naming a group process.

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This chapter is grounded in the standard texts (the source hierarchy below); each theory is attributed to its primary source, and landmark, contested or numeric claims carry a PubMed-verified journal citation. Every PMID here was checked against PubMed this build, and citations whose identifier did not resolve to the cited paper were corrected or dropped.

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PART VI

VI

Psychometry, Assessment & Descriptive Psychopathology

The instruments of the examination: the tests that measure the mind, and the language that describes it.

01 Psychometry and assessment

02 Descriptive psychopathology

03 Discriminate

04 Apply and consolidate

Psychometry, Assessment & Descriptive Psychopathology

Four sections · 22 topics · one complete notes document

This is a mixed set of notes that pairs the two things every clinical encounter rests on: the formal tools that measure the mind, and the descriptive vocabulary that names what is found in it. The first band is **psychometry and assessment**, a catalogue of psychological tests organised by what each one measures: how a test earns its reliability and validity, the intelligence scales and the deviation IQ with its classification bands, the projective techniques (Rorschach, TAT and the rest), the objective personality inventories (MMPI, 16PF, NEO), the neuropsychological batteries, the adaptive and developmental scales, the clinician-rated symptom scales, and the Indian adaptations that make all of this usable in an Indian clinic. The second band is **descriptive psychopathology**, the phenomenology that Jaspers, Fish and Sims built, split into the domains of mental life: disorders of perception, of thought, of the experience of self, of emotion, of memory, of consciousness and of movement, together with the delusions and the Schneiderian first-rank symptoms. The examinable skill is precision on both fronts: choosing the right test for a referral question, and telling one sign apart from its near-neighbour.

HOW TO USE THESE NOTES

The two bands read differently by design. In the **test catalogue**, every test ends with a **Good to remember** box giving its author, what it measures and how it is scored, so the reference facts sit apart from the reasoning. In **descriptive psychopathology**, every named sign carries a crisp one-line definition, most often in a definition list, because in phenomenology the exam rewards the exact word. Figures declare one axis and code it in colour and shape: **petrol** marks structure and the neutral case, **coral** marks pathology or the point of discrimination, and **marigold** highlights the answer. Two boundaries are worth stating up front: these notes cover the intelligence *tests* while the General and Developmental Psychology notes cover the intelligence *theories* and the mechanism-evolution of hallucination theories; the psychometric reliability and validity here are distinct from the research reliability and validity in the Research Methods, Biostatistics & Epidemiology notes. This is doctor-facing revision, so the full clinical vocabulary is used.

Psychometry and assessment

1 · Orientation: the taxonomy of psychological tests

The General and Developmental Psychology and the Social, Learning & Personality Psychology notes cover the **psychology of the normal mind**: how it learns, remembers, feels, and is measured in the abstract. Paper I now turns to the two working instruments of the clinical examination. This band, Band A, takes up the first instrument, the **test** that measures the mind and puts a number on a construct we cannot see directly. Band B takes up the second instrument, the descriptive language that names what the mind is doing when it goes wrong. Hold the pair in

view: one instrument quantifies, the other describes, and the mature psychiatrist reaches for both.

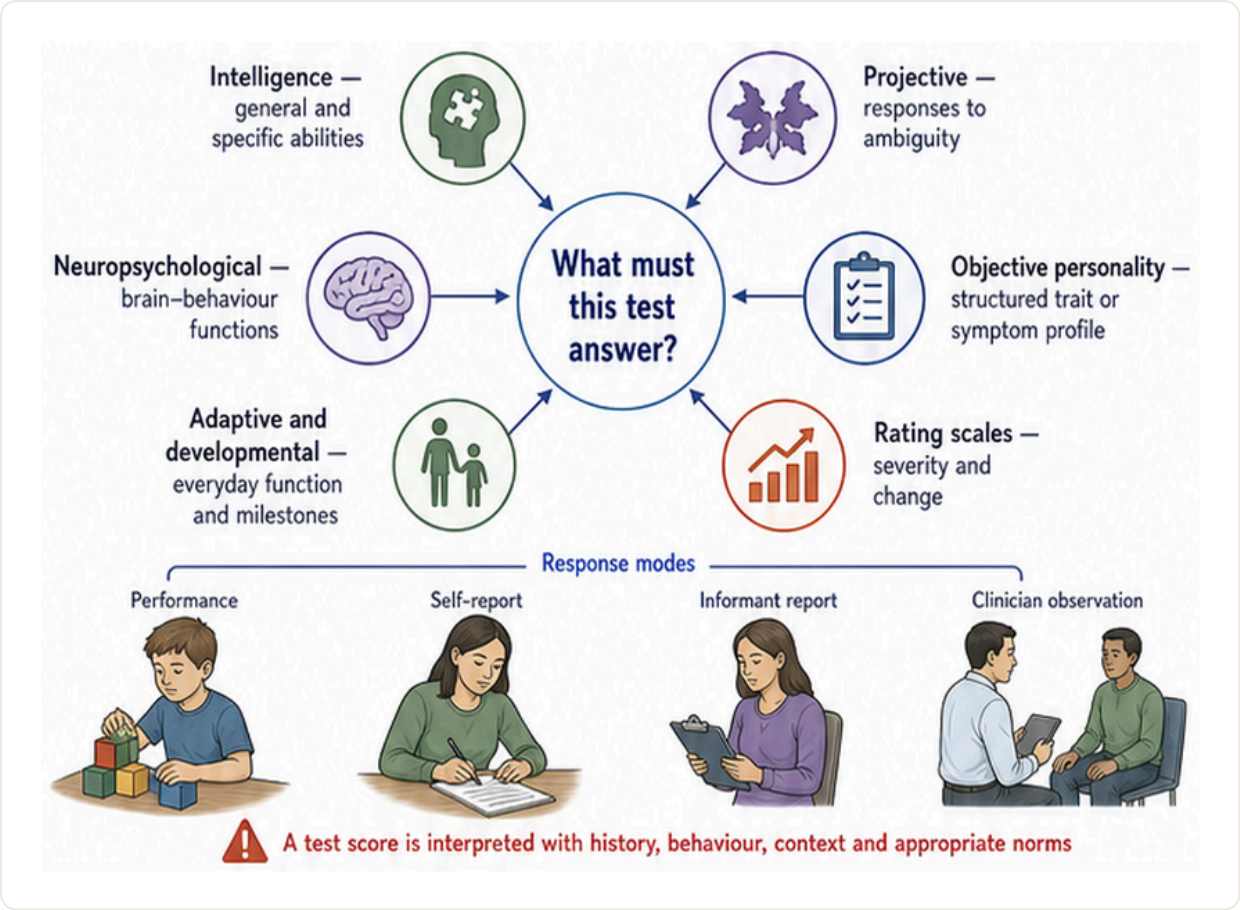


Fig 6.1 Test selection starts with the clinical question.

Why this opens these notes. Examiners love the map before the detail. Before you can defend the Wechsler indices or the Rorschach scoring, you must be able to place any named test into its family and say in one line what that family measures. The taxonomy is the skeleton on which every test in this band hangs, so learn it first and the individual catalogue entries will have somewhere to sit. This is the schema for Band A: a six-family map of **psychometry** that you can redraw from memory.

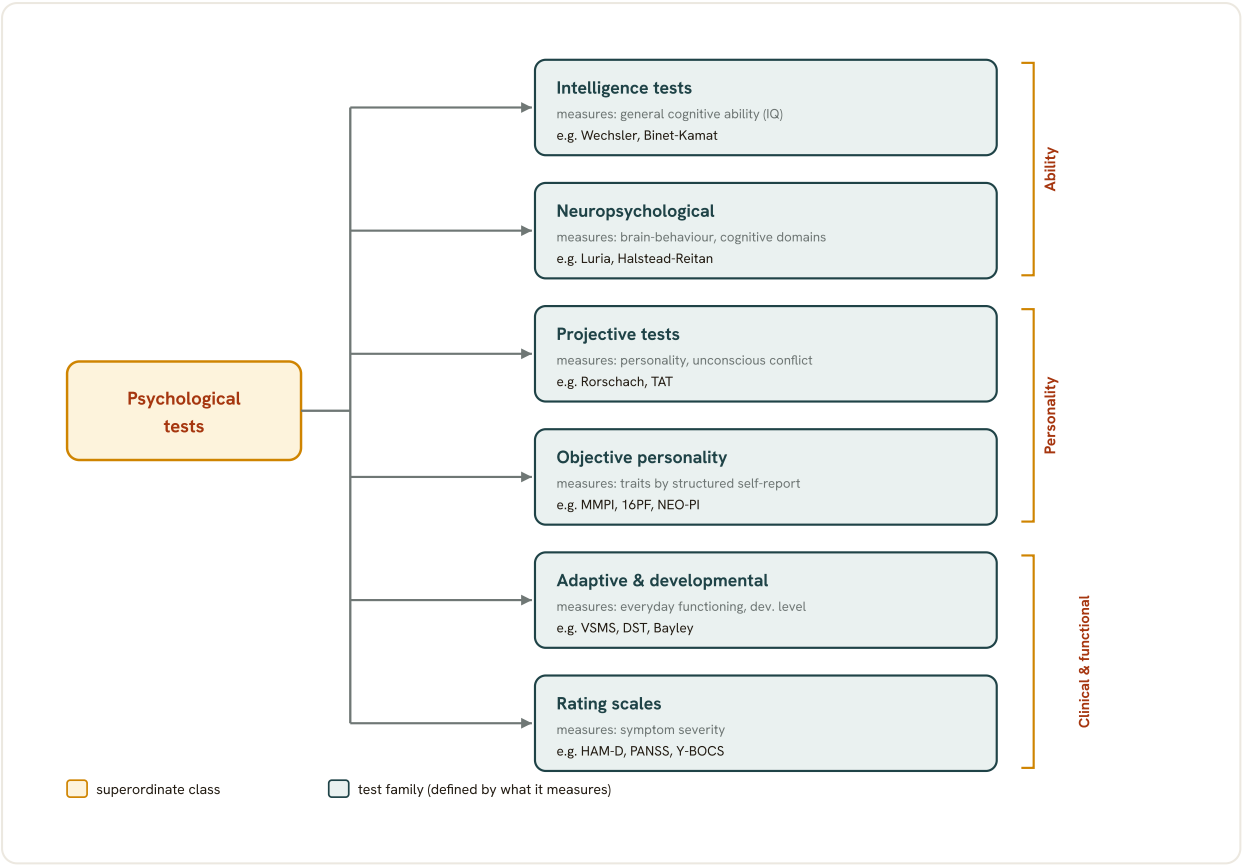


Fig 6.2 The taxonomy of psychological tests. Every test belongs to a family defined by what it measures: the ability tests (intelligence and neuropsychological), the personality tests (projective and objective), and the clinical and functional tests (adaptive-developmental scales and symptom rating scales). Reading a referral question is largely a matter of deciding which family it points to. The families, not the individual instruments, are the unit to learn first.

1.1 What a psychological test is

Definition. A psychological test is an **objective and standardised sample of behaviour**, from which we infer the level of some underlying construct (an ability, a trait, a symptom). The classic phrasing, traceable to Anastasi and repeated across texts, is that a test is a standardised sample of behaviour (Kaplan & Sadock 2024). Two words carry the weight. *Sample*: the test elicits only a slice of behaviour, never the whole person. *Standardised*: administration, scoring, and interpretation follow a fixed procedure against established norms, so that the score means the same thing across testers and occasions.

Psychometry

The science of measuring psychological constructs; the theory and practice of constructing, administering, and interpreting standardised mental tests (Kaplan & Sadock 2024).

Standardisation

Fixing the administration and scoring procedure, and referencing scores to a representative normative sample, so results are comparable.

Norm

The distribution of scores in a defined reference population, against which an individual score is read (percentile, standard score, quotient).

Reliability

The consistency of a test's measurement (test-retest, internal, inter-rater).

Validity
Whether the test measures the construct it claims to (content, criterion, construct validity).

Every catalogue entry in this band is an attempt to hang reliability and validity on a real instrument. A test with poor psychometric properties, however clever its theory, is clinically worthless; structured scales were developed precisely to improve the poor psychometric properties of unstructured clinical judgement (Kaplan & Sadock 2024).

1.2 The test-taxonomy map: six families

The map. Bind each family to a single question, "what does it measure?", and to one anchoring example. Learn this list cold; the rest of these notes is detail poured into these six containers.

Intelligence test
Measures general cognitive ability, expressed as an intelligence quotient (IQ). Anchor: Binet-Kamat, and the Wechsler scales (WAIS for adults, WISC for children).

Projective
Measures personality structure and unconscious conflict by asking the person to impose meaning on an ambiguous stimulus. Anchor: the Rorschach inkblots and the Thematic Apperception Test (TAT).

Objective personality
Measures personality traits and psychopathology through structured, self-report questionnaires with fixed-choice items and empirical scoring. Anchor: MMPI, 16PF, NEO-PI.

Neuropsychological
Measures brain-behaviour relationships across discrete cognitive domains (attention, memory, language, visuospatial, executive function). Anchor: the Luria-Nebraska and Halstead-Reitan batteries.

Adaptive and developmental scales
Measures everyday real-world functioning and developmental level rather than abstract ability. Anchor: Vineland Social Maturity Scale (VSMS), Developmental Screening Test (DST), Bayley Scales.

Rating scale
Measures the severity of a symptom cluster over time, rated by clinician or by patient. Anchor: HAM-D (depression), PANSS (psychosis).

RULE **Name the question, then the family, then the test.** Every test belongs to a family defined by one question - what does it measure - so place the referral before you reach for an instrument.

CLINICAL ANCHOR

The families answer different clinical questions. "How bright is this child?" is an intelligence-test question. "What is the structure of this personality?" is a projective or objective-personality question. "Is this cognitive complaint organic?" is a neuropsychological question. "Can this adult live independently?" is an adaptive-scale question. "Has this depression improved on treatment?" is a rating-scale question. Name the question first, then the family, then the test.

1.3 The intelligence test family

What it measures. General cognitive ability, summarised as an IQ. Population IQ approximates a normal distribution with a mean of 100 and a standard deviation of 15 points (New Oxford Textbook of Psychiatry). An **intelligence test** samples reasoning, comprehension, working memory, and processing speed, typically across separate verbal and performance (or nonverbal) subtests, and yields a global score plus a profile of strengths and weaknesses.

Anchors. The Binet-Kamat Test of Intelligence is the widely used Indian adaptation (Kamat) of the Stanford-Binet, standardised on Indian children. The Wechsler scales split by age: the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Intelligence Scale for Children (WISC). DSM-5 shifted the definition of intellectual disability so that severity is graded on **adaptive functioning**, not on the IQ number alone; the IQ locates the deficit, but adaptive behaviour grades its severity.

1.4 The projective family

What it measures. Personality organisation and unconscious conflict. The **projective** hypothesis holds that when a stimulus is deliberately ambiguous, the person must draw on their own inner world to give it meaning, and so "projects" their private structure onto the blot or the picture (Kaplan & Sadock 2024). Projective tests are, by design, indirect and unstructured, in contrast to the direct fixed-choice format of objective tests.

Anchors. The Rorschach presents a fixed series of symmetrical inkblots and asks what they might be; responses are coded, not read for content alone. Modern scoring uses the Exner Comprehensive System and, more recently, R-PAS (Rorschach Performance Assessment System), which put the method on a firmer psychometric footing. The Thematic Apperception Test (TAT), developed within Murray's personology, presents ambiguous interpersonal scenes and asks the person to tell a story; the recurring themes are taken to reveal needs and conflicts. (The plates and cards themselves are copyrighted and are described here in words only, never reproduced.)

1.5 The objective personality family

What it measures. Personality traits and psychopathology, through structured self-report. An **objective personality** test uses fixed-choice items (true-false or Likert), empirically or factor-analytically derived scales, and fixed scoring rules, so that interpretation does not depend on the tester's inference in the way a projective does.

Anchors. The MMPI (Minnesota Multiphasic Personality Inventory) is the archetype: an empirically keyed inventory yielding clinical scales plus validity scales that detect response distortion (the current forms are the MMPI-2, MMPI-2-RF, and MMPI-3). Cattell's 16PF measures sixteen primary personality factors by factor-analytic method. The NEO-PI, now NEO-PI-R, operationalises the Five Factor Model (FFM: neuroticism, extraversion, openness, agreeableness, conscientiousness), which is the dominant trait framework in modern personality science.

COMMON TRAP

Do not confuse the two personality routes. The **projective** and the **objective personality** families both measure personality, but by opposite logic: projectives use ambiguous stimuli and inferential scoring to reach the unconscious; objective tests use structured self-report and fixed scoring to map traits. "Objective" refers to the scoring being standardised and examiner-independent, not to the truth being more objective.

1.6 The neuropsychological family

What it measures. Brain-behaviour relationships. A **neuropsychological** assessment profiles performance across discrete cognitive domains, attention, memory, language, visuospatial ability, and executive function, to detect, localise, and characterise cerebral dysfunction, often where structural imaging is normal (Kaplan & Sadock 2024).

Anchors. The Luria-Nebraska Neuropsychological Battery derives from Luria's qualitative approach, systematised into scored scales. The Halstead-Reitan Battery is the classic fixed, quantitative battery yielding an impairment index. Both aim to answer whether a cognitive complaint reflects organic dysfunction and, if so, which systems are affected.

1.7 The adaptive and developmental family

What it measures. Everyday functioning and developmental level, not abstract ability. **Adaptive** scales quantify how well a person meets the practical demands of daily life (self-care, communication, social participation); developmental scales place an infant or young child on a normative developmental trajectory.

Anchors. The Vineland Social Maturity Scale (VSMS), in India the Malin adaptation, yields a social age and a social quotient from an informant interview and is a mainstay in the assessment of intellectual disability. The Developmental Screening Test (DST) and the Bayley Scales of Infant Development assess the developmental level of infants and young children. This family carries extra weight now that DSM-5 grades intellectual disability by adaptive functioning: the adaptive scale, not the IQ test, sets the severity.

1.8 The rating scale family

What it measures. The severity of a defined symptom cluster, quantified so it can be tracked across time and across patients. A **rating scale** is scored either by a clinician (observer-rated) or by the patient (self-rated), and its value lies in serial measurement: charting response to treatment.

Anchors. The Hamilton Depression Rating Scale (HAM-D) is a clinician-rated measure of depression severity. The Positive and Negative Syndrome Scale (PANSS) is a clinician-rated measure of symptom severity in schizophrenia. Rating scales are the instruments the DSM-5 itself now advocates as "emerging measures" to improve routine care (Kaplan & Sadock 2024).

1.9 The two axes of classification

Tests can be sorted along two independent axes, and a good answer names both. The first axis is **by what is measured**, which gives the six families above collapsed into three broad purposes:

ability (intelligence, neuropsychological), personality (projective, objective), and adaptive or symptom-severity (adaptive/developmental scales, rating scales). The second axis is **by structure**, the format of the instrument, cutting across purpose.

STRUCTURAL CONTRAST	ONE POLE	OTHER POLE
Stimulus and scoring	**Objective: fixed-choice items, standardised scoring**	**Projective: ambiguous stimulus, inferential scoring**
Persons tested at once	Individual: one examiner, one subject	Group: many subjects simultaneously
Task medium	Verbal: language-based items	Performance: manipulative or nonverbal tasks
Timing constraint	Power: no time pressure, difficulty graded	Speed: many easy items against the clock

The structural axis cuts across the content axis: an intelligence test can be individual, verbal or performance, and power-type; an objective personality test is group-administrable and objective.

HOLD THIS

A psychological test is a standardised sample of behaviour, placed by what it measures then how it is structured. Six families (I-PONAR), two axes: content (ability, personality, adaptive) and structure (objective vs projective, individual vs group, verbal vs performance).

MNEMONIC

"I Prefer Only Neat And Reliable tests"

The six families in order: **I**ntelligence, **P**rojective, **O**bjective personality, **N**europsychological, **A**daptive/developmental, **R**ating scales. Carry this master mnemonic through the whole set of notes; every catalogue entry that follows lands in one of these six slots.

PEARL

The taxonomy in one line: a psychological test is a **standardised sample of behaviour**, and every test is placed by asking *what it measures* (ability, personality, adaptive function, or symptom severity) and then *how it is structured* (objective or projective; individual or group; verbal or performance).

GOOD TO REMEMBER

- **Psychometry:** the science of measuring psychological constructs; a psychological test is a standardised sample of behaviour (Anastasi; Kaplan & Sadock 2024).
- **Intelligence test family:** measures general cognitive ability (IQ, mean 100, SD 15); examples Binet-Kamat, Wechsler WAIS (adults) and WISC (children).
- **Projective family:** measures personality and unconscious conflict via ambiguous stimuli and inferential scoring; examples Rorschach (Exner / R-PAS scoring), Thematic Apperception Test (TAT, Murray).
- **Objective personality family:** measures traits and psychopathology via structured self-report and fixed scoring; examples MMPI (validity plus clinical scales), 16PF (Cattell), NEO-PI-R (Five Factor Model).
- **Neuropsychological family:** measures brain-behaviour relationships across cognitive domains; examples Luria-Nebraska, Halstead-Reitan (impairment index).
- **Adaptive and developmental family:** measures everyday functioning and developmental level; examples Vineland Social Maturity Scale (social quotient), Developmental Screening Test (DST), Bayley Scales.
- **Rating scale family:** measures symptom severity over time, clinician or self rated; examples HAM-D (depression), PANSS (schizophrenia).
- **Two axes of classification:** by what is measured (ability vs personality vs adaptive) and by structure (objective vs projective; individual vs group; verbal vs performance).
- **Master mnemonic:** "I Prefer Only Neat And Reliable tests" = Intelligence, Projective, Objective personality, Neuropsychological, Adaptive/developmental, Rating scales.
- **Currency:** Rorschach now scored by Exner / R-PAS; NEO-PI-R operationalises the FFM; DSM-5 grades intellectual disability by adaptive functioning, not the IQ number alone; first-rank symptoms are no longer treated as pathognomonic.

2 · Test construction: reliability, validity, standardisation

This is the grammar of every test in these notes. Before you can catalogue the Wechsler, the MMPI or the Rorschach, you have to know what makes any psychometric instrument trustworthy. The examiner treats **test construction** as a set of properties a test must demonstrate before it can be used in the clinic or the courtroom: it must be standardised, reliable and valid, and it must be practical. Every other test in these notes is scored against these four yardsticks, so this topic is the lens for the whole set.

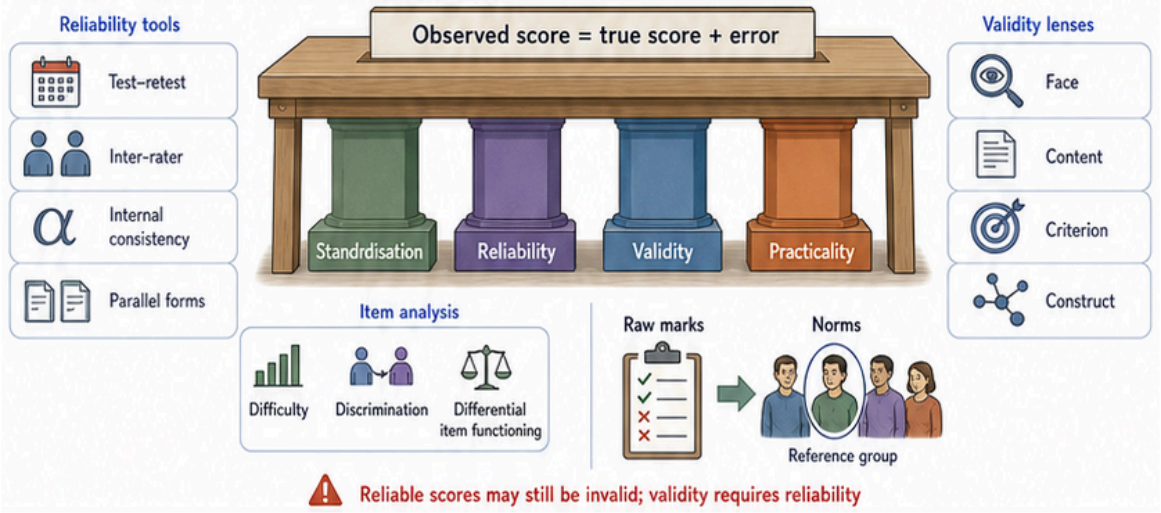


Fig 6.3 Building a sound psychological test.

The single most-tested idea is the relationship between the two central properties. **reliability** is consistency (does the test give the same answer twice?); **validity** is accuracy (does it measure what it claims?). A test can be reliable without being valid, but it can never be valid without first being reliable (Kaplan & Sadock 2024). A crucial boundary to hold: the **reliability** and **validity** taught here are *psychometric* properties of a measurement instrument. They are distinct from the *research* reliability and validity (sensitivity, specificity, internal and external validity of a study design) taught in the Research Methods, Biostatistics & Epidemiology notes. Same words, different domain: keep them in separate drawers.

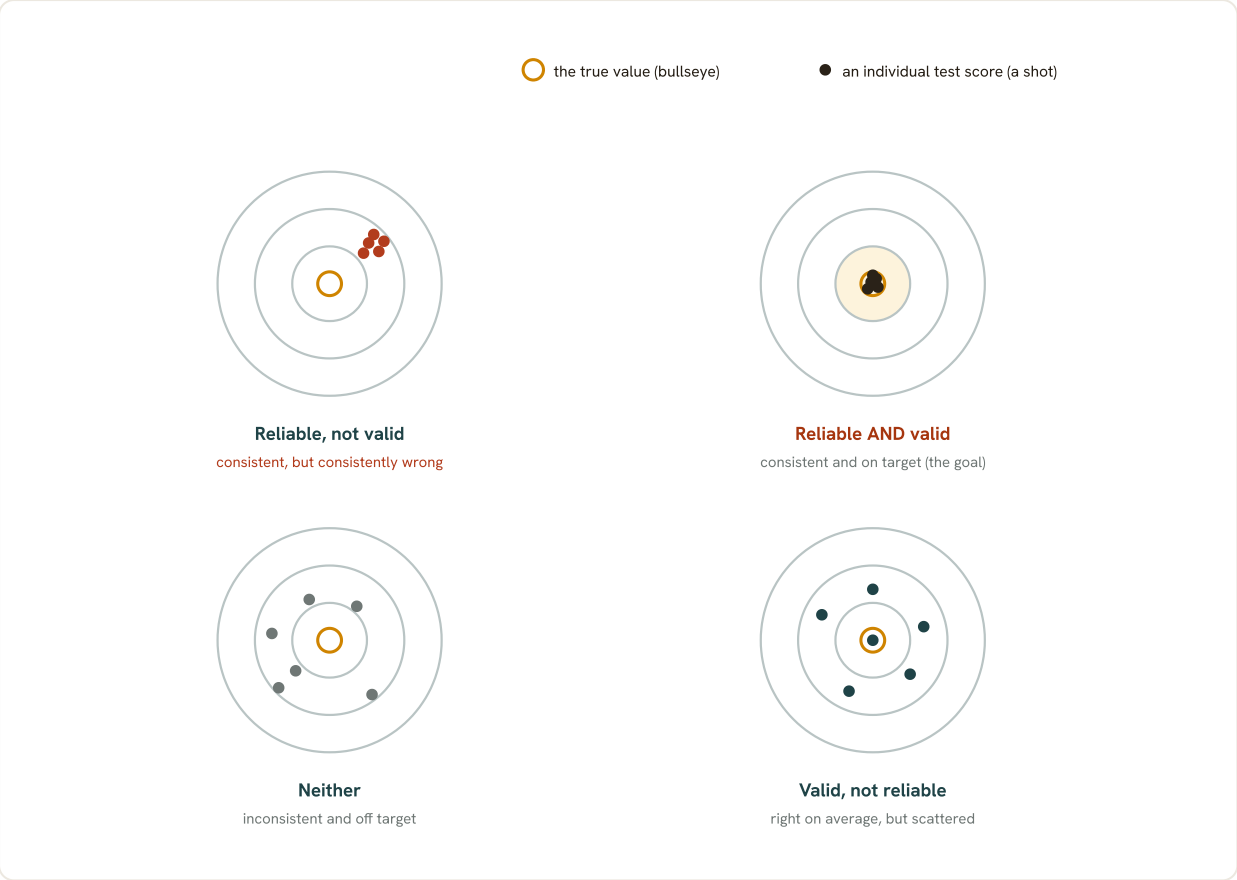


Fig 6.4 Reliability versus validity, the classic marksman analogy. Reliability is how tightly the shots cluster (consistency); validity is whether they land on the bull (accuracy). The two are independent: a test can be reliable but not valid (tight but off target, the dangerous case of a precise wrong answer), valid but not reliable (centred on average but scattered), neither, or both. The one dependency is that validity requires reliability, so a good test must be reliable first, then shown to be valid.

2.1 The four properties of a good test

Standardisation, reliability, validity, practicality. A psychometrically sound test must satisfy four requirements (Kaplan & Sadock 2024; Companion to Psychiatric Studies). **standardisation** (American: **standardization**) means the test is administered and scored in a uniform, fixed way for every examinee, and that a person's raw score is interpreted against **norms** from a representative reference sample. **reliability** is the consistency, or reproducibility, of the scores. **validity** is the degree to which the test actually measures the construct it claims to measure. *Practicality* (utility) is the down-to-earth fourth property: the test must be reasonable in cost, administration time, ease of scoring and acceptability to the patient. A perfectly reliable and valid instrument that takes six hours and a doctorate to score has little clinical utility. Reliability and validity are the two that carry marks; standardisation is their precondition; practicality is what decides bedside use.

2.2 Standardisation: uniform procedure and a reference sample

Two limbs, procedure and norms. **standardisation** has two components (Kaplan & Sadock 2024). The first is *uniform administration and scoring*: the same instructions, materials, time limits, order of items and scoring rules for every examinee, so that any difference in scores reflects the person and not the testing conditions. This is why a standardised test comes with a manual that scripts the examiner. The second is the derivation of **norms**: the test is given to a

large, carefully selected *standardisation (normative) sample* that represents the population the test is meant for, and the distribution of scores in that sample becomes the yardstick against which any individual's raw score is read. An individual's score is meaningless in isolation; it acquires meaning only as a position within the normative distribution.

2.3 Norms and derived scores: percentiles, z-scores, T-scores, standard scores

Turning a raw score into a position. Because a raw score has no inherent meaning, tests convert it into a *derived score* that locates the person on the normal curve (Kaplan & Sadock 2024). A *percentile rank* states the percentage of the reference sample the person scored at or above (a percentile of 84 means the person did better than 84 percent of the normative sample). A *z-score* expresses the raw score as the number of standard deviations above or below the mean (mean 0, standard deviation 1). A *T-score* is a rescaled standard score with a mean of 50 and a standard deviation of 10; it is the currency of the MMPI, where a T-score of 65 or above (1.5 standard deviations up) flags a clinically significant elevation. *Standard scores* more broadly are any transformation onto a fixed mean and standard deviation, the Wechsler IQ scale (mean 100, standard deviation 15) being the best-known example. Norms are almost always stratified: *age norms* are essential wherever performance changes with age (intelligence, memory, and the neuropsychological tests, where a 70-year-old is compared with age peers, not with 20-year-olds), and *education norms* matter because education strongly shapes cognitive test performance (Kaplan & Sadock 2024).

PEARL

The four derived scores are just four ways of saying the same sentence, "how far from average is this person?" Percentile answers in rank, z in raw standard deviations, T on a 50/10 scale, and the Wechsler standard score on a 100/15 scale. Memorise the two clinical anchors: MMPI T-score of 65 is the clinical cut-off, and a Wechsler IQ of 100 is dead average with each 15 points being one standard deviation.

50 / 10	65	100 / 15
T-SCORE MEAN / SD	MMPI CLINICAL CUT-OFF (T)	WECHSLER IQ MEAN / SD

2.4 Reliability: consistency of measurement

Does the test give the same answer twice? **reliability** is the consistency, stability or reproducibility of test scores (Kaplan & Sadock 2024). It is quantified by a *reliability coefficient*, a correlation running from 0 (no consistency) to 1.0 (perfect consistency); as a rough rule most instruments need a coefficient of about 0.80 or higher to be useful (Kaplan & Sadock 2024). A companion statistic is the *standard error of measurement* (SEM), which uses the reliability coefficient and the test's standard deviation to put a confidence band around any single obtained score: with an SEM of 3, a person scoring 90 today would score within 87 to 93 about 68 percent of the time on a retest, and within 84 to 96 about 95 percent of the time (Kaplan & Sadock 2024). The smaller the SEM, the more reliable the test. There are four ways reliability is estimated, and the examiner expects all four by name.

2.5 The four types of reliability

Temporal, inter-scorer, internal and parallel. Each type answers "consistent across what?" (Kaplan & Sadock 2024).

Test-retest reliability

Temporal stability: the same test given to the same people on two occasions, and the scores correlated. It answers whether the score holds across time. A coefficient of about 0.80 is expected if the two administrations are within roughly two weeks and the trait is stable. The main threat is the *practice (carry-over) effect*.

Inter-rater (inter-scorer) reliability

Agreement between different scorers rating the same performance. It answers whether the score is independent of who marks it, and is critical for any test with judgement in scoring (projectives, structured interviews, clinician rating scales). For categorical judgements it is quantified by *Cohen's kappa*, which corrects agreement for chance.

Internal consistency

Whether all the items measure the same single construct, estimated from one administration. The *split-half* method correlates one half of the test (often odd items) with the other (even items), corrected upward by the *Spearman-Brown formula*. The definitive index is *Cronbach's alpha*, the average of all possible split-half correlations, expressing the mean inter-item correlation; a higher value means a more internally consistent scale.

Parallel (alternate) forms reliability

Two equivalent versions of the same test, built from different items measuring the same construct, are administered and correlated. It answers whether two forms are interchangeable, and is the way to sidestep the practice effect of test-retest. A coefficient of about 0.90 or higher is expected.

2.6 Validity: the test measures what it claims

Accuracy, not mere consistency. **validity** is the degree to which a test measures what it purports to measure (Kaplan & Sadock 2024). A bathroom scale that always reads five kilograms heavy is perfectly reliable but invalid: it is consistent, but consistently wrong. Validity is not a single number but a body of evidence, gathered in four traditional forms of ascending rigour: **face validity**, **content validity**, **criterion validity** (with concurrent and predictive subtypes) and **construct validity** (with convergent and discriminant evidence). The first two are judged by inspection; the second two are established statistically.

2.7 The four types of validity

Face, content, criterion, construct. These run from superficial to deep (Kaplan & Sadock 2024; Companion to Psychiatric Studies).

Face validity

Whether the items *appear*, on the surface and to a lay reader, to measure what the test claims. It is the weakest form, a matter of appearance not evidence; a depression item that asks "do you feel sad?" has high face validity. High face validity aids acceptability but can also make a test easy to fake.

Content validity

Whether the items adequately sample the whole domain of the construct, judged by expert review. A test of depression with content validity covers mood, cognition, and the somatic and vegetative

features, not mood alone. It concerns the representativeness of the item pool, not appearance.

Criterion validity

Whether the test correlates with an external, independent criterion (a gold standard). It has two subtypes by timing. *Concurrent validity*: the test and the criterion are measured at the same time (a new depression scale correlated against a structured diagnostic interview done today). *Predictive validity*: the test predicts a criterion measured in the future (an aptitude test predicting later job performance; a suicide-risk scale predicting later attempts).

Construct validity

Whether the test measures the abstract theoretical construct it targets, the most demanding and encompassing form. It is built from a pattern of evidence: *convergent validity* (the test correlates highly with other measures of the same construct) and *discriminant (divergent) validity* (it does *not* correlate with measures of unrelated constructs). Together these show the test tracks its construct and nothing else.

COMMON TRAP

Do not confuse *discriminant validity* (a construct-validity concept: the test should not correlate with unrelated constructs) with a test's ability to *discriminate between groups* (e.g. depressed vs non-depressed patients), and do not confuse either with the item *discrimination index* in item analysis. Three different "discriminate" ideas at three different levels: the item, the group, and the construct.

2.8 Item analysis: difficulty and discrimination indices

How individual items earn their place. Before a test is finalised, each candidate item is evaluated statistically, a process called **item analysis** (Kaplan & Sadock 2024; Companion to Psychiatric Studies). The *item difficulty index* (p) is the proportion of examinees who answer an item correctly (or endorse it): a value near 1.0 means almost everyone passes it (too easy), near 0 means almost nobody does (too hard); items of moderate difficulty (around 0.5) usually carry the most information and spread people out best. The *item discrimination index* asks how well a single item separates high scorers from low scorers on the test as a whole: a good item is one that high total-scorers tend to get right and low total-scorers tend to get wrong (a positive point-biserial correlation between the item and the total score). An item that everyone passes, or that good and poor overall performers pass equally, discriminates poorly and is dropped. Item analysis is how the item pool is pruned so the finished test is reliable and valid.

2.9 Test bias and item bias (differential item functioning)

When a test is unfair to a subgroup. **test bias** exists when a test systematically over- or under-estimates the true standing of an identifiable group (defined by culture, language, sex, education or socioeconomic status), so that scores mean different things across groups (Kaplan & Sadock 2024). The item-level form is *differential item functioning* (DIF): a single item behaves differently for two groups *matched on the underlying trait*, so that equally able members of the two groups have unequal odds of answering it correctly for reasons unrelated to the construct (a vocabulary item that assumes a culturally specific term is the classic example). Detecting and removing biased items is central to fair test construction, and it is a major reason culture-fair and non-verbal tests were developed. In the Indian setting this is not academic: many Western

instruments must be translated, culturally adapted and re-normed on Indian samples before their scores can be trusted.

INDIA

A Western test cannot simply be handed to an Indian patient. The standard requirement is translation with *back-translation*, cultural adaptation of items, and fresh **standardisation** on a representative Indian sample to generate local **norms**; without local norms an imported test carries built-in **test bias**. This is why Indian adaptations and indigenously developed tests (for intelligence, adaptive behaviour and personality) exist, and why examiners expect you to name re-standardisation as the fix for cross-cultural bias.

2.10 The reliability-validity relationship: the bullseye

Reliable but not valid; valid requires reliable. This is the highest-yield single point of the topic. The two properties are asymmetrically linked: a test *can* be reliable without being valid, but it *cannot* be valid without being reliable (Kaplan & Sadock 2024). The standard teaching device is the target (bullseye) analogy. Imagine four archers, each firing several arrows. *Reliable but not valid*: the arrows land tightly clustered but off to one side, consistent yet wrong (a scale that always reads five kilos heavy). *Neither*: the arrows scatter all over, inconsistent and off-target. *Reliable and valid*: the arrows land tightly clustered on the bullseye, consistent *and* accurate, the goal of test construction. The logic of the asymmetry: reliability sets a ceiling on validity, because a test that cannot even agree with itself has no stable signal to correlate with any external criterion. So reliability is necessary but not sufficient for validity. This is exactly why we establish reliability first and validity second.

RULE **A test can be reliable without being valid, but never valid without first being reliable.** Reliability caps validity, so it is established first.

HOLD THIS

Reliability is consistency; validity is accuracy; validity requires reliability. Four types of each: reliability (test-retest, inter-rater, internal, parallel); validity (face, content, criterion, construct).

MNEMONIC

"Reliable = the same; Valid = the truth."

Reliability asks "same answer twice?" (consistency); validity asks "the right answer?" (accuracy). Pair it with the bullseye: tight cluster off-centre is reliable-not-valid; tight cluster on the bullseye is reliable-and-valid. You cannot hit the bullseye consistently (valid) without first grouping your arrows tightly (reliable).

2.11 Keeping psychometric and research reliability/validity apart

The same two words in two different examinations. Because the identical terms recur in the research-methodology paper, students routinely conflate them, and examiners probe the boundary. In *psychometrics* (this topic), **reliability** means score consistency (test-retest, inter-rater, internal consistency, parallel forms) and **validity** means the test measures its construct

(face, content, criterion, construct). In *research methodology* (covered in the Research Methods, Biostatistics & Epidemiology notes), the same words carry different technical meanings: the reliability and validity of a diagnostic test are expressed through *sensitivity* and *specificity*, and the validity of a *study* splits into internal validity (are the causal inferences sound within the study?) and external validity (do the findings generalise?). Do not import one framework into the other. When a psychometry question says "validity," it wants face/content/criterion/construct; the sensitivity-and-specificity and study-design material belongs to the Research Methods, Biostatistics & Epidemiology notes.

CLINICAL ANCHOR

These are not abstractions. When you read that the MMPI-2 has clinical utility, you are being told it was standardised on a large normative sample, has adequate test-retest and internal consistency reliability, and has criterion and construct validity against independent diagnoses (Kaplan & Sadock 2024). When a rating scale you use in the ward has published "good reliability and validity", it means precisely: raters agree (inter-rater), the scale is internally consistent, and its scores track true symptom severity. The four properties are the questions to ask of any instrument before you trust its number.

GOOD TO REMEMBER

- **Four properties of a good test:** standardisation, reliability, validity, practicality (utility).
- **Standardisation:** uniform administration and scoring + norms from a representative reference sample (age and education norms).
- **Derived scores:** percentile (rank in sample); z-score (mean 0, SD 1); T-score (mean 50, SD 10; MMPI clinical cut-off ~65); Wechsler standard score (mean 100, SD 15).
- **Reliability** = consistency of measurement; reliability coefficient 0 to 1.0, useful if ~0.80+; SEM puts a confidence band around a score.
- **Test-retest reliability:** temporal stability; same test twice, scores correlated; threatened by practice effect.
- **Inter-rater reliability:** agreement between scorers; categorical agreement corrected for chance by Cohen's kappa.
- **Internal consistency:** items measure one construct; split-half (Spearman-Brown corrected) and Cronbach's alpha (mean inter-item correlation).
- **Parallel (alternate) forms reliability:** two equivalent forms correlated; avoids the practice effect; expected ~0.90+.
- **Validity** = the test measures what it claims; body of evidence, not one number.
- **Face validity:** items appear to measure the construct (weakest; appearance only).
- **Content validity:** items adequately sample the whole domain (expert review).
- **Criterion validity:** correlation with an external criterion; concurrent (same time) and predictive (future).
- **Construct validity:** measures the theoretical construct; convergent (correlates with same-construct measures) and discriminant (does not correlate with unrelated ones).
- **Item analysis:** item difficulty index (p, proportion passing) and item discrimination index (separates high from low total-scorers).
- **Test bias / item bias:** systematic unfairness to a subgroup; item-level form is differential item functioning (DIF); fixed by re-standardisation and local norms.
- **Reliability-validity relationship:** a test can be reliable but not valid; validity requires reliability (bullseye analogy; reliability caps validity).
- **Cross-reference:** psychometric reliability/validity (here) are distinct from research reliability/validity (sensitivity, specificity, study internal/external validity) taught in the Research Methods, Biostatistics & Epidemiology notes.

3 · Intelligence tests and the deviation IQ

Intelligence **tests** are the oldest and most psychometrically mature instruments in clinical psychology, and they are the workhorse of any assessment for intellectual disability, developmental delay, or a suspected drop in premorbid ability. This topic is about the *tests* and about how a raw score becomes an IQ. The competing *theories* of what intelligence actually is (Spearman's g, Thurstone's primary abilities, Gardner's multiple intelligences, Sternberg's triarchic model, and the Cattell-Horn-Carroll or CHC hierarchy) belong to the General and Developmental Psychology notes; here we cross-refer to them and do not re-teach them.

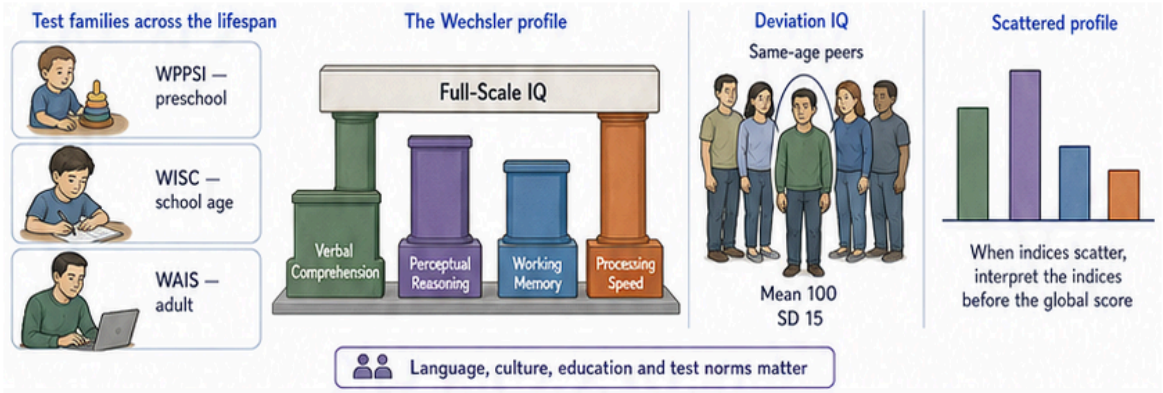


Fig 6.5 Intelligence testing: interpret the profile, not only FSIQ.

The single most examined idea here is the shift from the old **ratio IQ** to the modern **deviation iq**. Examiners love the exact **classification** bands and the intellectual-disability severity ranges, so verify and memorise them cold. A second favourite is the internal architecture of the **wechsler** scales: which subtests feed which of the four index scores, and how those roll up into the full-scale iq.

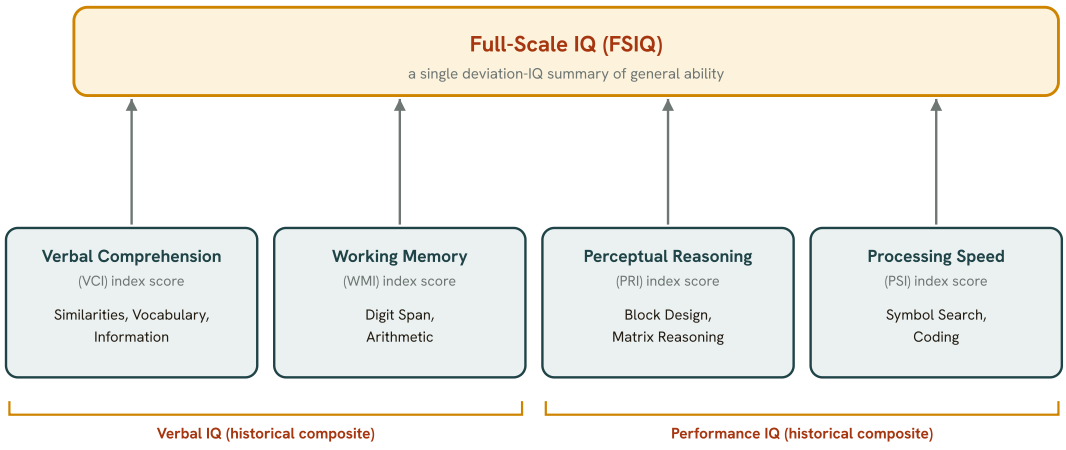
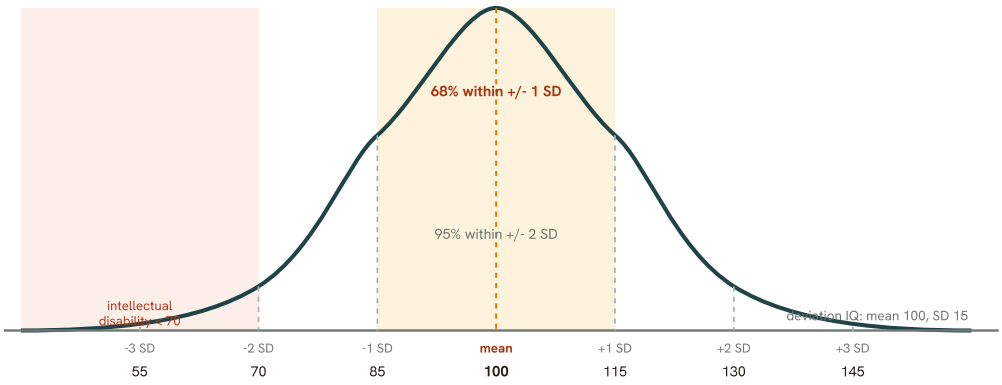


Fig 6.6 Structure of the Wechsler scales (WAIS for adults, WISC for children). Individual subtests aggregate into four index scores (verbal comprehension, working memory, perceptual reasoning, processing speed), which in turn combine into the single Full-Scale IQ. The older Wechsler editions summed the subtests into a Verbal IQ and a Performance IQ instead; the four-index structure is the modern replacement, and a wide split between indices is itself clinically informative.



Classification bands

Very superior 130 and above
Superior 120 to 129
High average 110 to 119
Average 90 to 109
Low average 80 to 89
Borderline 70 to 79

Intellectual disability (ICD-10 IQ, approx.)

Mild 50 to 69
Moderate 35 to 49
Severe 20 to 34
Profound below 20

DSM-5 and ICD-11 grade severity by adaptive functioning, not the IQ score alone.

Fig 6.7 The deviation IQ and its classification bands. IQ is scaled as a standard score with a mean of 100 and a standard deviation of 15, so about 68 per cent of people score within one SD (85 to 115) and about 95 per cent within two SD (70 to 130). The bands read off the distribution: average is 90 to 109, and the intellectual-disability range begins below 70. The ICD-10 severity bands are given by approximate IQ, but current systems (DSM-5, ICD-11) grade severity by adaptive functioning rather than the IQ number alone.

3.1 The intelligence quotient: ratio versus deviation

Ratio IQ. The original **intelligence quotient** was a ratio. William Stern proposed dividing mental age by chronological age; Lewis Terman popularised multiplying by 100 to remove the decimal, giving IQ = (mental age / chronological age) x 100. A child of mental age 10 and chronological age 8 scores 125. The ratio worked well in childhood but breaks down in adulthood, because mental age plateaus while chronological age keeps rising, so the ratio drifts spuriously downward after the late teens.

Deviation IQ. David Wechsler solved this by abandoning the ratio for a standard score. The **deviation iq** expresses where an individual sits on the normal distribution of same-age peers, scaled to a mean of 100 and a standard deviation of 15 (New Oxford Textbook of Psychiatry). It is not a quotient at all despite the retained name: it is a normalised z-score rescaled so that average is 100 and one SD is 15 points. This is the IQ used by every modern scale.

COMMON TRAP

Not every test uses SD 15. The historic Stanford-Binet (Form L-M) used an SD of 16, and Cattell's culture-fair test used SD 24. A "borderline" cut of two SDs therefore lands at 68 on an SD-16 test but at 70 on the modern SD-15 scales. Always ask which SD the norms use before interpreting a score near a cut-off.

RULE **The deviation IQ is a rescaled z-score, not a quotient.** Wechsler abandoned the ratio (mental age over chronological age) because it drifts spuriously downward in adulthood.

3.2 The Stanford-Binet lineage

Binet-Simon (1905). Alfred **binet** and Theodore Simon built the first practical intelligence test in Paris in 1905, commissioned to identify schoolchildren needing special education. It introduced the concept of mental age: a graded ladder of age-normed tasks a child of a given age should be able to pass.

Stanford-Binet (Terman). Lewis Terman at Stanford University revised and re-standardised the scale for American use, publishing the **stanford-binet** in 1916. This is the version that carried Stern's ratio IQ into wide clinical use. The scale is now in its fifth edition (SB5), which has itself moved to a deviation IQ with mean 100 and SD 15 and yields verbal and nonverbal domain scores plus a full-scale composite.

Indian adaptation (Binet-Kamat). The Stanford-Binet was adapted for Indian use as the Binet-**kamat** Test of Intelligence (V. V. Kamat), a locally normed verbal-loaded scale still used in some Indian centres for children (also recorded as the Binet-Simon or Binet-Kamath test).

3.3 The Wechsler family of scales

One design, three age bands. David **wechsler** built a single conceptual instrument spanning the lifespan, split into three age-banded versions. All use the deviation iq (mean 100, SD 15).

WAIS

Wechsler Adult Intelligence Scale; ages 16 to 90 (current edition WAIS-IV, and WAIS-V). The **wais** tradition began with the Wechsler-Bellevue scale of 1939 and is the "gold standard" adult measure (Companion to Psychiatric Studies).

WISC

Wechsler Intelligence Scale for Children; ages roughly 6 to 16. The **wisc** gives a profile of specific verbal and perceptual abilities plus a full-scale IQ.

WPPSI

Wechsler Preschool and Primary Scale of Intelligence; the youngest band, from about 2 years 6 months to 7 years 7 months (Kaplan and Sadock 2024).

3.4 Verbal and performance subtests: the historic dichotomy

The classic split. The original Wechsler design summed a set of subtests into a **verbal** IQ and a **performance** IQ, then combined both into a Full-Scale IQ (Companion to Psychiatric Studies). Verbal subtests (Vocabulary, Similarities, Arithmetic, Digit Span, Information, Comprehension) tap crystallised, language-loaded ability. Performance subtests (Picture Completion, Block Design, Matrix Reasoning, Digit Symbol coding, Picture Arrangement) tap fluid, visuospatial, timed ability. A large verbal-minus-performance discrepancy was traditionally read as a clue to lateralised deficit or to a specific learning disorder, though this interpretation is now used cautiously.

CLINICAL ANCHOR

In a suspected dementia or acquired brain injury, a preserved verbal score with a collapsed performance/processing-speed score is the classic pattern: crystallised knowledge (Vocabulary, Information) is relatively "hold" and resists decline, while timed fluid tasks are "don't-hold" and fall early. The verbal-performance gap is a quick bedside heuristic before formal neuropsychology.

3.5 The four index scores and the full-scale IQ

Modern structure. From WAIS-IV and WISC-IV onward the verbal/performance dichotomy was superseded by four factor-analytically derived **index score** composites, each a standard score with mean 100 and SD 15 (Companion to Psychiatric Studies). They aggregate into the overall **full-scale iq**.

Verbal Comprehension Index (VCI)

Crystallised verbal reasoning and acquired knowledge; core subtests such as Similarities, Vocabulary, Information.

Perceptual Reasoning Index (PRI)

Fluid, nonverbal, visuospatial reasoning; core subtests such as Block Design, Matrix Reasoning, Visual Puzzles. (Called Perceptual Organisation in older editions; Visual Spatial plus Fluid Reasoning in WAIS-V.)

Working Memory Index (WMI)

Attention, mental control, and manipulation of information; Digit Span, Arithmetic, Letter-Number Sequencing.

Processing Speed Index (PSI)

Speed of simple visual scanning and graphomotor output; Coding (Digit Symbol), Symbol Search.

Full-Scale IQ. The full-scale iq is the best single summary of general ability (a proxy for Spearman's g, see the General and Developmental Psychology notes). It is a weighted composite of the index scores. When the four indices scatter widely, clinicians are taught to interpret the individual indices rather than the full-scale iq, because a single global number then masks a clinically important profile.

PEARL

Of the perceptual subtests, Matrix Reasoning has the highest correlation with overall full-scale iq (Companion to Psychiatric Studies), which is why abbreviated screeners like the WASI use Vocabulary plus Block Design plus Matrix Reasoning plus Similarities to estimate FSIQ in about 30 minutes.

3.6 Deviation IQ classification bands

The Wechsler descriptive bands. These are the standard qualitative **classification** labels attached to deviation-iq ranges (mean 100, SD 15). They are among the most commonly asked exact-recall facts in the assessment paper.

DEVIATION IQ RANGE	DESCRIPTIVE CLASSIFICATION
130 and above	Very superior / gifted
120 to 129	Superior
110 to 119	High average
90 to 109	Average
80 to 89	Low average
70 to 79	Borderline
Below 70	Extremely low / intellectual disability range

Standard Wechsler deviation-IQ descriptive bands; the average band 90 to 109 captures roughly the middle 50 percent of the population, and 70 is two standard deviations below the mean.

100	15	70	130
MEAN DEVIATION IQ	ONE STANDARD DEVIATION	2 SD BELOW (ID RANGE BEGINS)	2 SD ABOVE (VERY SUPERIOR)

3.7 Intellectual disability severity: ICD-10 IQ ranges

The four ICD-10 severity levels. Below an IQ of about 70 (two SDs below the mean), ICD-10 subdivides intellectual disability into four severity levels by approximate IQ range. Learn these exact bands.

SEVERITY	APPROXIMATE ICD-10 IQ RANGE	ROUGH MENTAL AGE
mild	**50 to 69**	9 to under 12 years
moderate	**35 to 49**	6 to under 9 years
severe	**20 to 34**	3 to under 6 years
profound	**below 20**	under 3 years

ICD-10 (F70 to F73) intellectual disability severity by approximate IQ; the mental-age figures are the ICD-10 clinical descriptions. Mild covers the large majority of cases.

COMMON TRAP

DSM-5 and ICD-11 no longer set severity by the IQ number. They classify intellectual disability severity by *adaptive functioning* across the conceptual, social, and practical domains, because it is adaptive skill (not the test score) that determines the level of support a person needs. IQ still establishes the diagnosis (roughly two SDs below the mean, about 65 to 75 allowing for measurement error), but severity is graded on adaptive functioning. Do not quote IQ cut-offs as the DSM-5 severity criterion.

HOLD THIS

The IQ locates the deficit; adaptive functioning grades its severity. Deviation IQ (mean 100, SD 15) replaced the ratio IQ; ICD-10 still bands severity by IQ (mild 50-69, moderate 35-49, severe 20-34, profound below 20), but DSM-5 and ICD-11 grade by adaptive function.

3.8 Culture-fair and nonverbal tests

Raven's Progressive Matrices. The best-known culture-fair test is Raven's Progressive Matrices (J. C. Raven, 1938). It is a purely nonverbal test of inductive reasoning and eductive ability: the person completes a visual matrix pattern by choosing the missing piece from options. Because it needs no reading, spoken instructions, or culture-specific knowledge, it is used across language and educational backgrounds and loads heavily on Spearman's g (see the General and Developmental Psychology notes). Versions include Coloured Progressive Matrices (young children and adults with impairment), Standard Progressive Matrices, and Advanced Progressive Matrices (high-ability adults).

Other performance tests. Where language or literacy is a barrier, performance and form-board tests are used: Seguin Form Board, Gesell's Drawing Test, and, in India, Bhatia's Battery of Performance Tests of Intelligence (a widely used indigenous nonverbal battery for Indian populations).

INDIA

For Indian assessment, the go-to instruments are the Binet-Kamat Test (verbal, child), Bhatia's Battery of Performance Tests of Intelligence (nonverbal, for low-literacy and rural populations), Malin's Intelligence Scale for Indian Children (MISIC, an Indian adaptation of the WISC), and the Seguin Form Board (a quick performance screen). Raven's Matrices are also widely used because they are language-free.

3.9 Strengths, limits, and clinical use

Strengths. Modern intelligence tests are the most rigorously standardised, reliable (IQ-scale reliabilities of about 0.88 to 0.97 for the WAIS), and well-normed instruments in psychology, with excellent predictive validity for academic and occupational outcomes.

Limits. A single global IQ can obscure a scattered profile; scores are affected by motivation, sensory or motor impairment, language, education, and test-taking familiarity; the Flynn effect (secular rise in raw scores over decades) means norms date and old norms inflate scores, so a test must be re-normed periodically. Verbal-loaded tests disadvantage those from different linguistic or cultural backgrounds, which is exactly why culture-fair tests such as Raven's exist.

TRAP The Flynn effect means old norms inflate scores, so an outdated test over-estimates IQ; a scale must be periodically re-normed, and a score is only as current as the norms behind it.

MNEMONIC

"VW-PP" ages: Very-young WPPSI, then WISC-child, then WAIS-adult

WPPSI (preschool, ~2.5 to 7) then WISC (child, ~6 to 16) then WAIS (adult, 16+). The three Wechsler bands stack across the lifespan in that order.

GOOD TO REMEMBER

- **Ratio IQ (Stern, Terman):** measures childhood ability as (mental age / chronological age) x 100; scored as that ratio; breaks down in adulthood.
- **Deviation IQ (Wechsler):** measures ability relative to same-age peers; scored as a standard score with mean 100 and SD 15; used by all modern scales.
- **Binet-Simon (Binet and Simon, 1905):** first practical intelligence test; introduced mental age; graded age-normed tasks.
- **Stanford-Binet (Terman, 1916; now SB5):** measures general ability across the lifespan; SB5 scores as deviation IQ (mean 100, SD 15) with verbal and nonverbal domains.
- **Binet-Kamat (V. V. Kamat, India):** measures child intelligence, verbal-loaded; Indian adaptation of the Stanford-Binet, scored as an IQ.
- **WAIS (Wechsler):** measures adult intelligence (16 to 90); scored on four index scores and a full-scale iq (mean 100, SD 15).
- **WISC (Wechsler):** measures child intelligence (~6 to 16); same index-score and full-scale iq scoring.
- **WPPSI (Wechsler):** measures preschool intelligence (~2 yr 6 mo to 7 yr 7 mo); deviation-IQ scoring.
- **Four index scores:** Verbal Comprehension, Perceptual Reasoning, Working Memory, Processing Speed, each mean 100 / SD 15, combining into the full-scale iq.
- **Raven's Progressive Matrices (Raven, 1938):** measures nonverbal inductive reasoning and g; culture-fair, language-free; scored by percentile against norms.
- **Bhatia's Battery / MISIC / Seguin Form Board (India):** measure nonverbal or child intelligence; indigenous or adapted Indian performance tests.
- **Wechsler classification bands:** very superior/gifted 130 and above, superior 120 to 129, high average 110 to 119, average 90 to 109, low average 80 to 89, borderline 70 to 79.
- **ICD-10 intellectual disability by IQ:** mild 50 to 69, moderate 35 to 49, severe 20 to 34, profound below 20.
- **DSM-5 and ICD-11 shift:** intellectual disability severity is now graded by adaptive functioning, not the IQ score alone.

4 · The Rorschach inkblot test

The **rorschach** inkblot test is the archetypal projective test of personality: an ambiguous, unstructured stimulus onto which the examinee is presumed to project fundamental features of their personality organisation and thought process. **Why it matters.** It is the single most examined projective instrument, sits at the centre of the objective-versus-projective divide, and is a favourite viva vehicle for the psychometric reliability-and-validity debate. Exam answers must couple the classic clinical description (Hermann Rorschach, the 10 cards, the two administration phases) with the modern scoring standard (the Exner Comprehensive System, its successor R-PAS) and the honest caveat that its psychometric standing is contested (Kaplan & Sadock 2024).

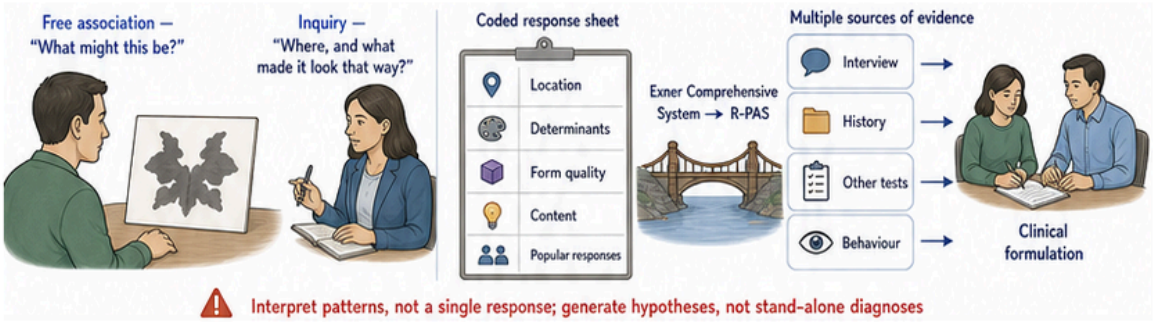


Fig 6.8 Rorschach: standardised performance, cautious inference.

Frame it as a catalogue entry: who built it and when, what construct it measures, how it is administered, how it is scored, what it is used for clinically, and where it is strong and weak. The **inkblot** is deliberately ambiguous, the projective hypothesis holding that when the stimulus is minimally structured the response is shaped by the respondent's own needs, conflicts and characteristic mode of perceiving reality (Kaplan & Sadock 2024).

4.1 Origin, authorship and what it measures

Author and date. Hermann Rorschach, a Swiss psychiatrist, published the test in his monograph *Psychodiagnostik* in 1921 (Kaplan & Sadock 2024, Tasman 2015); he died the following year, before the method matured. **Construct measured.** A projective assessment of whole-personality organisation, perceptual-associative processing and, clinically, thought process and reality testing, rather than any single narrow trait. It is a broad-band instrument: unlike an objective inventory that indexes one dimension (for example depression), the **rorschach** aims to sample personality as a whole and to expose latent, less consciously controlled aspects that the examinee cannot easily fake, because they do not know how a given response will be scored (Kaplan & Sadock 2024).

4.2 The stimulus material: describing the ten cards without reproducing them

The plates. There are 10 symmetrical **inkblot** cards, produced by dropping ink on paper and folding it so the two halves mirror each other, which is why every blot is bilaterally symmetrical. By convention the cards are labelled with Roman numerals I to X. This note describes them in words only and does not reproduce the copyrighted plates. In composition they divide into three groups.

Achromatic cards (5)

Cards I, IV, V, VI and VII are rendered in black and grey only, with no colour; several are large solid masses that commonly evoke whole-figure percepts such as a bat or a butterfly.

Black-and-red cards (2)

Cards II and III combine black-grey with prominent red detail; the red areas frequently draw colour-based and, on Card III, paired-human-figure responses.

Fully chromatic cards (3)

Cards VIII, IX and X are multicoloured; Card X in particular is broken into many separate coloured elements and tends to pull numerous discrete detail responses.

The 10 blots split 5 achromatic, 2 black-and-red, 3 fully chromatic; described in words only, plates never shown.

4.3 Administration: the free-association phase then the inquiry phase

Administration proceeds in two sequential phases, kept deliberately standardised with minimal examiner interaction so as not to contaminate the response (Kaplan & Sadock 2024).

Free-association (response) phase

Each card is handed over in turn with the open instruction, in effect "What might this be?" The examinee says whatever the blot could be; the examiner records the responses verbatim and notes any rotation of the card. This is also called the response-proper phase.

Inquiry phase

After all 10 cards are done, the examiner goes back through them and asks the examinee to point out where each percept was seen and what about the blot made it look that way. The inquiry supplies the information needed to code location and determinants; it is a clarification, not an invitation to give fresh responses.

Whole administration and scoring typically takes about 1.5 to 2 hours (Kaplan & Sadock 2024).

RULE **Free-association first, inquiry second, and the inquiry only clarifies.** The inquiry codes location and determinants; it never harvests fresh percepts.

4.4 Scoring systems: from Beck and Klopfer to the Exner Comprehensive System

The historical fragmentation. Several rival scoring-and-interpretation systems grew up around the test (K&S counts six), the best known being those of Samuel Beck and Bruno Klopfer, whose incompatible coding conventions long undermined comparability. **The modern standard.** John E. **exner** integrated the defensible elements of the earlier systems into the **exner** Comprehensive System, which became the most widely used and accepted framework and is the version examiners should name as current (Kaplan & Sadock 2024). Scoring yields a structural summary, an elaborate set of ratios and indices computed from the coded responses, and can generate dozens of variables.

4.5 The core scoring dimensions in the Exner Comprehensive System

Every response is coded along several axes. The location says which part of the blot was used, the determinants say what perceptual feature drove the percept, form quality says how well it fits the blot, content says what was seen, and popularity says how ordinary the percept is.

Location: Whole (W)

The response uses the entire blot; high W with good form can indicate integrative, organising capacity.

Location: Common detail (D)

The response uses a commonly selected, obvious sub-area of the blot.

Location: Unusual detail (Dd)

The response uses a small or rarely chosen area; a heavy load of Dd can signal an idiosyncratic, over-particular way of scanning the field.

Determinant: Form (F)

The percept is driven purely by the shape or contour of the blot; the workhorse determinant.

Determinant: Human movement (M)

The percept attributes human-like movement or action; M is linked interpretively to inner life, fantasy and ideation.

Determinant: Colour (C)

The percept is driven by the chromatic colour of the blot; colour determinants are read against form as an index of affect and its regulation.

Determinant: Shading

The percept is driven by the grey-black shading or texture of the blot; shading responses are tied interpretively to anxiety and dysphoric affect.

Form quality

How faithfully the percept matches the actual contour of the area used; good form quality reflects intact reality testing, poor form quality (distorted or arbitrary fit) is a key marker of disturbed perception.

Content

The category of what was seen, coded into classes such as human, animal, anatomy, nature and so on; the spread and any morbid or aggressive content carry interpretive weight.

Popular (P) responses

Percepts given so frequently by the normative population that they are catalogued as popular; a normal number of P responses reflects conventional, shared perception, a paucity suggests the examinee is not seeing the world as most people do.

Five coding axes of the Exner system: location, determinants, form quality, content, popularity.

4.6 R-PAS: the newer successor system

The Rorschach Performance Assessment System (R-PAS), introduced in 2011 by Meyer, Viglione, Mihura, Erard and Erdberg, is the newer successor to the **exner** Comprehensive System. It was built to retain only variables with defensible empirical support, to use internationally normed reference data, and to standardise the number of responses per card (a brief prompt for a second response, and a limit that discourages excessive responding), addressing the older systems' vulnerability to variable response productivity. For exams, cite it as the current evidence-driven refinement while the **exner** system remains the reference point most texts still teach (Kaplan & Sadock 2024).

4.7 Clinical uses and interpretation

Interpretation reads the structural summary as a whole rather than any single response. Its principal clinical yields:

Thought disorder and deviant verbalisation

Bizarre, illogical or contaminated verbalisations during the response phase (for example fusing two incompatible percepts, or reasoning arbitrarily from the blot) are read as formal thought disorder; the test has an established role in indexing disordered thinking, and in India the Rorschach Ink Blot Test is listed among instruments used to assess thought disorder (Clinical Methods in Psychiatry, AIIMS 2024).

Reality testing via form quality

Poor form quality, percepts that do not fit the contour used, is the direct operational marker of impaired reality testing.

Indices suggestive of psychosis

The Exner system carries a composite perceptual-thinking index built from form-quality and special-score variables that is used as a screen suggestive of psychotic-level disturbance; a positive index supports, but does not by itself diagnose, psychosis.

Depression and dysphoria

A depression-related index and a preponderance of shading and morbid content are read as pointing toward depressive affect.

Suicide risk

The system includes a suicide constellation, a cluster of variables interpreted as flagging heightened self-destructive risk that warrants clinical corroboration.

In all cases the finding is a hypothesis to be integrated with history, interview and other data, never a stand-alone diagnosis (Kaplan & Sadock 2024).

4.8 Strengths, limits and the psychometric controversy

Strengths. It is the most widely used and best-researched projective device, with a large interpretive literature; the standardised two-phase administration and the Exner structural summary imposed much-needed rigour; and its indirect, hard-to-fake nature can surface material that self-report inventories miss (Kaplan & Sadock 2024). **Limits and the controversy.** The central caveat is psychometric: the reliability and validity of several Rorschach variables are contested. Critics argue that many indices lack demonstrated validity and that scoring is labour-intensive and examiner-dependent; the debate has been sharp enough that some clinical-psychology programmes dropped formal Rorschach coursework, though many retain it (Kaplan & Sadock 2024). The honest exam position: a rich clinical instrument in experienced hands whose variable-by-variable psychometrics remain uneven, which is exactly what R-PAS was designed to tighten.

CLINICAL ANCHOR

Position the **rorschach** as adjunctive, not diagnostic. It is most defensibly used to generate hypotheses about thought process and reality testing (via poor form quality and deviant verbalisations) that are then cross-checked against the mental-state examination and history. A positive perceptual-thinking or suicide-constellation index prompts closer clinical evaluation; it never substitutes for it.

COMMON TRAP

Do not say the **rorschach** "diagnoses schizophrenia" or "measures IQ". It is a projective personality and thought-process measure, not a diagnostic or intelligence test. Also avoid crediting the modern scoring to Rorschach himself: the coding standard is the **exner** Comprehensive System (with R-PAS the successor), not the 1921 original. And never collapse the two phases: free-association first, inquiry second, and the inquiry only clarifies, it does not harvest new percepts.

MNEMONIC

"LoDeF-CoP" for the Exner coding axes

Location (W, D, Dd), **De**terminants (F, M, C, shading), **F**orm quality, **Co**ntent, **P**opular. Five axes: where they looked, what drove it, how well it fits, what it was, and how ordinary it is.

FEATURE	EXNER COMPREHENSIVE SYSTEM	R-PAS
Author / year	John E. Exner, 1974 onward	**Meyer and colleagues, 2011**
Design goal	Integrate rival systems into one standard	**Keep only empirically supported variables**
Response productivity	Not tightly controlled per card	**Standardised with prompts and a response limit**
Norms	Largely US-based reference data	**International reference data**
Exam status	The system most texts still teach	The current evidence-driven successor

Exner set the modern standard; R-PAS is the newer successor built to tighten its psychometrics.

HOLD THIS

Rorschach 1921, ten symmetrical inkblots, free-association then inquiry, scored on Exner's Comprehensive System (R-PAS the successor). A projective measure of thought process and reality testing, adjunctive only, with contested psychometrics.

GOOD TO REMEMBER

- **Author / year:** Hermann Rorschach, Swiss psychiatrist, *Psychodiagnostik*, 1921.
- **What it measures:** projective personality organisation, perceptual-associative process, and clinically thought process plus reality testing (broad-band, not one trait).
- **The stimulus:** 10 symmetrical inkblot cards, labelled I to X; composition = 5 achromatic (black-grey), 2 black-and-red, 3 fully chromatic. Described in words only, never reproduced.
- **Administration:** free-association (response-proper) phase first, then the inquiry phase (points out where and what made it look so); about 1.5 to 2 hours total.
- **Scoring, modern standard:** the Exner Comprehensive System, superseding the older Beck and Klopfer systems (K&S counts six historical systems).
- **Exner coding axes:** LOCATION (Whole W, common detail D, unusual detail Dd); DETERMINANTS (form F, human movement M, colour C, shading); FORM QUALITY; CONTENT categories; POPULAR responses.
- **Successor system:** R-PAS (Rorschach Performance Assessment System, Meyer et al. 2011), empirically pruned variables, international norms, controlled response count.
- **Clinical uses:** thought disorder and deviant verbalisations; reality testing via form quality; a perceptual-thinking index suggestive of psychosis; depression and suicide-constellation indices; always a hypothesis, integrated with history and interview.
- **Controversy:** contested reliability and validity of several variables; labour-intensive, examiner-dependent scoring; some programmes dropped it, many retain it.
- **Hard rule:** not a diagnostic test, not an intelligence test; adjunctive only.

5 · Projective tests: TAT, SCT, draw-a-person

Where the Rorschach uses inkblots, this family of **projective** tests hands the subject other kinds of ambiguous, unstructured material and watches what gets built from it. The governing idea is the **projective hypothesis**: when a stimulus is deliberately vague and the response space is almost unlimited, the person has nothing external to lean on, so their reply is shaped from within, and unconscious needs, conflicts and personality organisation are read off the material as if it were a screen onto which they are projected (Kaplan & Sadock 2024). Instructions are general, the scoring key is hidden, and the response is broad-band, meaning the whole personality is sampled rather than one narrow trait.

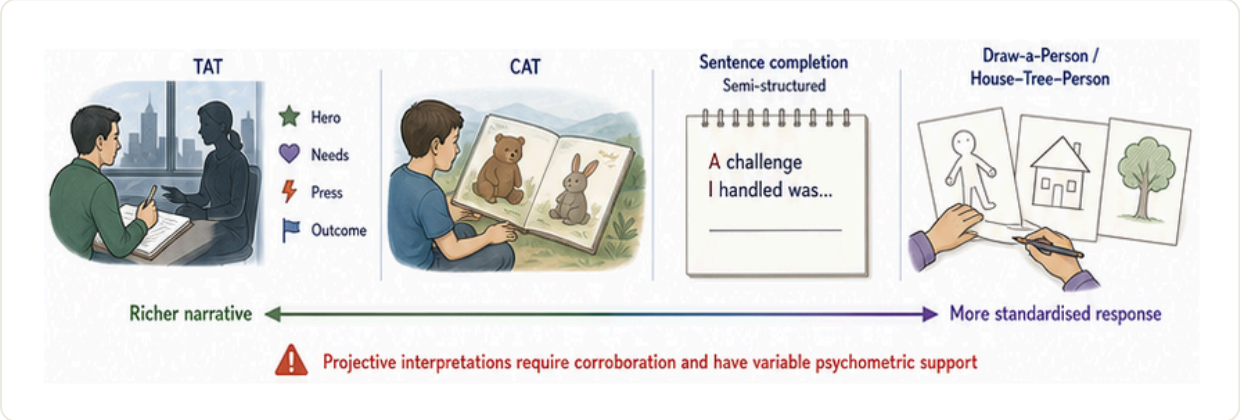


Fig 6.9 The projective family: structure changes the response.

Exam framing. Paper I loves this cluster as a compare-and-list station: name the test, its author and year, what it uses as stimulus, and what is scored. Examiners also probe the projective-versus-objective contrast and the reliability weakness. Treat each test below as a catalogue entry: stimulus, administration, scoring, use, and limits.

5.1 The projective hypothesis and what "projective" means

The core assumption. A **projective** test presents an ambiguous, unstructured stimulus for which there is no correct answer, so the subject must impose structure. That imposed structure, on the projective hypothesis, reflects fundamental aspects of personality: needs, drives, conflicts and characteristic defences (Kaplan & Sadock 2024). The term traces to psychoanalytic projection but is used descriptively here, not as a claim that projection (the defence) is the only mechanism. Because the subject does not know how responses will be scored, projective techniques are considered harder to fake than self-report inventories.

5.2 Thematic Apperception Test (TAT): stimulus and administration

What it is. The **thematic apperception** test (**tat**; Morgan and Murray, first described 1935; developed at the Harvard Psychological Clinic) is a story-telling projective. The full set is a series of ambiguous black-and-white picture cards depicting people, singly or in groups, in emotionally suggestive but unresolved situations. The classic Card 1 shows a young boy seated before a violin. Card 16 is a blank card. Cards carry age and sex codes so a tailored subset is chosen; a subject is typically shown around 20 cards over two sessions, though shorter clinical administrations of

about 10 cards are common. (HARD rule for this note: the cards themselves are copyrighted and are described in words only, never reproduced.)

The task. For each card the subject tells a story: what is happening now, what led up to it, what the figures are thinking and feeling, and how it will end. The dramatic, invented narrative is the raw data.

5.3 TAT scoring and interpretation: needs, press, the hero

Murray's framework. The **tat** is interpreted through Murray's personology. The interpreter identifies the **hero** (the figure the subject identifies with), the hero's **needs** (internal motivational forces such as need for achievement, affiliation, aggression), and the environmental **press** (forces acting on the hero from outside). The clinician tracks recurrent **themes** and **conflicts** across stories, the emotional tone, and how tensions are resolved (Kaplan & Sadock 2024). Formal quantitative systems exist (for example Bellak's scheme and the Defense Mechanisms Manual), but everyday clinical use is largely qualitative and impressionistic, which is exactly why interpreter dependence is a stated weakness.

5.4 Children's Apperception Test (CAT) and other apperception variants

The child analogue. The Children's Apperception Test (**cat**; Bellak, 1949) is the developmental analogue of the **tat** for younger children, classically ages 3 to 10. Its original version replaces human figures with anthropomorphic **animal figures** in familiar situations (feeding, toileting, sibling rivalry), on the assumption that young children project more readily onto animals; a human-figure form (CAT-H) was added later. Related child instruments include the Roberts Apperception Test for Children. The task and interpretive logic mirror the adult **tat**: tell a story, then read needs, conflicts and defences.

> **CLINICAL ANCHOR**
>
> The **tat** earns its keep when self-report is guarded or when object-relational and motivational material is the question, for example probing interpersonal conflict in a personality-disorder assessment. It is a supplement within a battery, never a standalone diagnostic test, and it does not yield a diagnosis.

5.5 Sentence completion tests (SCT): the semi-structured bridge

What it is. A **sentence completion** test (**sct**) presents a series of incomplete sentence stems ("My greatest fear...", "My father...") that the subject finishes with the first response that comes to mind. Because the stem constrains the response, the **sct** is the most direct of the projectives and is often called a **bridge between projective and objective** methods: more structured than the **tat**, less structured than a true-false inventory (Kaplan & Sadock 2024).

Named forms. The best-validated version is the **Rotter Incomplete Sentences Blank** (Rotter and Rafferty, 1950), 40 stems scored on a 7-point scale for degree of conflict or maladjustment to yield an overall adjustment index. The Sacks Sentence Completion Test (SSCT) samples defined attitude areas (family, sex, interpersonal relationships, self-concept). Stem counts vary widely across versions, from under 10 to over 75.

Strengths and limits. Quick, easy to administer and score, and flexible; but it is transparent, so it is easy to fabricate or deceive, and most versions other than Rotter's lack established reliability and validity data.

TRAP The sentence completion test is the most structured, most transparent projective, so it is the easiest to fake; only Rotter's Incomplete Sentences Blank has solid reliability and validity data.

5.6 Draw-a-Person test (Machover): projective figure drawing

What it is. The **draw-a-person** test in its projective form (Machover, 1949) asks the subject to draw a person, then to draw a person of the opposite sex. The drawing is interpreted qualitatively as a body-image projection: placement, size, line quality, omissions, distortions and the treatment of specific features are read for anxiety, conflict and self-concept. This is the interpretive descendant of Goodenough's earlier work, but Machover's use is clinical-projective rather than developmental.

Caveat. Machover-style sign interpretation of the **draw-a-person** has notoriously poor psychometric support; single-sign readings ("large eyes mean paranoia") are not defensible and it survives as a rapport-builder and hypothesis-generator, not as a validated instrument.

5.7 Goodenough-Harris Draw-a-Man and House-Tree-Person

Developmental use. The Goodenough Draw-a-Man test (Florence Goodenough, 1926), revised as the **Goodenough-Harris Drawing Test** (Harris, 1963), scores a child's human-figure drawing for the number of correct body details and proportions to yield a nonverbal estimate of intellectual maturity or mental age. Here the same act of drawing a person is used as a **developmental and screening** measure of cognitive maturity, not as a projective probe, a distinction examiners like to test.

House-Tree-Person. The House-Tree-Person test (Buck, 1948) extends the projective drawing idea: the subject draws a house, a tree and a person, each read for aspects of the self and the perceived environment, followed by an inquiry phase.

CLASSIC TRAP The same act of drawing a person is a projective probe in Machover's Draw-a-Person (body image, self-concept) but a developmental estimate of intellectual maturity in the Goodenough-Harris Draw-a-Man - same drawing, opposite purpose.

5.8 Other projective techniques worth naming

Rosenzweig Picture-Frustration Study (P-F Study; Rosenzweig, 1945)

Cartoon strips show one figure frustrating another; the subject supplies the frustrated figure's reply. Scored for direction of aggression (extrapunitive, intropunitive, impunitive) and type of reaction, giving a semi-projective measure of reaction to frustration.

Word-association test

The examiner reads a standard list of stimulus words; the subject gives the first word that comes to mind. Reaction-time delays, blocks and unusual associations flag emotionally charged complexes. Associated with Jung's complex work and the Kent-Rosanoff standardised list.

Object-sorting test (Goldstein-Scheerer)

The subject sorts objects or blocks into groups and explains the principle; concrete, idiosyncratic or overinclusive sorting is used to demonstrate concrete thinking and conceptual (formal thought) disturbance, classically in schizophrenia.

5.9 Projective versus objective tests: the trade-off

The contrast. Objective personality tests (self-report inventories such as the MMPI) use structured items with fixed scoring; **projective** tests use ambiguous stimuli with open scoring. Each buys something at a cost.

DIMENSION	PROJECTIVE TESTS	OBJECTIVE TESTS
Stimulus	Ambiguous, unstructured	Structured, fixed items
Data	**Rich, idiographic, whole-personality**	Narrow, quantified traits
Fakeability	**Harder to fake (scoring hidden)**	Easier to fake or fake-good
Reliability and validity	**Often low; interpreter-dependent**	Generally higher, normed
Scoring	Subjective, needs trained interpreter	Objective, can be automated

Projectives trade psychometric rigour for depth and resistance to faking; objective tests trade richness for reliability.

HOLD THIS

The projective family runs from least to most structured: TAT tells tales, SCT stops at a stem, DAP draws the self. All are broad-band, hard to fake, and low in reliability; all generate hypotheses, none names a diagnosis.

COMMON TRAP

Do not call any projective a "diagnostic test". None of them names a diagnosis; they generate hypotheses about personality and conflict that must be integrated with history and the rest of a battery. Equally, do not conflate the projective **draw-a-person** (Machover) with the developmental Goodenough-Harris Draw-a-Man: same drawing, opposite purpose (personality projection versus cognitive maturity).

MNEMONIC

TAT tells Tales; SCT Stops Short; DAP Draws the self

The **tat** elicits full narrative **tales** (least structured, richest), the **sct** stops the subject at a sentence **stem** (semi-structured bridge), and the **draw-a-person** reads the **self** off a figure drawing. Order of increasing structure: TAT to SCT.

INDIA

Indian residency texts (AIIMS Clinical Methods in Psychiatry 2024) list the Rorschach, **tat**, the Draw-a-Person test (DAPT) and the **sentence completion** test (often the Sacks form, SSCT) as the standard projective battery, and note that formal projective testing is done by a clinical psychologist, not at the bedside by the psychiatrist.

GOOD TO REMEMBER

- **Projective hypothesis:** ambiguous unstructured stimuli let the subject project unconscious needs, conflicts and personality onto the material.
- **Thematic Apperception Test (TAT):** Morgan and Murray, 1935 (Harvard) / measures needs, press, motives and interpersonal conflict via story-telling / scored by identifying the hero, needs, press, recurrent themes and conflicts (Murray's personology).
- **Children's Apperception Test (CAT):** Bellak, 1949 / child analogue of the TAT (ages ~3 to 10) / same needs-and-conflict interpretation, uses animal figures (CAT-A; human form CAT-H).
- **Sentence Completion Test (SCT):** semi-structured stems, a bridge between projective and objective / measures attitudes, conflicts and adjustment / Rotter Incomplete Sentences Blank (Rotter and Rafferty 1950), 40 stems, 7-point conflict scoring, overall adjustment index; Sacks SSCT samples attitude areas.
- **Draw-a-Person (Machover, 1949):** projective figure drawing / measures body image, self-concept, anxiety and conflict / qualitative sign interpretation of the drawn figure (weak psychometrics).
- **Goodenough-Harris Draw-a-Man (Goodenough 1926; Harris 1963):** developmental and screening measure / estimates intellectual maturity / scored by counting correct body details and proportions for a mental-age estimate.
- **House-Tree-Person (Buck, 1948):** projective drawing of house, tree and person / self and perceived environment / qualitative interpretation plus an inquiry phase.
- **Rosenzweig Picture-Frustration Study (Rosenzweig, 1945):** cartoon frustration scenes / reaction to frustration / scored for direction of aggression (extrapunitive, intropunitive, impunitive) and reaction type.
- **Word-association test (Jung; Kent-Rosanoff list):** respond with first word to a stimulus word / detects emotionally charged complexes / scored on reaction time, blocks and atypical associations.
- **Object-sorting test (Goldstein-Scheerer):** sort and explain groupings / conceptual (formal-thought) disturbance / concrete or overinclusive sorting flags concrete thinking, classically in schizophrenia.
- **Projective vs objective:** projectives are rich and harder to fake but low in reliability and interpreter-dependent; objective inventories are reliable and normed but narrow and easier to fake.

6 · Objective personality tests: MMPI, 16PF, NEO

An **objective personality** test is a structured self-report inventory built from a fixed set of items (usually true or false, or a Likert scale), scored by a standardised key against published norms, so that the same protocol yields the same profile in any hands. This is the defining contrast with projective testing: the stimulus is unambiguous, the response format is closed, and the scoring is mechanical, not interpretive. The tests taught here **operationalise** the trait theories of personality you met in the Social, Learning & Personality Psychology notes, translating abstract dimensions (Cattell's source factors, Eysenck's superfactors, the Big Five) into measurable scale scores.

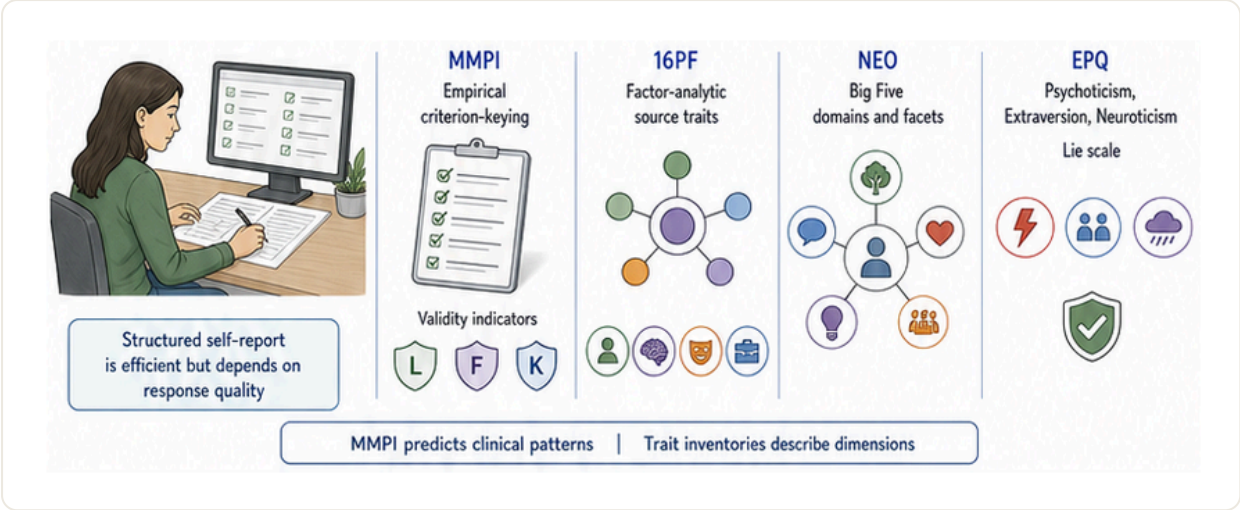


Fig 6.10 Objective personality tests: different construction logics.

For the exam, master three things per test: **who built it and on what logic** (empirical criterion-keying versus factor analysis), **what construct it measures**, and **how it detects faking**. The MMPI validity scales are the classic answer to the central weakness of self-report, that respondents can distort. Kaplan and Sadock (2024) and the Companion to Psychiatric Studies remain the depth bar.

6.1 What makes a test "objective"

Fixed stimulus, fixed scoring. Objective tests are typically pencil-and-paper (or digital) instruments made of specific items that yield numerical scores and profiles amenable to statistical analysis (Kaplan & Sadock 2024). Because administration and scoring are standardised, inter-rater variance is near zero: two clinicians scoring the same answer sheet get the same T-scores. Reliability and validity are formally established against a normative base, and it is the size and representativeness of those norms that largely determine a test's usefulness. This is the whole appeal, and the whole vulnerability, of the class: rigour bought at the price of relying on what the person is willing to report.

6.2 The MMPI: empirical criterion-keying

Origin and logic. The **mmpi** (Minnesota Multiphasic Personality Inventory) was developed by Starke R. Hathaway and J. Charnley McKinley at the University of Minnesota, the original version published in 1943 (Hathaway & McKinley 1943; Kaplan & Sadock 2024). Its innovation was **empirical criterion-keying**: items were retained on a clinical scale not for face content but because they were answered differently by a criterion group (say, diagnosed depressives) than by normal controls. The test is deliberately descriptive and atheoretical, not derived from psychoanalytic theory. It is a true-or-false questionnaire for persons aged 16 and over, coded into multiple scales. A scoring innovation was the T-score, a standardised metric with mean set at 50 and standard deviation at 10, which let scores be compared across scales; a T-score at or above 65 (MMPI-2) is the usual clinical cut-off.

6.3 MMPI validity scales: detecting response style

The faking detectors. The MMPI's signature contribution is a set of **validity scales** that gauge how the person approached the test before any clinical scale is trusted. The three classical ones:

L (Lie scale)

Items describing minor human faults most people admit; high L means the person claims implausible virtue ("naive" or unsophisticated faking-good).

F (Infrequency)

Items endorsed by fewer than 10 percent of the normative sample; high F suggests over-reporting, random responding, severe pathology, or "faking bad".

K (Correction)

A subtler defensiveness index; detects a guarded, image-managing test-taking set, and a fraction of K is statistically added back to several clinical scales to correct for under-report.

Later forms add F-family scales (Fb, Fp) and consistency indices (VRIN, TRIN). The L, F, K configuration ("validity triangle") is read first: an invalid protocol voids clinical interpretation.

RULE **Read L, F, K before any clinical scale.** An invalid protocol (implausible virtue, over-reporting or defensiveness) voids the whole profile, so the validity triangle comes first.

6.4 MMPI clinical scales and code types

Ten basic clinical scales. The original MMPI carries ten numbered clinical scales, each empirically keyed to a criterion group. Scales are read by number and by two-point **code type** (the two highest scales), for example a 2-7 code (depression plus psychasthenia) suggesting anxious-depressive presentation.

NO.	SCALE	WHAT HIGH SCORES FLAG
1	Hs Hypochondriasis	Bodily preoccupation, somatic complaints
2	D Depression	Dysphoria, pessimism, low morale
3	Hy Hysteria	Conversion tendency, denial, stress-related somatics
4	Pd Psychopathic deviate	Rebelliousness, antisocial traits, poor authority relations
5	Mf Masculinity-femininity	Interest patterns departing from gender-role norms
6	Pa Paranoia	Suspiciousness, sensitivity, ideas of reference
7	Pt Psychasthenia	Anxiety, obsessions, doubt, tension
8	Sc Schizophrenia	Bizarre ideation, alienation, unusual experience
9	Ma Hypomania	Elevated energy, expansive-ness, overactivity
0	Si Social introversion	Withdrawal, shyness, low sociability

The ten clinical scales in order; scales 5 and 0 are non-clinical dimensions, the other eight index symptom domains.

6.5 MMPI-2, the RF and MMPI-3

The modern versions. The MMPI-2 (1989) re-standardised the instrument on a large contemporary US normative sample and added content and supplementary scales while keeping the ten clinical scales for continuity. The MMPI-2-RF (Restructured Form) is a shorter psychometric revision built around Restructured Clinical (RC) scales that strip out a shared "demoralisation" factor. The MMPI-3, the newest edition, brings new norms and updated items (Kaplan & Sadock 2024). All remain heavily used in clinical, forensic, and employment-screening contexts, and the validity indicators carry into every version.

6.6 The 16PF: Cattell's source factors

Factor-analytic architecture. The **16pf** (Sixteen Personality Factor Questionnaire) was devised by Raymond B. Cattell (1905 to 1998) in 1949, on a factor-analytic logic that contrasts sharply with the MMPI's criterion-keying (Kaplan & Sadock 2024). Starting from the **lexical hypothesis** (that every trait important in social life becomes encoded in language), Cattell reduced Allport and Odbert's roughly 4,000 trait terms to 35 variable clusters, factored them, and derived sixteen primary **source factors** (for example warmth, reasoning, emotional stability, dominance, vigilance, apprehension, tension). These sixteen primaries themselves load onto five second-order "global" factors that broadly anticipate the Big Five. The 16PF measures normal-range personality rather than psychopathology, so it is used in occupational, counselling, and research settings more than in psychiatric diagnosis.

6.7 The NEO-PI-R: operationalising the Big Five

The five-factor instrument. The **neo-pi** (NEO Personality Inventory, current research forms the NEO-PI-R and NEO-PI-3) was built by Paul T. Costa Jr and Robert R. McCrae as the operationalisation of the **five-factor model** (FFM), the Big Five (Costa & McCrae; Kaplan & Sadock 2024). The five domains carry the mnemonic OCEAN: Openness to experience, Conscientiousness, Extraversion, Agreeableness, Neuroticism. Crucially the neo pi is hierarchical: each of the five domains is measured by six specific **facet** scales (thirty facets in total), so Neuroticism decomposes into anxiety, angry hostility, depression, self-consciousness, impulsiveness, and vulnerability. This facet-level resolution gives a more detailed personality portrait than a domain score alone and is why the FFM and the neo pi now dominate trait research and inform dimensional models of personality pathology.

> **CLINICAL ANCHOR**
>
> DSM-5's alternative model of personality disorders (Section III) maps disorders onto FFM-derived trait domains, and the PID-5 is its self-report instrument. When an examiner asks how modern classification links to trait psychology, the neo pi and the Big Five are the bridge: categories reframed as extreme standings on continuous dimensions.

6.8 The Eysenck Personality Questionnaire: the PEN model

Three superfactors. Hans Eysenck argued that Cattell's sixteen factors were needlessly complex and non-replicable, and reduced personality to a small number of higher-order dimensions. The

eysenck personality questionnaire (**epq**), developed by Hans and Sybil Eysenck (Eysenck & Eysenck 1975), measures the **PEN model**: Psychoticism, Extraversion, and Neuroticism, with a Lie scale for response validity. Extraversion and Neuroticism were his original two superfactors (from the earlier EPI); Psychoticism (tough-mindedness, hostility, non-conformity) was added later. Eysenck grounded these biologically, tying introversion to higher cortical arousal and easier conditioning. The epq is a brief, dimensional, heavily biologically-anchored instrument, and its E and N reappear inside the Big Five.

6.9 Criterion-keyed versus factor-analytic construction

Two ways to build a personality test. The exam loves this contrast, because it explains why the MMPI looks and behaves so differently from the 16PF and neo pi.

FEATURE	EMPIRICAL CRITERION-KEYING (MMPI)	FACTOR-ANALYTIC (16PF, NEO, EPQ)
Item selection	Retained if it discriminates a criterion group	**Retained if it loads on a statistical factor**
Guiding aim	Predict clinical group membership	**Describe the structure of normal traits**
Face validity	Often low (item content may seem unrelated)	**Usually high (items obviously tap the trait)**
Typical use	Psychopathology, forensic, screening	**Normal-range description, research, occupational**

The MMPI predicts; the trait inventories describe. Different logic, different clinical niche.

HOLD THIS

The MMPI was built by empirical criterion-keying (it predicts group membership); the 16PF, NEO and EPQ were built by factor analysis (they describe trait structure). The MMPI's validity scales are the answer to the fakeability of all self-report.

6.10 Objective versus projective assessment

Strengths and the fakeability problem. Against projective techniques (Rorschach, TAT), objective tests offer clear advantages: standardised administration, established reliability and validity, representative norms, quantified scores, and objectivity of scoring. Their central weakness is transparency: because items are structured and often obvious, respondents can consciously distort ("fake good" for custody or employment, "fake bad" for compensation or disability). This is precisely the gap the MMPI validity scales close, and why any credible objective inventory now carries validity or consistency indices. Projective tests trade the norms and objectivity away in exchange for being harder to fake and richer on unconscious material, a trade-off the personality-theory discussion in the Social, Learning & Personality Psychology notes frames.

COMMON TRAP

Do not call the 16PF or NEO-PI-R "projective" because they concern personality: they are firmly objective (structured, keyed, normed). Projective means an ambiguous stimulus (inkblot, picture) with an open response. Also do not confuse the MMPI's empirical criterion-keying with factor analysis: the MMPI was NOT built by factor analysis, the 16PF, NEO and EPQ were.

MNEMONIC

"Lie, Frequency, correction" then "OCEAN" and "PEN"

MMPI validity trio in order = **L, F, K**. Big Five (neo pi) domains = **OCEAN** (Openness, Conscientiousness, Extraversion, Agreeableness, Neuroticism). Eysenck (epq) = **PEN** (Psychoticism, Extraversion, Neuroticism).

PEARL

Everything reduces to a family tree of extraversion and neuroticism. Eysenck's E and N (epq) are two of Cattell's second-order factors and two of the Big Five domains; the neo pi simply adds Openness, Agreeableness and Conscientiousness. If asked "what unifies the trait inventories", the answer is that they are competing resolutions of the same underlying factor space.

GOOD TO REMEMBER

- **Objective personality test:** structured self-report, fixed items, standardised key, norm-referenced scoring; contrast with projective (ambiguous stimulus, open response).
- **MMPI / MMPI-2 / MMPI-3:** Hathaway and McKinley (1943); measures psychopathology and response style; empirical criterion-keying; scored as T-scores (mean 50, SD 10), clinical cut-off T at or above 65.
- **MMPI validity scales:** L (lie, faking-good), F (infrequency, over-reporting/faking-bad), K (correction, defensiveness); read before clinical scales.
- **MMPI ten clinical scales:** 1 Hypochondriasis, 2 Depression, 3 Hysteria, 4 Psychopathic deviate, 5 Masculinity-femininity, 6 Paranoia, 7 Psychasthenia, 8 Schizophrenia, 9 Hypomania, 0 Social introversion; interpreted by two-point code types.
- **16PF:** Raymond Cattell (1949); measures sixteen normal-range source factors derived by factor analysis (lexical hypothesis); occupational and research use.
- **NEO-PI-R / NEO-PI-3:** Costa and McCrae; operationalises the five-factor model (OCEAN); scored as five domains, each with six facets (thirty facets total).
- **Eysenck Personality Questionnaire (EPQ):** Hans and Sybil Eysenck (1975); measures the PEN dimensions (Psychoticism, Extraversion, Neuroticism) plus a Lie scale; biologically anchored.
- **Construction logic:** MMPI = empirical criterion-keying (predicts group membership, low face validity); 16PF, NEO, EPQ = factor-analytic (describe trait structure, high face validity).
- **Fakeability:** the core limit of objective tests; addressed by validity/consistency scales (the MMPI L, F, K being the exemplar).

7 · Neuropsychological testing

This is where psychometry meets the brain. A **neuropsychological** test is a standardised task whose performance is known to depend on a particular brain structure or pathway, so that a deficit on the task can be read as a statement about the integrity of that system. The discipline

studies **brain-behaviour relationships**, and a neuropsychological assessment can be thought of as an elaboration and refinement of the cognitive component of the mental status and neurological examination (Kaplan & Sadock 2024). No single instrument covers the brain; instead a battery samples five cognitive domains: **attention**, **memory**, **language**, **visuospatial function** and **executive function**.

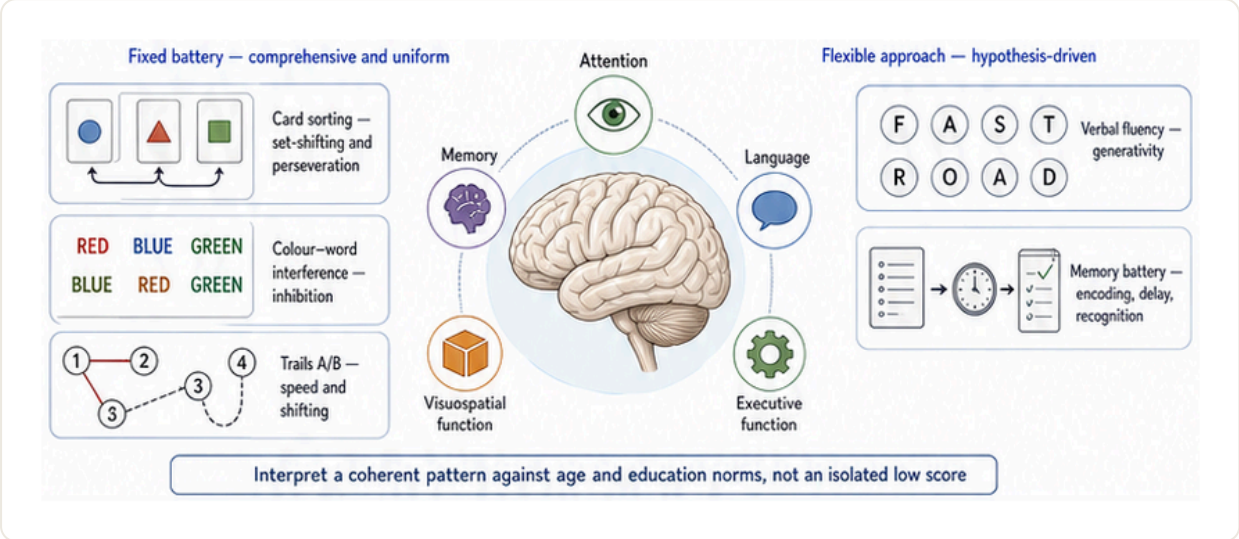


Fig 6.11 Neuropsychological assessment: test the pattern.

For the examiner this topic sits at the junction of psychometry and organic psychiatry, so it is examined twice: once as a catalogue of named batteries and tests (who built them, what construct each measures, how each is scored), and once as a clinical tool (dementia work-up, traumatic brain injury, lesion localisation, capacity and rehabilitation). Two organising axes run through the whole topic: the *fixed battery versus flexible hypothesis-driven* distinction in approach, and the frontal/executive tests, which carry the most marks because they are the hardest deficits to catch at the bedside.

7.1 The two approaches: fixed batteries versus the flexible, hypothesis-driven method

Standard battery or tailored investigation. Neuropsychological assessment is organised along two philosophies (Kaplan & Sadock 2024). The *fixed (standard) battery* approach administers the same comprehensive, pre-set set of tests to every patient regardless of the referral question; its strength is a uniform, quantitative, normed profile that will not miss an unexpected deficit, and its weakness is length and inefficiency. The **halstead-reitan** battery and the **luria**-Nebraska battery are the two classic fixed batteries. The *flexible, hypothesis-driven* (or process) approach, historically exemplified by **luria** and formalised as the Boston Process Approach by Edith Kaplan, selects and sequences tests to test a specific hypothesis about the patient's complaint, honing in efficiently on the suspected area of impairment and describing the *quality* of errors, not just the score; its shortcoming is that it may overlook an unexpected deficit outside the hypothesis (Kaplan & Sadock 2024). Most modern clinical neuropsychology is flexible-hypothesis-driven, drawing tests from many batteries.

RULE **Diagnose impairment on a pattern consistent with a known condition, never on isolated low scores.** A long battery yields some low scores even in healthy people, read against age and education norms.

7.2 The Halstead-Reitan battery: a fixed battery for organicity

Category Test, Tactual Performance Test, Impairment Index. The **halstead-reitan** Neuropsychological Test Battery (HRNTB) is the prototype fixed battery, assembled by Ward Halstead and extended by Ralph Reitan, with versions for adults and children (Kaplan & Sadock 2024). It is a compilation of tests designed to detect and localise brain damage and to lateralise it. Three components are named repeatedly:

Category Test

A test of abstraction and concept formation: the patient works out an organising principle for sets of stimuli using the examiner's right/wrong feedback. It is regarded as one of the most sensitive single measures of general brain dysfunction in the battery, and, like the Wisconsin, it taps the ability to benefit from feedback and shift strategy (Kaplan & Sadock 2024).

Tactual Performance Test (TPT)

A blindfolded test of visuospatial and tactile-kinaesthetic function: the patient places blocks into a form-board by touch alone, then draws the board from memory. It yields measures of tactile problem-solving, and of incidental memory and localisation (Kaplan & Sadock 2024).

Halstead Impairment Index

The summary score of the battery: the proportion of the core tests on which the patient falls in the brain-damaged range, running from 0.0 (none impaired) to 1.0 (all impaired). A higher index means more pervasive dysfunction; it is the battery's single global organicity figure.

Other HRNTB components (finger tapping, grip strength, the rhythm and speech-sounds perception tests, and double simultaneous stimulation) provide the lateralising and sensory-motor data.

7.3 The Luria-Nebraska Neuropsychological Battery: qualitative Luria, quantified

A fixed battery built on Luria's qualitative approach. The **luria**-Nebraska Neuropsychological Battery (LNNB), developed by Golden and colleagues, took the qualitative, syndrome-analytic bedside method of the Russian neuropsychologist A. R. **luria** and repackaged it as a standardised, quantitatively scored fixed battery (Kaplan & Sadock 2024). It is organised into clinical scales spanning motor, rhythm, tactile, visual, receptive speech, expressive speech, writing, reading, arithmetic, memory and intellectual processes, each generating a score referenced to norms; it thus tries to preserve **luria**'s functional-systems logic while giving the actuarial, normed output that the pure qualitative method lacks. A Children's Revision exists for younger patients.

7.4 Frontal and executive testing: the highest-yield cluster

Why the frontal lobe needs special tests. Executive functions (planning, initiation, self-monitoring, inhibition of inappropriate responses, set-shifting, and control of complex problem-solving) are the most vulnerable to frontal and frontal-subcortical damage and the least reliably caught by a routine mental status examination, so a distinct set of tests targets them (Kaplan &

Sadock 2024). A patient can score normally on the MMSE and intelligence testing yet be grossly dysexecutive. The examiner expects the following tests by name and by the specific process each isolates.

7.5 The Wisconsin Card Sorting Test: set-shifting and perseveration

The signature test of frontal set-shifting. The **wisconsin card** Sorting Test (WCST) is the classic measure of set-shifting and cognitive flexibility, functions compromised by frontal lobe damage (Companion to Psychiatric Studies). In the standard version four target cards (one red triangle, two green stars, three yellow crosses, four blue circles) are laid out, and the patient sorts a deck of 128 response cards under them by an unstated rule (colour, form or number), learning the rule only from the examiner's right/wrong feedback. After ten consecutive correct sorts the rule is silently changed and the patient must shift to the new principle (Companion to Psychiatric Studies). Performance is scored as the number of categories achieved and, critically, the percentage of *perseverative errors*, the hallmark of frontal dysfunction, where the patient keeps applying the old rule after it has stopped working. Nelson's modified WCST uses 48 rather than 128 cards to reduce the distress of continuous negative feedback. Schizophrenia patients perform poorly, with reduced dorsolateral prefrontal activation on imaging during the task (Tasman 2015).

HOLD THIS

The Wisconsin Card Sorting Test is the signature test of set-shifting, and perseverative errors are its frontal marker. It is not a memory test - the patient keeps applying a rule after it has stopped working.

7.6 The Stroop test: response inhibition and interference

Naming the ink, not the word. The **stroop** test measures response inhibition and the ability to suppress a prepotent, automatic response, an executive function anchored in frontal control (Companion to Psychiatric Studies). The patient must name the ink colour of a colour word while the word itself spells a different colour (for example the word printed in green ink); reading the word is automatic and must be inhibited to name the ink, so the *interference* condition is slower and more error-prone than neutral naming. The size of this **stroop** interference effect indexes the integrity of inhibitory control. The paradigm generalises: the *emotional Stroop*, in which emotionally salient words slow colour-naming, is widely used in anxiety research.

7.7 The Trail Making Test: attention and set-shifting in two parts

Part A speed, Part B shifting. The **trail making** test requires rapid and efficient integration of attention, visual scanning and cognitive sequencing (Kaplan & Sadock 2024). It has two parts. *Part A* asks the patient to connect numbered circles (1-2-3...) in order as fast as possible, indexing visual attention, scanning and psychomotor speed. *Part B* requires alternating between numbers and letters (1-A-2-B-3-C...), adding a set-shifting and working-memory load to the same visuomotor task; the B-minus-A difference isolates the executive shifting cost from simple speed. A markedly prolonged or failed Part B is a sensitive, quick sign of executive impairment.

7.8 Verbal fluency and the Frontal Assessment Battery

Generativity and a bedside frontal screen. *Verbal fluency* tests measure the capacity to self-generate words to a rule against the clock, a frontally mediated generative function (Companion to Psychiatric Studies). *Phonemic (letter) fluency*, also called the Controlled Oral Word Association Test (COWAT), asks for as many words as possible beginning with F, A and S, sixty seconds per letter; *semantic (category) fluency* asks for exemplars of a category such as animals. Impaired letter fluency follows left or bilateral frontal damage. The *Frontal Assessment Battery* (FAB), the broader bedside frontal lobe test battery, is a short six-item screen (conceptualisation and similarities, lexical/verbal fluency, motor programming via the Luria hand sequence, conflicting instructions, a go/no-go for inhibitory control, and prehension behaviour) scored out of a maximum of 18, with lower scores indicating greater frontal dysfunction; it is sensitive to frontal lobe damage and useful where a full battery is impractical (Clinical Methods in Psychiatry AIIMS 2024).

EXECUTIVE TEST	CORE PROCESS ISOLATED	KEY SCORE
Wisconsin Card Sorting Test	**Set-shifting; perseveration**	Categories achieved; % perseverative errors
Stroop test	**Response inhibition of a prepotent response**	Interference effect (time/errors)
Trail Making Test A and B	**Attention/speed (A); set-shifting (B)**	Time to complete; B minus A
Verbal fluency (COWAT)	**Generativity/self-activation**	Words in 60 seconds (F, A, S; or a category)
Frontal Assessment Battery	**Global frontal/executive screen**	Total out of 18

The frontal/executive tests, each mapped to the one process it best isolates and its scoring currency.

128	18	0.0-1.0
WCST RESPONSE CARDS (NELSON: 48)	FAB MAXIMUM (LOWER IS WORSE)	HALSTEAD IMPAIRMENT INDEX (HIGHER IS WORSE)

MNEMONIC

"SWIFT" frontal tests: Stroop, Wisconsin, Interference, Fluency, Trails.

Five executive tests to name: **S**troop (inhibition), **W**isconsin card sort (set-shifting/perseveration), **I**nterference is what both Stroop and the emotional Stroop measure, **F**luency (verbal/COWAT, plus the FAB), and **T**rails A and B. If asked for one bedside frontal test, say FAB (out of 18); if asked for the signature perseveration test, say Wisconsin.

7.9 The Bender Gestalt test: visuoconstruction and an organicity screen

Copying nine designs. The **bender** Gestalt test (the Bender Visual-Motor Gestalt Test, Lauretta Bender) asks the patient to copy a set of nine geometric designs, sampling visuoconstruction and visuomotor integration (Clinical Methods in Psychiatry AIIMS 2024). Distortions, rotations, perseveration and integration failures in the reproductions are read as soft signs of organic (especially parietal and constructional) impairment, so historically it served as a quick *organicity screen*; it is also used as a low-stress opening task to build rapport before more demanding testing.

A recall administration (drawing the designs from memory) adds a visual-memory element. In modern practice it is a screen and a projective adjunct, not a stand-alone diagnostic instrument.

7.10 Memory testing: the Wechsler Memory Scale

The reference memory battery. The **neuropsychological** assessment of memory is anchored by the Wechsler Memory Scale (WMS), a comprehensive set of subtests measuring attention, encoding, retrieval and recognition of both verbal and visual material, with immediate recall and delayed retention and excellent age-stratified norms up to about age 90 (Kaplan & Sadock 2024). It was co-normed with the Wechsler Adult Intelligence Scale so that memory can be compared directly against intellectual level, which is how a disproportionate memory deficit (as in an amnestic syndrome or early dementia) is demonstrated. Complementary list-learning tests (the California Verbal Learning Test, the Rey Auditory Verbal Learning Test, the Hopkins Verbal Learning Test) dissect encoding versus retrieval, and the Rey-Osterrieth Complex Figure tests non-verbal (visual) memory and construction.

7.11 Clinical uses and Indian batteries

What the referral actually asks. Neuropsychological testing is requested for five broad purposes (Kaplan & Sadock 2024; Clinical Methods in Psychiatry AIIMS 2024): the *dementia work-up* (detecting early impairment, profiling the deficit, and distinguishing dementia from pseudodementia and from normal ageing); *traumatic brain injury* (documenting deficits, guiding return-to-work and medicolegal opinion); *lesion localisation* (a profile of preserved and impaired functions points to frontal, temporal, parietal or lateralised pathology, complementing imaging); *capacity assessment* (financial, testamentary and treatment-decision capacity in the elderly and the brain-injured); and *rehabilitation* (baseline profiling and serial re-testing to track recovery or decline, which is why parallel-form and repeatable batteries exist). A key cautionary principle: because a long battery yields many scores, some low scores occur even in healthy people, so a diagnosis of impairment rests on a *pattern* consistent with a known condition, interpreted against age and education norms, not on isolated abnormal scores (Kaplan & Sadock 2024).

INDIA

Western neuropsychological tests must be adapted and re-normed before use here, and three indigenous batteries are examinable. The *PGI Battery of Brain Dysfunction* (PGI-BBD; Pershad and Verma 1990) gives a global organicity score and comprises five subscales: the PGI Memory Scale, the Bhatia Short Battery, a Verbal Adult Intelligence Scale, the Nahor-Benson test of perceptual acuity, and the Bender Visual Motor Gestalt Test. The *NIMHANS Neuropsychology Battery* (Rao, Subbakrishna and Gopukumar 2004) is a comprehensive, domain-wise Indian battery. The *AIIMS Comprehensive Neuropsychological Battery in Hindi* (Gupta et al 2000) applies **luria**-Nebraska principles with ten basic scales plus secondary scales. The *PGI Memory Scale* is the workhorse memory instrument in Indian practice.

CLINICAL ANCHOR

A 68-year-old man referred for capacity after a stroke might show, on a flexible battery: MMSE 23/30, FAB 9/18, Trail Making Test B unable to complete, and perseverative errors on the Wisconsin Card Sorting Test (a pattern drawn from a real medicolegal report structure). Read together this is a dysexecutive, frontally weighted profile with preserved gross orientation, exactly the picture that supports impaired financial capacity while a bare MMSE would have under-called it. This is why executive tests are added when capacity is the question.

COMMON TRAP

Do not equate the Halstead *Impairment* Index (0.0 to 1.0, proportion of core tests in the brain-damaged range) with a fluency or FAB *score*, and do not call the Wisconsin a memory test: it is set-shifting. Also remember the direction of scoring differs: on the FAB a *lower* score is worse, whereas a *higher* Halstead Impairment Index is worse. And screening tests (MMSE, Bender Gestalt) are not interchangeable with a full neuropsychological battery; they under-call deficits in the educated and over-call them in the poorly schooled.

GOOD TO REMEMBER

- **Two approaches:** fixed (standard) battery (uniform, comprehensive, cannot miss the unexpected but long) versus flexible hypothesis-driven/process approach (Luria, Boston Process Approach of Edith Kaplan; efficient but can miss the unexpected).
- **Halstead-Reitan battery (Halstead 1947; Reitan):** measures presence, severity and lateralisation of brain damage; scored via the *Halstead Impairment Index* (0.0 to 1.0, proportion of core tests in the impaired range). Named components: Category Test, Tactual Performance Test.
- **Category Test:** abstraction/concept formation from feedback; one of the most sensitive single measures of general brain dysfunction in the Halstead-Reitan battery.
- **Tactual Performance Test:** blindfolded form-board placement by touch; scores tactile problem-solving plus incidental memory and localisation.
- **Luria-Nebraska Neuropsychological Battery (Golden, from A. R. Luria):** measures brain dysfunction across motor, tactile, rhythm, speech, reading, writing, arithmetic, memory and intellectual clinical scales; standardised quantitative scores on each scale.
- **Wisconsin Card Sorting Test:** measures set-shifting and cognitive flexibility; 128 cards sorted to an unstated shifting rule; scored as categories achieved and percentage of *perseverative errors* (frontal marker). Nelson modification uses 48 cards.
- **Stroop test (Stroop 1935):** measures response inhibition of a prepotent response; scored as the interference effect (extra time/errors when naming ink colour of an incongruent colour word).
- **Trail Making Test A and B:** measures attention, scanning and psychomotor speed (A) and set-shifting/working memory (B); scored as time to complete, with B minus A isolating the executive shifting cost.
- **Verbal fluency (COWAT):** measures generativity/self-activation; scored as number of words in 60 seconds to letters F, A, S (phonemic) or to a category such as animals (semantic).
- **Frontal Assessment Battery (FAB):** measures global frontal/executive function at the bedside; six subtests; scored out of a maximum of 18 (lower is worse).
- **Bender Gestalt test (Lauretta Bender):** measures visuoconstruction/visuomotor integration; scored by distortions, rotations, integration failures in copying nine designs; classic organicity screen and rapport-builder.
- **Wechsler Memory Scale (WMS):** measures attention, encoding, retrieval and recognition of verbal and visual material, immediate and delayed; age-stratified index scores, co-normed with the WAIS for direct comparison against IQ.
- **Five domains sampled:** attention, memory, language, visuospatial function, executive function.
- **Clinical uses:** dementia work-up, traumatic brain injury, lesion localisation, capacity assessment, rehabilitation (with serial/parallel-form re-testing).
- **Indian batteries:** PGI Battery of Brain Dysfunction (Pershad and Verma 1990; global organicity score, five subscales); NIMHANS Neuropsychology Battery (Rao et al 2004); AIIMS Comprehensive Neuropsychological Battery in Hindi (Gupta et al 2000; Luria-Nebraska principles).
- **Interpretation rule:** diagnose impairment on a *pattern* consistent with a known condition against age/education norms, never on isolated low scores.

8 · Adaptive behaviour and developmental scales

Intelligence testing tells only half the story of a child's functioning. The other half is **adaptive behaviour**: the conceptual, social and practical skills a person actually deploys in everyday life. Since DSM-5, adaptive functioning sits alongside measured IQ as a co-equal, indeed *defining*, axis of intellectual disability, and severity is graded by the adaptive domains rather than by an IQ band alone (Kaplan & Sadock 2024). A parallel family of **developmental scales** extends the same

logic downward to infants and preschoolers who are too young for a formal IQ test: they yield a developmental quotient by comparing observed milestones against age norms. This topic is a high-yield catalogue for Paper I: examiners want author, construct, and scoring for each instrument.

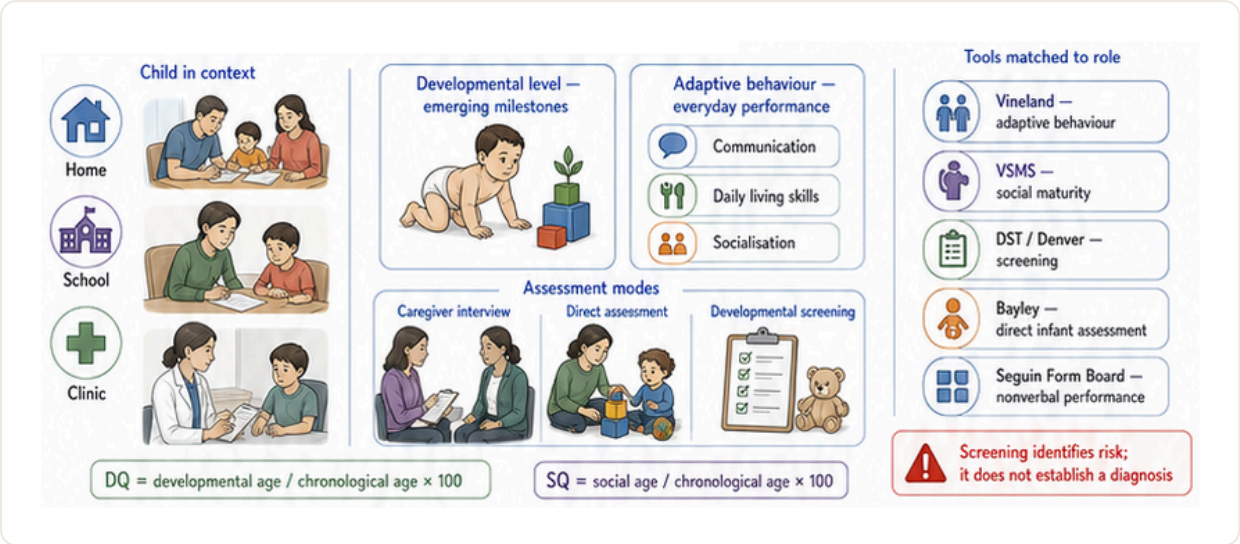


Fig 6.12 Adaptive behaviour and developmental assessment.

Two derived scores anchor the whole area. A **social quotient (SQ)** is social age divided by chronological age times 100, exactly parallel to the classic ratio IQ (mental age over chronological age). A **developmental quotient (DQ)** is developmental age over chronological age times 100. Both read like an IQ: 100 is average, and a score well below expectation flags delay. Note the required British and American spellings both appear in the literature: "adaptive behaviour" (Shorter Oxford, IPS) and "adaptive behavior" (the Vineland's own American title).

8.1 Adaptive behaviour as a construct

Definition. Adaptive behaviour is the person's ability to meet the responsibilities of social, personal, occupational and interpersonal life appropriate to their age, sociocultural setting and education. It is operationalised across three broad clusters.

Conceptual skills

Language, literacy, money, time, number and self-direction.

Social skills

Interpersonal skills, social responsibility, following rules, gullibility, avoiding victimisation.

Practical skills

Activities of daily living, occupational skills, healthcare, travel, safety and use of money in the real world.

CLINICAL ANCHOR

A diagnosis of intellectual disability requires a deficit in *both* general intellectual functioning *and* adaptive behaviour, with onset in the developmental period (DSM-5). An IQ below 70 alone does not make the diagnosis; equally, IQ near 70 with grossly deficient adaptive skills still counts. Under DSM-5 the severity label (mild to profound) is set by the adaptive domains, not the IQ number.

8.2 Vineland Adaptive Behavior Scales

The vineland (VABS). The modern flagship of adaptive assessment, now in its third edition (Vineland-3, Sparrow, Cicchetti and Saulnier). It is a caregiver or teacher informant instrument, age-normed from birth into late adult life (Kaplan & Sadock 2024).

Format

Semi-structured caregiver interview or rating form; self-report, parent and teacher versions exist.

Domains scored

Four adaptive domains: communication, daily living skills, socialisation, and motor skills (Shorter Oxford, Table 17.6), rolling up to an Adaptive Behavior Composite.

Extra domain

An optional maladaptive behaviour index captures internalising and externalising problems.

Clinical use

Diagnosing and grading intellectual disability, autism spectrum disorder, and tracking developmental progress over time.

> **PEARL**
>
> The vineland is one of the few instruments that spans birth to roughly age 90, which is why it is the reference adaptive scale in both child and adult intellectual-disability work. It is informant-based, so it can be completed even when the patient cannot be tested directly.

8.3 Vineland Social Maturity Scale (VSMS)

The vsms. The direct ancestor of the vineland, devised by Edgar Doll (the original Vineland Social Maturity Scale). It is the Indian workhorse: an informant scale that yields a **social age (SA)** and, from it, a **social quotient (SQ)**. An Indian adaptation (Malin) is a recognised instrument for issuing disability certificates for persons with intellectual disability in India (Clinical Methods in Psychiatry, AIIMS 2024).

Author

Edgar A. Doll (Vineland Training School, New Jersey).

What it measures

Social maturity across areas such as self-help (general, eating, dressing), self-direction, occupation, communication, locomotion and socialisation.

Scoring

Items credited by informant report give a social age; SQ = social age / chronological age times 100.

> **INDIA**
>
> The vsms is heavily used in Indian practice for the disability-certification workup, often paired with a performance IQ test. A worked medico-legal example from the AIIMS Clinical Methods text describes a patient with a mental age of about three years and a social quotient of 20 on VSMS, used to support a finding of incapacity to manage her person and property (AIIMS 2024).

8.4 The developmental screening test (DST, Bharat Raj)

The developmental screening test. The DST is an Indian instrument developed by J. Bharat Raj (NIMHANS). It is a caregiver-report screen that plots achieved milestones against age to yield a developmental age, and from it a developmental quotient. It is popular in Indian child-psychiatry and developmental-paediatric clinics because it is quick, informant-based and locally normed.

Author

J. Bharat Raj (Indian instrument).

What it measures

Overall development from infancy through early childhood, screening for developmental delay.

Scoring

Yields a developmental age; developmental quotient (DQ) = developmental age / chronological age times 100.

> **COMMON TRAP**
>
> Do not confuse the two "DST"s. In this topic DST is the developmental screening test (Bharat Raj). Elsewhere in psychiatry DST means the dexamethasone suppression test, a neuroendocrine probe of the HPA axis. Read the context.

8.5 Denver Developmental Screening Test

The denver (DDST). The most widely known international developmental screen (Frankenburg and Dodds). It screens, rather than diagnoses, sorting children into normal, questionable or abnormal so that delayed children are referred onward.

What it measures

Four sectors: gross motor, fine motor-adaptive, language, and personal-social development.

Age range

Birth to about six and a half years (Shorter Oxford; Indian developmental-milestone charts are modelled on the DDST sectors).

Scoring

Each item is placed as pass, fail or refusal against the age at which most children achieve it; a pattern of delays flags an abnormal screen for further assessment.

8.6 Bayley Scales of Infant Development

The bayley. The gold-standard directly administered developmental assessment for infants and toddlers (Nancy Bayley; now the Bayley Scales of Infant and Toddler Development, currently Bayley-4). Unlike informant screens, a trained assessor elicits and scores the child's own responses (Kaplan & Sadock 2024).

What it measures

Cognitive, language, motor, social-emotional and adaptive-behaviour scales.

Age range

Approximately 16 days to 42 months (Bayley-4, Kaplan & Sadock 2024).

Scoring

Standard tasks scored on mental, motor and behaviour scales, compared with norms; comprehensive developmental quotients / composite indices are derived.

PEARL

Bayley is a performance-based assessment, not a screen: it is used when a rigorous, examiner-administered estimate of infant development is needed (early diagnosis, research, tracking preterm or at-risk infants).

8.7 Gesell Developmental Schedules

The gesell. Arnold Gesell's developmental schedules (Yale Child Study Center) were the foundational normative maps of infant development, and remain a byword for milestone-based assessment. Gesell's data underlie many later schedules.

What it measures

Developmental landmarks across four fields: motor, adaptive, language, and personal-social behaviour.

Age range

Roughly 8 weeks (4 weeks in some editions) to 3.5 years, by direct observation of responses to standard toys and situations (Kaplan & Sadock 2024).

Scoring

Observed behaviour is matched to normative milestones to give a developmental age and a developmental quotient.

A simplified derivative, the Gesell Drawing Test (GDT), asks the child to copy geometric forms of increasing difficulty and gives a rapid rough estimate of mental age; it is used in Indian practice as a quick performance measure (AIIMS 2024).

8.8 Seguin Form Board

The seguin form board. A classic nonverbal performance test (traced to Edouard Seguin, who pioneered educational methods for the intellectually disabled; the Seguin Form Board Test, SFBT). The child fits solid geometric blocks into matching recesses as fast as possible.

What it measures

Visuomotor speed, eye-hand coordination and nonverbal problem-solving; a culture-fair, language-free estimate of intelligence.

Best use

Young children and language-impaired, deaf, or non-verbal individuals, where verbal tests are invalid.

Scoring

Timed: the shortest (best) of three trials is converted, via norms, to an estimate of mental age.

CLINICAL ANCHOR

The seguin form board is the go-to quick nonverbal screen in an Indian intellectual-disability workup when language is a barrier, often alongside the vsms and a Bhatia or Raven's performance measure.

8.9 How DQ and SQ are derived and read

The shared arithmetic. Every ratio quotient in this area follows one template: an age equivalent (mental, social or developmental) is divided by the actual chronological age and multiplied by 100.

QUOTIENT	NUMERATOR	FORMULA	INSTRUMENTS
IQ (ratio)	Mental age	**MA / CA times 100**	Stanford-Binet, Binet-Kamat
Social quotient (SQ)	Social age	**SA / CA times 100**	vsms
Developmental quotient (DQ)	Developmental age	**DA / CA times 100**	dst, gesell, bayley

All three ratio quotients share the same age-over-age arithmetic; only the numerator (the kind of age) differs.

RULE **Every ratio quotient is an age-equivalent over chronological age, times 100.** Only the numerator changes: mental age gives IQ, social age gives SQ, developmental age gives DQ; 100 is average throughout.

Reading the score. A quotient of 100 is average. Because a young child's chronological age is small, a modest lag in age-equivalent produces a proportionally low quotient, so early delay shows up clearly. In intellectual disability, SQ and DQ track roughly with IQ and are used both to support the diagnosis and to grade severity when a full IQ test is impractical.

8.10 Choosing the right tool: screen vs assessment, informant vs performance

Two axes organise the catalogue. First, screen versus full assessment: DDST and DST are screens that sort children for referral, whereas bayley and the vineland are full assessments that quantify functioning. Second, informant-report versus direct performance: vsms, vineland, DST and DDST rely on caregiver report or observation, whereas bayley, gesell and the seguin form board require the child's own elicited performance.

INSTRUMENT	TYPE	SCORE YIELDED	AGE BAND
vineland (VABS-3)	Informant, full assessment	**Adaptive Behavior Composite (4 domains)**	Birth to ~90 y
vsms	Informant	**Social age, SQ**	Birth to adulthood
developmental screening test (dst)	Informant screen (India)	**Developmental age, DQ**	Infancy to early childhood
denver (DDST)	Observation screen	**Normal / questionable / abnormal**	Birth to ~6.5 y
bayley	Performance, full assessment	**Cognitive/motor/language indices, DQ**	~16 days to 42 mo
gesell	Observation schedule	**Developmental age, DQ**	~8 wk to 3.5 y
seguin form board	Nonverbal performance	**Mental age (timed)**	Young / language-impaired

A single decision grid: pick a screen to triage, a full assessment to quantify, and a nonverbal test when language cannot be used.

HOLD THIS

Adaptive behaviour is now a co-defining axis of intellectual disability, not a supplement. The VSMS gives a social quotient and is the Indian disability-certification workhorse; screens (DST, Denver) triage, full assessments (Bayley, Vineland) quantify.

MNEMONIC

"Very Very Direct Doctors Believe Good Seguin"

vineland, vsms, developmental screening test (dst), denver (DDST), bayley, gesell, seguin: the seven scales of this topic in a single string.

GOOD TO REMEMBER

- **Adaptive behaviour / adaptive behavior:** conceptual, social and practical everyday skills; a co-defining axis of intellectual disability alongside IQ (DSM-5). Both spellings are in use.
- **vineland (VABS-3):** Sparrow, Cicchetti and Saulnier. Measures adaptive functioning in four domains (communication, daily living skills, socialisation, motor skills) plus a maladaptive index. Informant/caregiver interview, birth to ~90 y; yields an Adaptive Behavior Composite.
- **vsms (Vineland Social Maturity Scale):** Edgar Doll. Measures social maturity (self-help, self-direction, occupation, communication, locomotion, socialisation). Scores social age, then SQ = SA / CA times 100. Indian disability-certification workhorse.
- **developmental screening test (dst):** J. Bharat Raj (Indian instrument). Screens overall development; scores a developmental age and DQ = DA / CA times 100.
- **denver (DDST):** Frankenburg and Dodds. Screens gross motor, fine motor-adaptive, language and personal-social sectors; birth to ~6.5 y; scores normal / questionable / abnormal.
- **bayley (Scales of Infant and Toddler Development):** Nancy Bayley. Examiner-administered; cognitive, language, motor, social-emotional and adaptive scales; ~16 days to 42 months; yields developmental indices / DQ.
- **gesell (Developmental Schedules):** Arnold Gesell. Direct observation of motor, adaptive, language and personal-social behaviour; ~8 weeks to 3.5 y; yields developmental age and DQ. Gesell Drawing Test (GDT) is the rapid drawing-copy derivative.
- **seguin (form board):** Edouard Seguin. Nonverbal, timed block-fitting test of visuomotor speed and nonverbal intelligence; for young or language-impaired individuals; best of three trials gives an estimated mental age.
- **Social quotient (SQ):** social age / chronological age times 100.
- **Developmental quotient (DQ):** developmental age / chronological age times 100. Both read like an IQ (100 = average).

9 · Symptom rating scales

A symptom **rating scale** is a standardised instrument that turns a clinical construct (depression, mania, psychosis, obsessions) into a number, so that severity can be quantified, tracked over time, and compared across patients and studies. This topic is a working catalogue organised *by clinical domain*, so that when the exam (or the ward) asks "which scale for this?" you can reach for the right one and say what it measures, who rates it, and roughly how it scores. The point of a rating scale is not diagnosis but the **measurement of severity and change**: it converts the impressionistic "the patient seems a bit better" into a defensible delta on a validated metric (Kaplan & Sadock 2024).

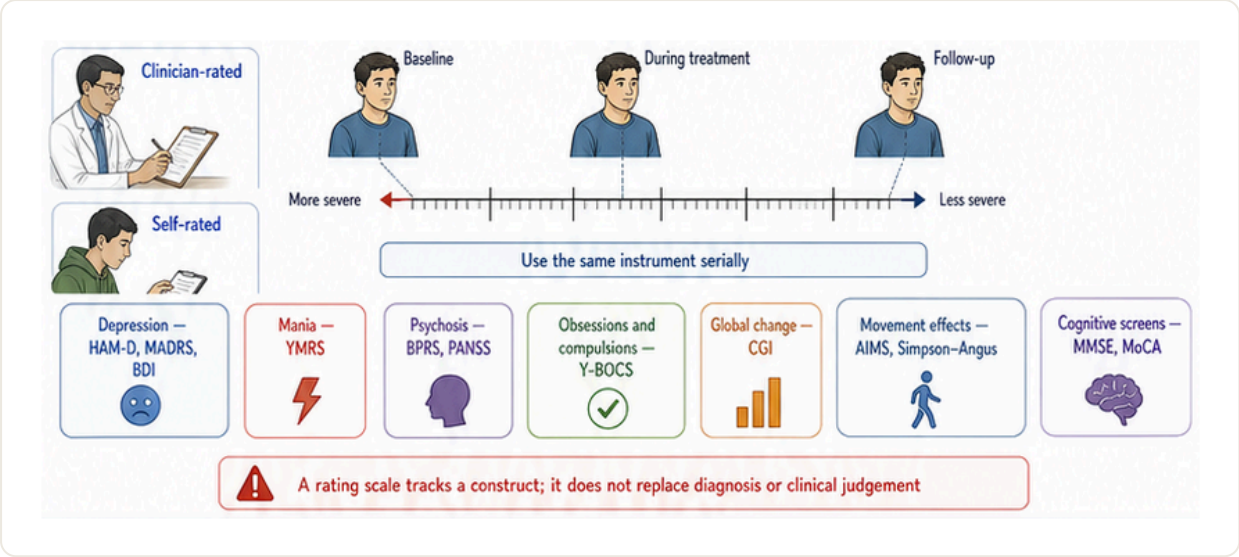


Fig 6.13 Rating scales: measure severity and change.

The single most examined distinction here is **clinician-rated** versus **self-rated**. A clinician-rated (observer-rated) scale is scored by a trained rater from a clinical interview and observation; a self-rated scale is a questionnaire the patient completes. Examiners also love the exact "signature" facts of the flagship scales: item counts, the number of items in the two Hamilton depression forms, and which scales are the standard primary outcome measures in drug trials. A fuller rating-scale catalogue (including screening, functional, quality-of-life and paediatric instruments) is developed in a Paper III chapter; here we stay with the core clinician-rated symptom scales by disorder.

9.1 What a rating scale is for: severity, response, remission

Three clinical jobs. A symptom rating scale is used to (1) quantify baseline severity, (2) track change with treatment, and (3) define trial endpoints. In trials, a fixed cut in the total score defines *response* (conventionally a 50 percent reduction from baseline) and a low absolute score defines *remission* (Kaplan & Sadock 2024). This is why the same scales that clinicians use to monitor a patient are also the primary outcome measures of the randomised controlled trials that licensed the drugs.

Scale versus diagnosis. A rating scale measures a construct on a continuum; it does not, by itself, make a categorical diagnosis. A cut-off can be applied to a continuous scale to flag likely caseness (for example an MMSE below 24 suggesting dementia, or a HAM-D above a threshold suggesting a depressive episode), but the diagnosis remains a clinical, criterion-based judgement (Kaplan & Sadock 2024).

9.2 Clinician-rated versus self-rated

Clinician-rated (observer-rated)

A trained clinician scores the item from a semi-structured interview plus observation. Strength: robust where insight is poor (mania, psychosis, cognitive disorders) and it captures observed signs. Cost: rater time, and the need for training to keep inter-rater reliability high. Examples: HAM-D, MADRS, YMRS, BPRS, PANSS, Y-BOCS.

Self-rated (self-report)

The patient completes a questionnaire; quick, cheap, captures the inner experience directly. Cost: depends on insight, literacy and honesty, and is vulnerable to response bias. Examples: Beck Depression Inventory (BDI), PHQ-9, GAD-7.

CLINICAL ANCHOR

The choice tracks insight. For a manic or floridly psychotic patient a self-rated scale is nearly useless (the patient does not experience the elevated mood or the delusion as pathological), so the clinician-rated YMRS or PANSS is used. For an ambulant patient with depression, a self-rated BDI or PHQ-9 can be posted to the waiting room and is a reasonable severity screen; but the trial-grade severity metric remains the clinician-rated HAM-D or MADRS.

RULE **Where insight is poor, use a clinician-rated scale.** Mania and psychosis need observer-rated instruments (YMRS, PANSS) because the patient does not experience the state as pathological.

9.3 Depression: HAM-D, MADRS and the Beck Depression Inventory

Hamilton Depression Rating Scale. The **hamilton** Depression Rating Scale (**ham-d**, also HDRS; Hamilton 1960) is the historic gold-standard clinician-rated depression scale and, for six decades, the most common primary outcome in antidepressant trials. The original published form has 17 items; a widely used extended form adds items to make 21 (Tasman describes it as a 17 to 21 item clinician scale with a strong focus on somatic and neurovegetative symptoms). It is scored by the clinician from interview; higher total means more severe depression. Its criticised feature is exactly that somatic loading, which can inflate scores in the physically ill.

Montgomery-Asberg Depression Rating Scale. The MADRS (**montgomery** and Asberg 1979) is a 10-item clinician-rated depression scale, explicitly designed to be *sensitive to change* and therefore favoured as a trial outcome; it is lighter on somatic items than the HAM-D, which makes it useful when physical illness would otherwise confound a depression score. Each item is rated 0 to 6.

Beck Depression Inventory. For contrast, the Beck Depression Inventory (BDI; Beck, current BDI-II 1996) is the classic *self-rated* depression questionnaire: 21 self-report items, quick, and weighted toward the cognitive symptoms of depression (guilt, worthlessness, pessimism). It is a severity and screening tool, not a diagnostic instrument, and shows the self-rated trade-off: convenient and patient-centred, but dependent on insight and honesty.

COMMON TRAP

Do not conflate the HAM-D and the BDI as interchangeable "depression scales". They differ on the axis examiners test: the HAM-D and MADRS are **clinician-rated** (the standard trial outcome measures), the BDI is **self-rated**. And the two Hamilton forms are 17 and 21 items, not "the 17-item Hamilton" alone.

9.4 Mania: the Young Mania Rating Scale

YMRS. The Young Mania Rating Scale (**ymrs**; Young, Biggs, Ziegler and Meyer 1978) is the standard clinician-rated mania severity scale and the usual primary outcome in acute-mania

trials. It has 11 items; seven items are scored 0 to 4 and four items (irritability, speech, thought content, and disruptive-aggressive behaviour) are given double weight and scored 0 to 8, so that harder-to-rate but clinically salient items are not lost. Because manic patients characteristically lack insight, a self-rated mania scale is unreliable, which is precisely why the observer-rated YMRS is the field standard.

9.5 Psychosis: BPRS and PANSS

Brief Psychiatric Rating Scale. The **bprs** (Overall and Gorham 1962) is one of the oldest clinician-rated scales for overall psychiatric symptom severity in psychotic and severe illness. The classic form has 18 items, each rated 1 to 7, covering a broad spread (anxiety, depression, hostility, hallucinatory behaviour, unusual thought content, blunted affect). It is quick and remains widely used to track global change, but it assesses positive and disorganised symptoms far better than it assesses negative symptoms.

Positive and Negative Syndrome Scale. The **panss** (Kay, Fiszbein and Opler 1987) is the modern flagship clinician-rated schizophrenia scale and the standard primary outcome in antipsychotic trials. It has 30 items, each rated 1 to 7, structured into three subscales: a 7-item Positive scale, a 7-item Negative scale, and a 16-item General Psychopathology scale. Its virtue over the BPRS is the explicit, separately scored negative-symptom dimension, which matters because positive and negative symptoms respond differently to treatment.

FEATURE	BPRS	PANSS
Items	18	**30 (7 positive, 7 negative, 16 general)**
Item anchor	1 to 7	1 to 7
Negative symptoms	**poorly captured**	separate 7-item negative subscale
Rating	clinician-rated	clinician-rated
Typical role	quick global severity	**standard antipsychotic-trial outcome**

BPRS versus PANSS: both clinician-rated and anchored 1 to 7, but the PANSS is larger and scores the negative syndrome on its own subscale, which is why it displaced the BPRS as the trial standard in schizophrenia.

17 / 21 HAM-D ITEM FORMS	**11** YMRS ITEMS (4 DOUBLE-WEIGHTED)	**30** PANSS ITEMS (7+7+16)	**0-40** Y-BOCS TOTAL (10 ITEMS)

9.6 Negative and positive symptoms: SANS and SAPS

The Andreasen pair. Before the PANSS folded both dimensions into one instrument, Nancy Andreasen built two dedicated clinician-rated scales for schizophrenia (Andreasen). The **rating scale** pair is the SANS (Scale for the Assessment of Negative Symptoms) and the SAPS (Scale for the Assessment of Positive Symptoms). The SANS rates affective flattening, alogia, avolition-apathy, anhedonia-asociality, and attentional impairment; the SAPS rates hallucinations,

delusions, bizarre behaviour, and formal thought disorder. They remain the reference standard specifically for detailed negative-symptom research.

9.7 Obsessive-compulsive disorder: the Y-BOCS

Yale-Brown Obsessive Compulsive Scale. The **y-bocs** (Goodman and colleagues 1989) is the standard clinician-rated OCD severity scale and the primary outcome in OCD trials. It has 10 items (five rating obsessions, five rating compulsions), each scored 0 to 4, giving a total of 0 to 40. Crucially it rates the *severity* of obsessions and compulsions (time occupied, interference, distress, resistance, control) independently of their *content*, which is captured separately on a symptom checklist. That form-over-content design is what makes it usable across the very different symptom pictures of OCD.

9.8 The global scale and the anxiety scale: CGI and HAM-A

Clinical Global Impression. The CGI (Clinical Global Impression; Guy 1976, from the NIMH battery) is the great pragmatic all-rounder: a clinician-rated global judgement independent of any single disorder. It has two brief parts, CGI-Severity (how ill is the patient now, rated 1 = normal to 7 = among the most extremely ill) and CGI-Improvement (how much has the patient changed since baseline, 1 = very much improved to 7 = very much worse). Its simplicity is its strength: it is applied across every disorder and is a near-universal secondary outcome in trials.

Hamilton Anxiety Rating Scale. The HAM-A (Hamilton 1959) is the standard clinician-rated anxiety severity scale, with 14 items covering psychic and somatic anxiety, each rated 0 to 4. It is the anxiety counterpart to the HAM-D and, like it, is a common trial outcome. Its self-rated primary-care counterpart is the GAD-7.

9.9 Drug-induced movement disorders: AIMS and Simpson-Angus

AIMS. The Abnormal Involuntary Movement Scale (AIMS; NIMH, Guy 1976) is the standard clinician-rated scale for tardive dyskinesia in patients on antipsychotics. It has 12 items, each rated 0 to 4: ten cover the abnormal movements themselves (by body region, plus global severity), and two concern dental status that can mimic dyskinesia. It requires a brief structured motor examination, not just an interview. Mild dyskinetic movements in two body areas, or moderate movements in one, on adequate neuroleptic exposure, suggest tardive dyskinesia (Kaplan & Sadock 2024).

Simpson-Angus Scale. The Simpson-Angus Scale (Simpson and Angus 1970) is the clinician-rated scale for antipsychotic-induced *parkinsonism* and other extrapyramidal side effects. It has 10 items rated 0 to 4, strongly weighted to rigidity, plus one akathisia item; the score is reported as the mean of the items, with about 0.3 as the upper limit of normal, and it correlates with antipsychotic dose (Kaplan & Sadock 2024). Akathisia specifically is more often rated on the dedicated Barnes Akathisia Rating Scale.

PEARL

Remember the movement scales as a triad: AIMS for tardive dyskinesia, Simpson-Angus for drug-induced parkinsonism, and the Barnes Akathisia Rating Scale for akathisia. All three are clinician-rated and all three need you to *examine* the patient, not just ask questions.

9.10 Cognitive screens: MMSE and MoCA

Mini-Mental State Examination. The MMSE (Folstein, Folstein and McHugh 1975) is the classic clinician-administered cognitive screen, scored out of 30, sampling orientation, registration, attention and calculation, recall, language and construction. A score below 24 is the traditional cut suggesting cognitive impairment (Kaplan & Sadock 2024), though education and age shift the threshold. It is a screen for global cognitive impairment, not a diagnostic or a detailed neuropsychological test.

Montreal Cognitive Assessment. The MoCA (Nasreddine and colleagues 2005) is also scored out of 30 but is more sensitive than the MMSE to *mild* cognitive impairment and to executive and visuospatial deficits, because it adds trail-making, clock-drawing, abstraction and more demanding delayed recall. A one-point education adjustment is added for fewer than 12 years of schooling. It is now often preferred where early or subtle impairment is the question.

INDIA

The MMSE and MoCA are language and literacy loaded, so raw Western cut-offs misclassify illiterate or non-English-speaking Indian patients. Validated Indian and vernacular adaptations are used instead, such as the Hindi Mental State Examination (HMSE) and other locally normed cognitive screens; the Addenbrooke's Cognitive Examination (ACE-III) also has Indian-language versions. Always screen cognition in a language the patient is literate in, and apply local norms rather than the standard cut of 24 or 26.

HOLD THIS

A rating scale measures severity and change, not diagnosis. Know the flagship per domain: depression HAM-D/MADRS, mania YMRS, psychosis PANSS, OCD Y-BOCS, cognition MMSE/MoCA (both out of 30, MMSE cut below 24).

MNEMONIC

"Doctors Manage Patients' Obsessive Complaints" → Depression, Mania, Psychosis, OCD, plus the Cognitive and movement screens

Walk the domains in order and name the flagship clinician-rated scale for each: Depression (HAM-D, MADRS), Mania (YMRS), Psychosis (BPRS, PANSS), OCD (Y-BOCS), then the add-ons: global (CGI), anxiety (HAM-A), movement (AIMS, Simpson-Angus), cognition (MMSE, MoCA). Self-rated contrast: BDI for depression.

GOOD TO REMEMBER

- **Clinician-rated vs self-rated:** clinician-rated (HAM-D, MADRS, YMRS, BPRS, PANSS, Y-BOCS) is scored by a trained rater and is robust when insight is poor; self-rated (BDI, PHQ-9, GAD-7) is a patient questionnaire, quick but insight-dependent.
- **HAM-D / HDRS (Hamilton 1960):** rates depression severity; clinician-rated; 17-item and extended 21-item forms; historic trial gold standard, somatically loaded.
- **MADRS (Montgomery & Asberg 1979):** rates depression severity, designed to be sensitive to change; clinician-rated; 10 items each 0 to 6; less somatic than HAM-D.
- **Beck Depression Inventory (Beck; BDI-II 1996):** rates depression severity; self-rated; 21 items; cognitively weighted; screening not diagnostic.
- **YMRS (Young et al 1978):** rates mania severity; clinician-rated; 11 items (four double-weighted); standard acute-mania trial outcome.
- **BPRS (Overall & Gorham 1962):** rates overall psychotic/psychiatric severity; clinician-rated; 18 items each 1 to 7; weak on negative symptoms.
- **PANSS (Kay, Fiszbein & Opler 1987):** rates schizophrenia symptoms; clinician-rated; 30 items each 1 to 7; positive (7), negative (7), general (16) subscales; standard antipsychotic-trial outcome.
- **SANS / SAPS (Andreasen):** rate negative and positive symptoms of schizophrenia respectively; clinician-rated; reference standard for negative-symptom research.
- **Y-BOCS (Goodman et al 1989):** rates OCD severity; clinician-rated; 10 items (5 obsessions, 5 compulsions) each 0 to 4, total 0 to 40; rates severity independent of content.
- **CGI (Guy 1976, NIMH):** global severity and improvement; clinician-rated; CGI-Severity and CGI-Improvement each 1 to 7; disorder-independent, near-universal trial secondary outcome.
- **HAM-A (Hamilton 1959):** rates anxiety severity; clinician-rated; 14 items each 0 to 4; psychic and somatic anxiety; self-rated counterpart GAD-7.
- **AIMS (NIMH, Guy 1976):** rates tardive dyskinesia; clinician-rated with motor exam; 12 items each 0 to 4.
- **Simpson-Angus (Simpson & Angus 1970):** rates antipsychotic-induced parkinsonism/EPS; clinician-rated exam; 10 items each 0 to 4, reported as item mean.
- **Barnes Akathisia Rating Scale:** rates akathisia; clinician-rated; completes the movement-scale triad with AIMS and Simpson-Angus.
- **MMSE (Folstein et al 1975):** screens global cognition; clinician-administered; scored out of 30; traditional impairment cut below 24.
- **MoCA (Nasreddine et al 2005):** screens cognition; clinician-administered; out of 30; more sensitive to mild cognitive impairment; +1 point if under 12 years of schooling.

10 · Indian test adaptations

Every imported Western test carries a hidden assumption: that the person taking it grew up inside the culture, language and schooling the norms were built on. In India that assumption fails, so the standard batteries were not merely translated but **adapted** and re-normed. This topic is the India-context marker for the whole assessment band. It is the single reliable place an examiner can drop a "name the Indian adaptation and who standardised it" question, and it recurs in the ID, disability-certification and neuropsychology sections. Teach each instrument as a catalogue entry: what Western parent it adapts, who built it, the language or population it serves, and where its Indian norms come from.

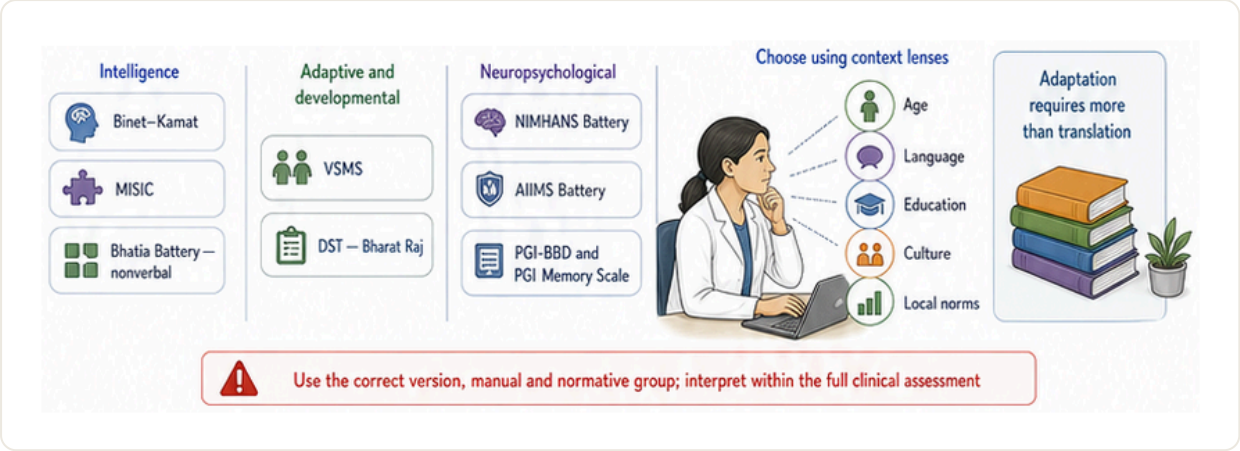


Fig 6.14 Indian psychological tests: match norms to context.

Why adaptation is not optional. Four forces make a foreign test invalid in an Indian testee, and each is a separable exam point. First, **norms**: a raw score only becomes an IQ or a percentile against a reference sample, and an American or British sample mis-scores an Indian child. Second, **language**: verbal items translated word-for-word lose difficulty gradation and cultural sense; Indian adaptations rebuild the verbal ladder in Kannada, Marathi, Hindi and other languages. Third, **cultural fairness**: item content (foods, festivals, idioms, pictures) must map onto the testee's world or it measures acculturation, not ability. Fourth, **literacy** and schooling: much of India is rural and non-literate, so performance (non-verbal) tests that do not depend on reading or writing become essential rather than optional (AIIMS Clinical Methods 2024).

INDIA

The through-line for the whole test band: for almost every Western instrument on this exam there is a locally standardised Indian counterpart, and the examiner wants the pair. Intelligence: Stanford-Binet becomes the **binet-kamat** test (BKT); WISC becomes **malin**'s Intelligence Scale for Indian Children (MISIC); Bhatia's Battery of Performance Tests of Intelligence serves illiterate and rural testees. Adaptive/developmental: the Vineland Social Maturity Scale gains an Indian adaptation with **indian norms**, and the Developmental Screening Test (DST) is India's own screener. Neuropsychology: the NIMHANS Neuropsychological Battery, the AIIMS Comprehensive Neuropsychological Battery, the PGI Battery of Brain Dysfunction (PGI-BBD) and the PGI Memory Scale are all Indian-normed.

10.1 Binet-Kamat Test (BKT): the Indian Stanford-Binet

What it adapts. The **binet-kamat** test (**bkt**) is V. V. Kamat's Indian adaptation of the Stanford-Binet (itself the Terman revision of the Binet-Simon scale). Kamat standardised it in the 1930s on Indian children, originally in Kannada and Marathi, giving India its first indigenous individually administered intelligence scale (AIIMS Clinical Methods 2024; also recorded as the Binet-Simon or Binet-Kamat test).

What it measures and how it scores. Like its parent it is a verbally loaded, age-graded scale that yields a mental age and, classically, a ratio IQ = (mental age / chronological age) x 100. Items are arranged by age level; testing runs from a basal age (all items passed) up to a ceiling age (all items failed), and mental age is summed across the ladder. It suits children and lower ability ranges and

is still used in some Indian centres, though it is verbal-heavy and therefore language and schooling dependent.

10.2 Malin's Intelligence Scale for Indian Children (MISIC): the Indian WISC

What it adapts. **misic** is **malin**'s Intelligence Scale for Indian Children, Arthur J. Malin's Indian adaptation of the Wechsler Intelligence Scale for Children (WISC). It is the workhorse individual IQ test for Indian children in clinical and disability settings (AIIMS Clinical Methods 2024).

What it measures and how it scores. It preserves the Wechsler architecture: a set of verbal subtests and a set of performance subtests, each yielding scaled scores that combine into a Verbal IQ, a Performance IQ and a Full-Scale IQ (deviation-IQ scoring). AIIMS Clinical Methods notes that its objective subtests, for example the arithmetic and digit-span items, are borrowed for bedside cognitive testing in adults too, which shows how embedded MISIC is in Indian practice.

10.3 Bhatia's Battery of Performance Tests of Intelligence: for illiterate and rural populations

What it adapts and why it matters. Bhatia's Battery of Performance Tests of Intelligence (C. M. Bhatia, 1955) is a purely non-verbal, performance-based intelligence test built specifically so that illiterate, poorly schooled and rural Indian testees can be assessed fairly, because it needs no reading or writing (AIIMS Clinical Methods 2024). It is India's canonical answer to the literacy problem.

What it measures and how it scores. It is administered as a set of performance subtests, classically the Koh's Block Design, the Alexander Pass-Along, the Pattern Drawing, the Immediate Memory (digit span) and the Picture Construction tests. Each is timed and scored, and the summed performance yields an intelligence estimate. Its non-verbal, culture-reduced format is exactly why it also survives as a sub-scale inside the PGI Battery of Brain Dysfunction (as the "Bhatia Short Battery").

RULE **For low-literacy or rural Indian testees, reach for a non-verbal performance test.** Bhatia's Battery, the Seguin Form Board and Raven's Matrices bypass the reading and language barrier that invalidates verbal-loaded scales.

10.4 Vineland Social Maturity Scale: Indian adaptation and Indian norms

What it adapts. The Vineland Social Maturity Scale (VSMS) is Doll's American measure of adaptive behaviour; its Indian adaptation with **indian norms** (A. J. Malin, Nagpur adaptation) is the standard Indian adaptive-behaviour instrument and is central to certifying intellectual disability in India (AIIMS Clinical Methods 2024).

What it measures and how it scores. It is an informant-based interview (parent or caregiver, not the child directly) covering everyday social competence across domains such as self-help, self-direction, occupation, communication, locomotion and socialisation. Scored items across age levels give a **social age**, which divided by chronological age and multiplied by 100 gives a **social quotient** (SQ). Because DSM-5 and modern ID definitions anchor severity to adaptive functioning rather than IQ alone, an adaptive measure like VSMS is now essential, not supplementary.

10.5 Developmental Screening Test (DST, Bharat Raj): India's developmental screener

What it is. The Developmental Screening Test (DST) is Jayanti Bharat Raj's Indian developmental screening instrument, built to give a quick developmental quotient in Indian infants and young children as an indigenous alternative to Western screeners like the Denver Developmental Screening Test.

What it measures and how it scores. It screens developmental attainments from early infancy through childhood, converting the pass pattern into a **developmental age** and a developmental quotient (developmental age / chronological age x 100). It is a screening tool, flagging children who need fuller assessment, not a diagnostic IQ test.

> **COMMON TRAP**
>
> Do not confuse the three quotient families that all look like "age over age times 100": intelligence gives an *IQ* (mental age, from BKT or MISIC), adaptive behaviour gives a *social quotient* (social age, from VSMS), and screening gives a *developmental quotient* (developmental age, from DST). Also, in exams "DST" almost always means the Developmental Screening Test here, not the Dexamethasone Suppression Test from the biology chapter: read the stem.

10.6 NIMHANS Neuropsychological Battery: the Indian normative neuropsychology battery

What it is. The **nimhans neuropsychological** battery (Rao, Subbakrishna and Gopukumar, 2004) is the Indian normative neuropsychology battery developed and standardised at NIMHANS, Bengaluru. The adult form comprises 19 neuropsychological tests, adapted largely from the Halstead-Reitan tradition, with Indian norms for ages 16 to 65 years (AIIMS Clinical Methods 2024).

What it measures and how it scores. It is modular: the clinician selects tests by referral question rather than running all 19. It samples attention and visual search, psychomotor speed and perseveration, working memory, executive and visuospatial planning, block design and object assembly, and verbal memory (its Rey Auditory Verbal Learning Test is a standard verbal-memory measure). There are companion versions: the NIMHANS Neuropsychological Battery for children (Kar et al., 2004, ages 5 to 15, probing frontal, parieto-occipital and temporal function) and the NIMHANS Neuropsychological Battery for Elderly (NNB-E, Tripathi et al., 2013). Each subtest is scored against the Indian norms; deficits are read for localisation and lateralisation.

10.7 AIIMS Comprehensive Neuropsychological Battery

What it is. The AIIMS Comprehensive Neuropsychological Battery in Hindi, adult form (Gupta et al., 2000), applies the principles of the Luria-Nebraska Neuropsychological Battery to an Indian, Hindi-medium population (AIIMS Clinical Methods 2024).

What it measures and how it scores. It contains 160 items organised into ten basic scales plus secondary scales spanning motor, tactile, visual, receptive and expressive speech, reading, writing, arithmetic, memory and intellectual processes, rolling up into left-hemisphere, right-hemisphere and total-score scales. It is used to detect lateralisation (right versus left lesion) and localisation of brain lesions. Indian norms cover ages 15 to 80 years; its length is its main limitation.

10.8 PGI Battery of Brain Dysfunction (PGI-BBD) and the PGI Memory Scale

What it is. The PGI Battery of Brain Dysfunction (Pershad and Verma, 1990) is the Chandigarh (PGIMER) battery for detecting and quantifying organic brain damage in Indian adults (AIIMS Clinical Methods 2024).

What it measures and how it scores. PGI-BBD combines five sub-scales: the PGI Memory Scale, the Bhatia Short Battery, the Verbal Adult Intelligence Scale, the Nahor-Benson test of perceptual acuity and the Bender Visual Motor Gestalt Test. It yields a global dysfunction score built from 19 variables, with norms for ages 20 to 59 years; a cut-off above 20 signifies organic brain damage, which is why it is heavily used in disability certification (for example in traumatic brain injury). The **PGI Memory Scale** is its embedded memory instrument and is also used standalone: it tests immediate and delayed recall across items such as paired and unpaired associations, logical memory and recognition, and its items (like digit span) are borrowed for bedside memory testing.

CLINICAL ANCHOR

The India disability-certification chain runs through these adaptations. For an intellectual-disability certificate you pair an Indian IQ test (MISIC or BKT) with the VSMS Indian adaptation for adaptive behaviour; for an organicity or head-injury certificate you reach for the PGI-BBD (cut-off above 20) or the NIMHANS Neuropsychological Battery. Knowing which instrument certifies what is the practical, and examinable, payoff of this whole topic.

10.9 The Indian adaptations at a glance

INDIAN TEST	ADAPTS / PARENT	LANGUAGE / POPULATION
Binet-Kamat Test (BKT), V. V. Kamat	**Stanford-Binet**	Kannada, Marathi; Indian children
MISIC, A. J. Malin	**Wechsler WISC**	Indian children; verbal + performance
Bhatia's Battery of Performance Tests, C. M. Bhatia (1955)	**performance/non-verbal intelligence**	**illiterate and rural populations**
VSMS Indian adaptation, A. J. Malin	**Vineland (Doll) adaptive behaviour**	informant-based; Indian norms; ID certification
Developmental Screening Test (DST), Bharat Raj	**developmental screening (cf. Denver DDST)**	Indian infants and young children
NIMHANS Neuropsychological Battery (Rao et al., 2004)	**Halstead-Reitan tradition**	Indian norms, ages 16 to 65
AIIMS Comprehensive Battery (Gupta et al., 2000)	**Luria-Nebraska**	Hindi; ages 15 to 80; 160 items
PGI-BBD and PGI Memory Scale (Pershad and Verma, 1990)	**organicity battery + memory scale**	Indian adults, ages 20 to 59

The India-context pairing table: each Western instrument on the exam has a locally standardised Indian counterpart, and the examiner wants the pair with its author and population.

HOLD THIS

For almost every Western test the examiner wants the Indian pair with its author. Stanford-Binet to Binet-Kamat (Kamat); WISC to MISIC (Malin); adaptive to VSMS Indian norms; organicity to the PGI-BBD (cut-off above 20) or the NIMHANS battery.

GOOD TO REMEMBER

- **Binet-Kamat Test (BKT):** V. V. Kamat's Indian adaptation of the Stanford-Binet; verbal, age-graded; yields mental age and ratio IQ; standardised in Kannada and Marathi for Indian children.
- **MISIC:** A. J. Malin's Intelligence Scale for Indian Children; adapts the Wechsler WISC; verbal and performance subtests giving Verbal, Performance and Full-Scale IQ; workhorse child IQ test in India.
- **Bhatia's Battery of Performance Tests of Intelligence:** C. M. Bhatia (1955); purely non-verbal performance battery (Koh's Block Design, Alexander Pass-Along, Pattern Drawing, Immediate Memory, Picture Construction) for illiterate and rural populations; timed subtests summed to an IQ estimate.
- **VSMS Indian adaptation:** A. J. Malin's Indian adaptation of the Vineland Social Maturity Scale with Indian norms; informant-based adaptive behaviour; social age gives a social quotient (SQ); used for ID certification.
- **Developmental Screening Test (DST):** Bharat Raj; Indian developmental screener for infants and young children; developmental age gives a developmental quotient; a screener, not a diagnostic IQ test.
- **NIMHANS Neuropsychological Battery:** Rao, Subbakrishna and Gopukumar (2004); Indian normative neuropsychology battery from NIMHANS; 19 adult tests from the Halstead-Reitan tradition; norms 16 to 65; modular, scored for localisation and lateralisation; child (Kar et al., 2004) and elderly (NNB-E, 2013) versions exist.
- **AIIMS Comprehensive Neuropsychological Battery:** Gupta et al. (2000); Hindi adult form on Luria-Nebraska principles; 160 items, ten basic scales; detects lateralisation and localisation; Indian norms ages 15 to 80.
- **PGI Battery of Brain Dysfunction (PGI-BBD):** Pershad and Verma (1990); five sub-scales (PGI Memory Scale, Bhatia Short Battery, Verbal Adult Intelligence Scale, Nahor-Benson, Bender-Gestalt); global score from 19 variables; norms 20 to 59; cut-off above 20 signifies organic brain damage; used for disability certification.
- **PGI Memory Scale:** Indian memory instrument (immediate and delayed recall, paired and unpaired associations, logical memory, recognition); used standalone and as the memory sub-scale of PGI-BBD.
- **Why adapt at all:** norms, language, cultural fairness, literacy; a foreign test's norms mis-score an Indian testee, so instruments are re-standardised, re-languaged and, for non-literate testees, made non-verbal.

Descriptive psychopathology

11 · Orientation: descriptive psychopathology and the domains of mental life

Before any diagnosis is named, the psychiatrist must be able to *describe* what is wrong with precision. That skill has a name and a lineage. **Descriptive psychopathology** is the objective, theory-free description of abnormal states of mind, limited to conscious experience and

observable behaviour, avoiding preconceived aetiological ideas (Sims 2015, Shorter Oxford 2018). Its aim, in Jaspers's phrase, is to elucidate the essential qualities of morbid mental experiences and so to understand each patient's illness from the inside. It has been called the fundamental professional skill of the psychiatrist, and for the exit examination it is the spine of the whole signs-and-symptoms section: every later topic (perception, thought, self, mood, memory, consciousness, motor) is a chapter within this one framework.

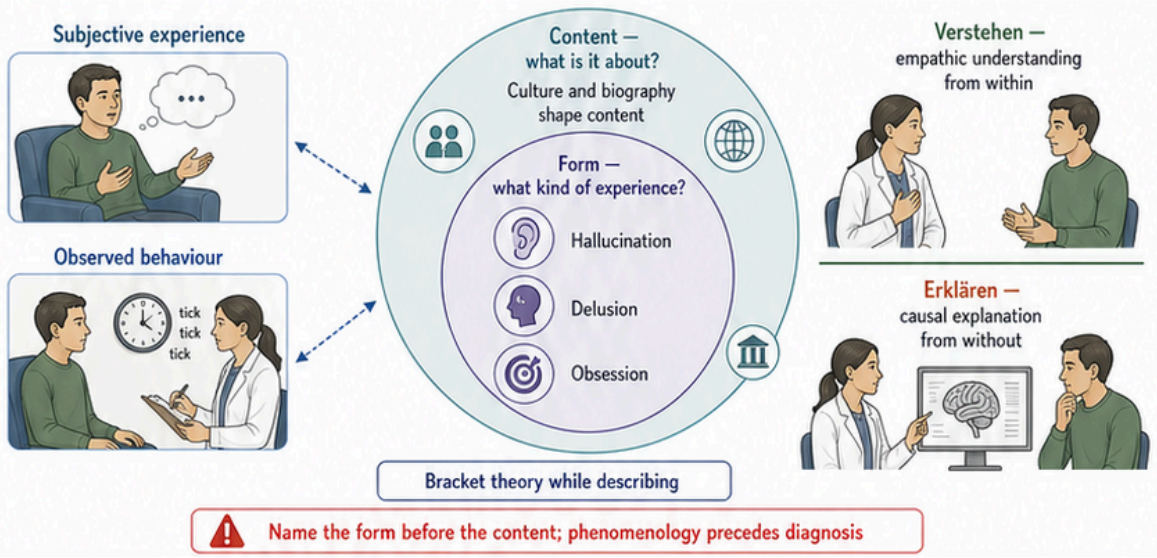


Fig 6.15 Describe the phenomenon before explaining it.

Why this opener matters. Band B of these notes is a map, not a list. This topic lays the map: it fixes the **method** (empathic description, form over content), names the three canonical texts you cite in a viva (jaspers, fish, sims), and gives the domains-of-mental-life scaffold onto which every individual sign hangs. Learn the scaffold once here and the rest of these notes becomes filling in cells.

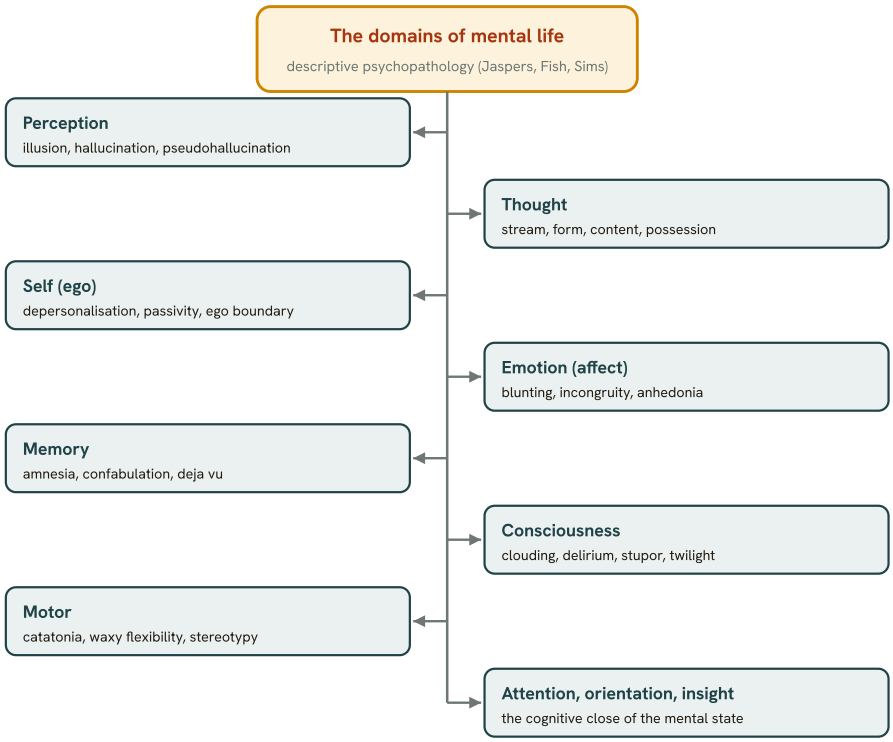


Fig 6.16 The domains of descriptive psychopathology, the map that organises the whole of Band B. Each branch is a domain of mental life with its characteristic disorders; naming a sign precisely means first knowing which domain it belongs to. The delusions and the Schneiderian first-rank symptoms sit within the thought branch and are drawn out separately. Following Jaspers, the aim throughout is to describe the form of an experience before interpreting its content.

11.1 Descriptive psychopathology defined

The definition to memorise. Descriptive psychopathology is the objective description of abnormal states of mind, avoiding as far as possible preconceived ideas or theories, and limited to the description of conscious experiences and observable behaviour (Sims 2015). Two commitments are load-bearing. First, it is *atheoretical*: it describes the phenomenon, it does not explain its cause. Second, it stays with what is *conscious and observable*: it does not appeal to unconscious mechanisms (that is the province of psychoanalytic or experimental psychopathology, not descriptive). This is why a Freudian reading of a persecutory delusion as projection is explanation, not description, and sits outside the descriptive method.

TRAP Reading a persecutory delusion as unconscious projection is explanation (erklaren), not description; descriptive psychopathology stays with conscious, observable experience and appeals to no unconscious mechanism.

11.2 Phenomenology and the two words for the same skill

Phenomenology. In clinical psychiatry, **phenomenology** is used almost synonymously with descriptive psychopathology: the careful study and categorisation of subjective mental experiences as the patient reports them. Strictly the terms are not identical (phenomenology carries additional philosophical meanings from Husserl and from Jaspers's own borrowing, per

Berrios 1992), but in exam and ward usage, phenomenology = the description of inner experience, one wing of descriptive psychopathology, the other wing being the observation of behaviour and signs.

11.3 Jaspers, and the method of empathic understanding

Jaspers 1913. Karl Jaspers, psychiatrist and philosopher, published *Allgemeine Psychopathologie* (General Psychopathology) in 1913; it remains the most complete account of the subject (Jaspers 1913, cited in Sims 2015). His central methodological gift was the distinction between two modes of grasping a mental state.

Verstehen (understanding)

Grasping a mental state *from within* by empathy: how one experience meaningfully arises from another (grief follows loss, jealousy follows infidelity). The tool of descriptive psychopathology.

Erklaren (explanation)

Grasping a phenomenon *from without* by causal, natural-science laws (a lesion, a neurotransmitter, a genetic mechanism). The tool of the biological sciences.

A phenomenon that empathy can enter is *understandable*; one that empathy cannot bridge (the primary delusion, the true first-rank symptom) is *un-understandable* and points to process, not development. This verstehen versus erklaren axis is Jaspers's signature and a recurring viva question.

11.4 The clinical distillations: Fish and Sims

From Jaspers to the ward. Jaspers is dense and philosophical; two English texts translated him into daily clinical use, and these are the ones you name.

fish, Clinical Psychopathology

Frank Fish's concise British manual (carried forward by Casey and Kelly, Fish 2007); the standard signs-and-symptoms crib for trainees, tightly organised by domain.

sims, Symptoms in the Mind

Andrew Sims's *Symptoms in the Mind: An Introduction to Descriptive Psychopathology* (Sims 2015); the fuller, more readable exposition, now the reference text most cited in Indian and UK postgraduate exams.

Cite the trio in one breath in a viva: the method is Jaspers, the crib is Fish, the exposition is Sims.

11.5 Form versus content: the central Jasperian rule

The single most examinable distinction. For any abnormal experience, separate its **form** from its **content**.

Form

The *kind* of experience, its structure: is this a hallucination, a delusion, an obsession, a thought that is being withdrawn? The form is what defines the sign and carries diagnostic weight. Phenomenology attends to form.

Content

What the experience is *about*: the theme, its subject matter (persecution by neighbours, guilt over a sin, a voice saying a particular sentence). Content is shaped by culture and biography; it is clinically interesting but does not by itself fix the diagnosis.

Worked example: two patients each believe the neighbours are poisoning them. Same content. If patient A holds it as an unshakeable false belief arising fully formed and un-understandably, the form is a delusion; if patient B has heard a voice announce it, the form is an auditory hallucination with secondary belief. The form differs, and it is the form that guides you. Sims's formulation is the one to quote: descriptive psychopathology is concerned with form, the phenomenologist deliberately brackets the content (Sims 2015).

RULE **Name the form before the content.** The form (hallucination, delusion, obsession) carries the diagnostic weight; the content (its theme) is culture-shaped and does not fix the diagnosis.

COMMON TRAP

Chasing content and missing form. A candidate who lists what the delusion is about, but cannot say whether the experience is a delusion, a hallucination or an overvalued idea, has described nothing diagnostically useful. Always name the form first, then the content.

11.6 Why phenomenology precedes diagnosis

The sign is the unit. Diagnosis in psychiatry is the recognition of a pattern of signs and symptoms. You cannot recognise a pattern you cannot first describe. A precisely elicited sign (a third-person auditory hallucination, thought insertion, a mood-congruent delusion) is the atomic unit of the mental state examination; the diagnosis is the molecule assembled from those atoms against operational criteria. As the New Oxford text puts it, phenomenology precedes diagnosis, reflecting both observed signs and the subjective experience of the person (New Oxford 2020). Precision at the level of the single sign is therefore not pedantry; it is what makes the diagnosis defensible. Reverse the order (decide the diagnosis, then relabel the phenomena to fit) and you confabulate.

11.7 The domains of mental life: the map

The scaffold. Descriptive psychopathology partitions abnormal experience into domains that mirror the structure of the mental state examination. Learn these headings as the master index for the whole set of notes; each expands into its own topic.

disorders of perception

Abnormalities of sensory experience: illusions, hallucinations across modalities, pseudohallucinations, and perceptual distortions.

disorders of thought

Abnormalities of thought stream, form (formal thought disorder), possession (insertion, withdrawal, broadcast) and content (delusions, overvalued ideas, obsessions).

disorders of self

Disturbance of the awareness of one's own existence and boundaries: depersonalisation, derealisation, and the disorders of ego boundary and agency (the Ich-Storungen).

disorders of emotion
Abnormalities of affect and mood: their intensity, quality, congruity, stability and reactivity (blunting, incongruity, lability, anhedonia, elation, depression).

disorders of memory
Abnormalities of registration, retention and recall: the amnesias, confabulation, and the false-recognition phenomena (deja vu, jamais vu).

disorders of consciousness
Abnormalities of the level and clarity of awareness: clouding, delirium, stupor, and the twilight and oneiroid states.

disorders of motor function
Abnormalities of movement and volition, chiefly the catatonic phenomena: stupor, negativism, waxy flexibility, echopraxia, mannerisms and stereotypies.

Two cross-cutting domains complete the map. **Attention and orientation** (the capacity to focus and to know time, place and person) is the substrate the whole examination sits on; a patient disoriented in time cannot give a reliable account of anything else. **Insight and judgement** (awareness of being ill, of the need for treatment, and the ability to act sensibly on that awareness) is graded, not all-or-none, and closes the mental state examination.

MNEMONIC

Please Think Slowly, Every Memory Counts Meaningfully, And Insightfully

Perception, Thought, Self, Emotion, Memory, Consciousness, Motor, then Attention/orientation and Insight/judgement. The seven core "disorders of ..." domains plus the two cross-cutting ones, in mental-state-examination order.

11.8 The domains against the mental state examination

Same map, two uses. The domains are also the running order of the MSE, so learning them once serves both the phenomenology paper and the clinical long case.

DOMAIN	MSE HEADING IT FEEDS	ANCHOR SIGN
disorders of perception	Perception	Third-person auditory hallucination
disorders of thought	Thought (stream, form, content, possession)	Thought insertion; primary delusion
disorders of self	Perception / thought (ego boundary)	Depersonalisation
disorders of emotion	Mood and affect	Blunted or incongruous affect
disorders of memory	Cognition	Confabulation
disorders of consciousness	Consciousness / sensorium	Clouding, delirium
disorders of motor function	Behaviour and motor	Waxy flexibility
Attention and orientation	Cognition	Disorientation to time

DOMAIN	MSE HEADING IT FEEDS	ANCHOR SIGN
Insight and judgement	**Insight**	Denial of illness

The domains of mental life read top-to-bottom are, near enough, the running order of the mental state examination.

HOLD THIS

The method is Jaspers, the crib is Fish, the exposition is Sims; describe form by empathy, do not explain content by cause. Phenomenology precedes diagnosis: the precisely named sign is the unit of the mental state examination.

PEARL

The domains in one line: perception, thought, self, emotion, memory, consciousness, motor, plus attention/orientation and insight, described by form not content, understood by empathy not explained by cause.

CLINICAL ANCHOR

In a viva, when asked "how would you describe this patient's symptoms", do not lead with a diagnosis. Lead with the method: "I would describe the phenomena in each domain, attending to the form of each experience rather than its content, in the order perception, thought, self, emotion, memory, consciousness and motor." You have then shown you own the framework, which scores before any single sign is named.

INDIA

For the Indian postgraduate exams, Sims's *Symptoms in the Mind* and Fish's *Clinical Psychopathology* are the two most-cited phenomenology texts, and the AIIMS *Clinical Methods in Psychiatry* (2024) reproduces the same Jasperian framework. Content of delusions is often culture-shaped (possession, black magic, the evil eye); describe the form precisely and record the content faithfully without pathologising a culturally normative belief.

GOOD TO REMEMBER

- **Descriptive psychopathology:** objective, theory-free description of abnormal states of mind, limited to conscious experience and observable behaviour (Sims 2015).
- **Phenomenology:** the study and categorisation of subjective mental experience; in clinical use, near-synonymous with descriptive psychopathology.
- **jaspers, General Psychopathology (1913):** the founding text; the method of empathic understanding.
- **Verstehen versus erklaren:** understanding a state from within by empathy versus explaining it from without by cause; understandable versus un-understandable phenomena.
- **fish, Clinical Psychopathology (2007):** the concise British signs-and-symptoms crib, domain-organised.
- **sims, Symptoms in the Mind (2015):** the fuller exposition; the most-cited exam reference.
- **Form:** the kind or structure of an experience (hallucination, delusion, obsession); phenomenology attends to form; form carries diagnostic weight.
- **Content:** what the experience is about (its theme); culture- and biography-shaped; not diagnostic by itself.
- **Phenomenology precedes diagnosis:** a precisely elicited sign is the unit of the mental state examination; the diagnosis is assembled from signs.
- **disorders of perception:** illusions, hallucinations, pseudohallucinations, perceptual distortions.
- **disorders of thought:** stream, form, possession, content (delusions, obsessions, overvalued ideas).
- **disorders of self:** depersonalisation, derealisation, ego-boundary and agency disturbance.
- **disorders of emotion:** intensity, quality, congruity and stability of affect and mood.
- **disorders of memory:** amnesias, confabulation, deja vu and jamais vu.
- **disorders of consciousness:** clouding, delirium, stupor, twilight and oneiroid states.
- **disorders of motor function:** the catatonic phenomena and disorders of volition.
- **Cross-cutting:** attention/orientation (the substrate) and insight/judgement (graded, closes the MSE).

12 · Disorders of perception

Perception is the process by which sensory data reaching the brain are organised and interpreted into a meaningful representation of the outside world; it is more than raw sensation, which is the mere registration of a stimulus at a receptor. The descriptive psychopathology of perception classifies the ways this process goes wrong, and it is a perennial Paper I favourite because the whole subject rewards precise definitions and clean discriminations rather than mechanism. This note gives the **phenomenology** only, in the tradition of Jaspers, Fish and Sims (Jaspers 1913, Fish 2007, Sims 2015): what each abnormality looks like at the level of description, form over content.

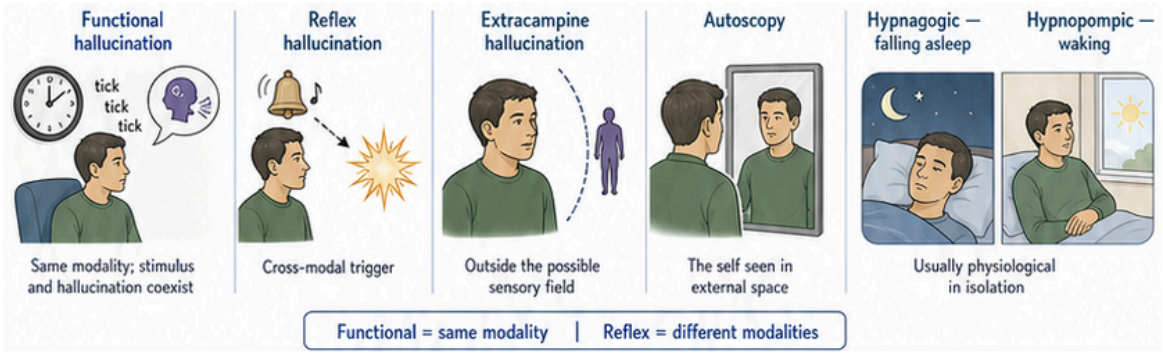


Fig 6.17 Special hallucinatory experiences.

Exam framing. The examiner wants three levels kept apart cleanly: a real percept altered (**sensory distortion**), a real stimulus misperceived (**illusion**), and a percept with no stimulus at all (**hallucination**), plus the halfway house of the **pseudohallucination**. The mechanistic theories of hallucination (perceptual-release, aberrant salience, predictive coding) belong to the General and Developmental Psychology notes and are cross-referred there; here the task is to name and define, ideally with a one-line clinical example each. Aetiology and the theories live in the General and Developmental Psychology notes, not here.

Discriminator	Illusion	Hallucination	Pseudo-hallucination
Real external stimulus?	Yes: a real object misperceived	No stimulus	No stimulus
Where perceived	outer objective space	outer objective space	inner subjective space
Reality status	a real percept, misjudged	full force of a true perception	lacks full substantiality
Insight	corrects on closer attention	absent (believed real)	relatively preserved
Typical setting	fear, inattention; organic states	psychosis; organic states	grief, dissociation, hypnagogic

Fig 6.18 Telling perceptual phenomena apart. An illusion is a real external stimulus misperceived; a hallucination is a percept without any stimulus, experienced in outer objective space with the full force of a true perception and without insight; a pseudohallucination arises in inner subjective space, lacks the full substantiality of a true perception, and leaves insight relatively preserved. The two discriminators that carry most of the work are the locus (outer versus inner space) and the reality status.

12.1 The three-level framework and its discriminators

Orientation. Every perceptual abnormality can be placed by asking four questions: is there a real external stimulus, where is the experience located (objective external space versus inner subjective space), does it carry the full substantiality and involuntary force of a true percept, and is insight retained. A **sensory distortion** and an **illusion** both start from a real stimulus; a

hallucination and a **pseudohallucination** do not. A hallucination sits in external space with full force and insight lost; a pseudohallucination sits in inner subjective space, lacks that substantiality, and insight is relatively preserved (Sims 2015). Hold this scaffold and the named subtypes below slot in without confusion.

RULE **Two discriminators do most of the work: the presence of a real stimulus, and the locus (outer objective versus inner subjective space).** Stimulus separates the illusion; locus separates the hallucination from the pseudohallucination.

12.2 Sensory distortions: a real percept altered

Definition. A **sensory distortion** is a change in the intensity, quality or spatial form of a percept arising from a real external object; the object is correctly identified, but its perceived attributes are altered (Fish 2007).

Hyperaesthesia

Increased intensity of perception: sounds seem unbearably loud, colours vivid; seen in migraine, hangover, some drug states and the heightened arousal of mania and anxiety.

Hypoaesthesia

Decreased intensity of perception: the world seems dull, muffled or grey; seen in delirium, depression (where colours are described as washed out) and clouded consciousness.

Changes in quality

Altered perceived quality, chiefly of colour: chromatopsia, e.g. xanthopsia (yellow vision), chloropsia (green) or erythropsia (red), typically from drugs or toxins such as digitalis or santonin.

Changes in spatial form (dysmegalopsia)

The perceived size or shape of an object is altered. **Micropsia**: objects seem smaller or further away. **Macropsia** (megalopsia): objects seem larger or nearer. Metamorphopsia: objects appear irregular or distorted in shape. Seen in retinal disease, temporal and parietal lesions, migraine (the Alice-in-Wonderland complex) and, rarely, epilepsy.

12.3 Illusions: a real stimulus misperceived

Definition. An **illusion** is a misperception, a false perception, of a real external stimulus, in which the actual object is transformed into a different percept (Sims 2015). Illusions occur in the healthy (a coat on a door mistaken for an intruder in poor light) and are not in themselves pathological; the classical trigger conditions are reduced sensory clarity, inattention and strong affect.

Completion illusion

Depends on inattention: the mind fills in gaps, so misprints are read as the intended word, e.g. "-ook" with the first letter faded is read as "book" when the word was "look". Abolished by attention.

Affect illusion

Arises out of a particular mood state: a bereaved person momentarily "sees" the deceased, or a delirious, frightened patient perceives innocent gestures as threatening.

Pareidolia

Vivid illusions produced without effort, indeed sometimes against will, from ambiguous stimuli, e.g. seeing faces or figures in clouds or in the embers of a fire. Unlike the other two, pareidolia is intensified, not abolished, by attention.

12.4 Hallucinations: definition and modality classification

Definition. A **hallucination** is a percept experienced in the absence of any external stimulus, arising in external objective space, with the full force and substantiality of a true perception, and not subject to conscious manipulation (Jaspers 1913, Fish 2007). It is not a distorted image, not a misperception, and not under voluntary control. Hallucinations are classified first by sensory **modality**.

Auditory (elementary)

Unstructured or rudimentary noises: buzzing, tapping, banging, music, whistling. Common in organic states and early psychosis.

Auditory (second-person)

Voices addressing the patient directly ("you are worthless"). Second-person derogatory or command voices are typical of severe depression; command hallucinations carry risk.

Auditory (third-person)

Voices discussing or arguing about the patient in the third person ("he is a sinner"), or a **running commentary** narrating the patient's actions as they occur. These are Schneiderian first-rank symptoms, classically of schizophrenia.

Visual

From elementary flashes (photopsiae) to fully formed figures and scenes. Prominent, well-formed or Lilliputian visual hallucinations point strongly toward an organic cause: delirium, occipital or temporal lesions, drug intoxication and withdrawal.

Olfactory and gustatory

Hallucinations of smell and taste, often unpleasant (burning rubber, rotten flesh). Raise suspicion of temporal lobe epilepsy (uncinate fits) and other organic disease; also seen in psychotic depression as congruent themes of decay.

Somatic and tactile

Superficial (haptic, on or under the skin), kinaesthetic (of limb movement) and visceral (deep, of the internal organs). **Formication** is the tactile hallucination of insects crawling on or under the skin, classically in cocaine and alcohol-related states ("cocaine bugs") and delirium tremens.

12.5 Special named hallucinations: functional and reflex

Two easily confused stimulus-bound types. Both involve a real stimulus, but the relation differs, and this discrimination is high-yield.

Functional hallucination

A real external stimulus is *necessary* to provoke the hallucination, and the normal perception of that stimulus and the hallucination are experienced *together in the same modality*, e.g. hearing the voice of God only while, and each time, a tap runs or a clock ticks, the running water still heard as running water alongside the voice (Fish 2007). Unlike an illusion, the voice is not an elaboration of the sound; the sound merely triggers a separate hallucination.

Reflex hallucination

A stimulus in one sensory modality triggers a hallucination in a *different* modality, e.g. feeling a cold sensation in the spine on hearing a fingernail scratch a blackboard, or seeing a flash when a bell rings. A pathological cross-modal analogue of synaesthesia.

12.6 Special named hallucinations: extracampine, autoscopy and the physiological types

Extracampine hallucination

A hallucination experienced *outside the limits of the possible sensory field*, e.g. hearing voices talking from another city hundreds of miles away, or seeing a figure standing behind the head, beyond the field of vision. May occur in schizophrenia and in organic and epileptic states; not to be confused with the **extracampine** being merely "distant".

Autoscopy (phantom mirror image)

The experience of seeing oneself and knowing that it is oneself, projected into external space. In *negative* autoscopy the subject looks in a mirror and sees no image; in *internal* autoscopy the subject perceives their own internal organs. Seen in delirium, epilepsy, parietal lesions and dissociative states.

Hypnagogic hallucination

A hallucination (visual, auditory or tactile) occurring while *falling asleep*. A physiological, non-pathological phenomenon in the healthy; when frequent and vivid, part of the narcolepsy tetrad.

Hypnopompic hallucination

The same phenomenon occurring on *waking*. Rarer than hypnagogic; likewise usually of no pathological significance in isolation.

> **COMMON TRAP**
>
> Do not confuse the functional hallucination with the reflex hallucination. In a **functional hallucination** the trigger and the hallucination share the *same* modality and are heard together (tick plus voice, both auditory); in a **reflex hallucination** the trigger is in *one* modality and the hallucination in *another* (sound triggering a bodily sensation). Same modality equals functional; cross modality equals reflex.

12.7 Pseudohallucination: the inner-space percept

Definition (Jaspers). A **pseudohallucination** is a clear and vivid mental image that, although experienced in full consciousness, *lacks the full substantiality of a true perception*, is located in *inner subjective space* rather than external objective space, is known by the subject not to be a real perception, and so leaves insight *relatively preserved* (Jaspers 1913, Sims 2015). It is more vivid and involuntary than ordinary imagery but less concrete and less "real" than a true hallucination, occupying the ground between them.

Two usages, a caution. Kaplan and Sadock note the term is used in two ways: the Jaspersian sense above (perceived within the mind, in inner space), and a looser sense of a hallucination whose reality the patient doubts, for which "partial hallucination" is the better label (Kaplan & Sadock 2024). For the exam, lead with the Jaspers definition. Pseudohallucinations are common in grief, dissociative states and post-traumatic conditions and, unlike true hallucinations, are not by themselves evidence of psychosis.

12.8 Discriminating the four: the summary table

Read down the discriminators. The whole topic reduces to five axes: presence of a real stimulus, locus of the experience, whether it can be controlled, its reality-status, and insight.

AXIS	SENSORY DISTORTION	ILLUSION	PSEUDOHALLUCINATION	HALLUCINATION
Real external stimulus	Yes (percept altered)	Yes (misperceived)	**No**	**No**
Locus	External space	External space	**Inner subjective space**	**External objective space**
Voluntary control	No	No	Involuntary but image-like	No
Reality-status (substantiality)	Real object, altered	Real object, transformed	**Lacks full substantiality**	**Full force of true percept**
Insight	Usually retained	Corrected on attention	**Relatively preserved**	**Typically lost**

The four levels separate cleanly on stimulus, locus, reality-status and insight; the pseudohallucination is the diagnostic pivot between imagery and true hallucination.

HOLD THIS

Illusion = real stimulus misperceived; hallucination = percept without a stimulus, in outer space, full reality, insight lost; pseudohallucination = inner space, lacks full substantiality, insight preserved. A pseudohallucination is not itself evidence of psychosis.

CLINICAL ANCHOR

Modality guides aetiology at the bedside. Third-person and running-commentary auditory voices steer toward schizophrenia; second-person derogatory voices toward severe depression; well-formed visual, olfactory, gustatory and vivid tactile (formication) hallucinations should trigger an *organic* workup (delirium, epilepsy, substance intoxication or withdrawal) before a primary psychotic label. This is descriptive triage, not a diagnosis named to the patient.

PEARL

First-rank auditory hallucinations (third-person voices, running commentary) are *suggestive* of schizophrenia but are **not pathognomonic**: they occur in affective psychosis and organic states, and the modern consensus (reflected in DSM-5 dropping their special weighting) is that they are not diagnostically decisive. Form over content still holds, but form alone does not fix the diagnosis.

MNEMONIC

"FREAK-Hy": the special hallucinations

Functional, **Re**flex, **E**xtracampine, **A**utoscopy, and the physiological **K** (hypnagogic and hypnopompic) plus **Hy**pnopompic, the named non-modality types to rattle off when asked to enumerate special hallucinations.

GOOD TO REMEMBER

- **Perception:** organisation and interpretation of sensory data into a meaningful representation of the world; more than raw sensation.
- **Sensory distortion:** a real percept altered in intensity, quality or spatial form.
- **Hyperaesthesia / hypoaesthesia:** increased / decreased intensity of perception (mania, migraine / delirium, depression).
- **Chromatopsia:** altered colour quality, e.g. xanthopsia (yellow), chloropsia (green), erythropsia (red); usually toxic or drug-induced.
- **Dysmegalopsia:** altered perceived size or shape: micropsia (smaller), macropsia/megalopsia (larger), metamorphopsia (distorted shape).
- **Illusion:** a misperception of a real external stimulus; can be normal.
- **Completion illusion:** gap filled by inattention (misprints read as intended word); abolished by attention.
- **Affect illusion:** misperception driven by mood (bereaved "sees" the deceased).
- **Pareidolia:** effortless vivid illusions from ambiguous stimuli (faces in clouds/fire); intensified by attention.
- **Hallucination:** a percept with no external stimulus, in external space, with full force of a true perception, not controllable; insight typically lost.
- **Auditory (elementary / second-person / third-person / running commentary):** noises / voices to the patient / voices about the patient and narration of actions; third-person and running commentary are Schneiderian first-rank.
- **Visual / olfactory / gustatory hallucinations:** well-formed forms of these raise suspicion of an organic cause (delirium, temporal lobe epilepsy, drugs).
- **Formication:** tactile hallucination of insects on/under the skin ("cocaine bugs"); cocaine, alcohol withdrawal, delirium tremens.
- **Functional hallucination:** a real stimulus is needed and is perceived together with the hallucination in the *same* modality (voice heard as a tap runs).
- **Reflex hallucination:** a stimulus in one modality triggers a hallucination in a *different* modality (sound producing a bodily sensation).
- **Extracampine hallucination:** experienced outside the limits of the possible sensory field (voices from another city; figure behind the head).
- **Autoscopy (phantom mirror image):** seeing oneself, knowing it is oneself; negative and internal variants; organic/dissociative.
- **Hypnagogic / hypnopompic hallucinations:** physiological, on falling asleep / on waking; part of the narcolepsy tetrad; usually non-pathological.
- **Pseudohallucination:** vivid image in inner subjective space, lacking full substantiality, insight relatively preserved (Jaspers); not itself evidence of psychosis.
- **First-rank symptoms:** suggestive of schizophrenia but *not* pathognomonic (occur in affective and organic psychoses; de-weighted in DSM-5).
- **Mechanism note:** theories of hallucination (perceptual-release, aberrant salience, predictive coding) are covered in the General and Developmental Psychology notes, not here.

13 · Disorders of thought

The **disorders of thought** are the descriptive psychopathology of thinking as it is inferred from speech, and they are examined most cleanly when parcelled into four classic headings: disorders of the **stream** (tempo and continuity), of the **form** (the structure and connectedness of thinking), of the **content** (what is being thought), and of the **possession** (the sense of ownership and control of one's own thoughts). This carving is the one used in the classical texts (Fish 2007, Sims

2015) and in Indian teaching (Clinical Methods in Psychiatry, AIIMS 2024), and it is a perennial Paper I favourite because it rewards precise definitions and clean discriminations, not mechanism.

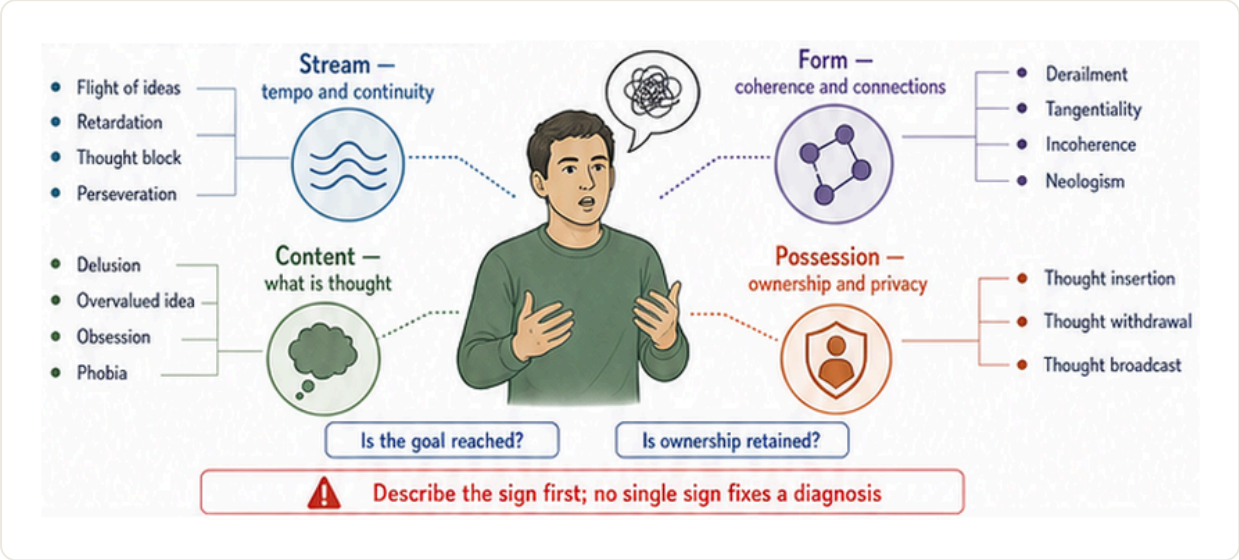


Fig 6.19 Four axes of thought disorder.

Exam framing. Keep the four axes rigidly apart, because the same clinical phenomenon can be pigeonholed differently by different authors (flight of ideas is a disorder of stream to Fish but of form to some; circumstantiality is placed under stream by Sims). Teach the **description**, not the explanation, form over content, in the tradition of Jaspers, Fish and Sims (Jaspers 1913). Thinking is never observed directly: it is read off speech, so a "thought disorder" is always an inference from disordered language. Delusions, though a disorder of content, are dealt with in the next topic and are only signposted here; the possession disorders are the Schneiderian first-rank symptoms and are cross-referred to the perception and first-rank notes.

13.1 The four-axis framework and how to place any sign

Orientation. Any abnormality of thinking can be located by asking four questions in turn: is the *speed or continuity* of the flow abnormal (stream), is the *logical structure and connectedness* lost (form), is *what* is being thought abnormal (content), or is the patient's *sense of owning and controlling* the thought disturbed (possession). Stream is about tempo and flow, form is about coherence, content is about the ideas themselves, possession is about ego-boundary. Hold this scaffold and the named signs below slot in without confusion. A useful cross-cut, from Andreasen's work on the Scale for the Assessment of Thought, Language and Communication (TLC), divides formal disturbances into *positive* (a wealth of disorganised output: derailment, incoherence, neologisms) and *negative* (impoverished output: poverty of speech and of content) (Andreasen 1979).

13.2 Disorders of the stream: tempo of thought

Definition. Disorders of the stream (or tempo) concern the *rate and pressure* of the flow of thought, either accelerated or slowed, independent of whether the logical links are preserved (Fish 2007).

Flight of ideas

The manic acceleration of thinking: a rapid, pressured stream in which thoughts follow each other by *chance associations*, and where the goal of thinking is repeatedly lost. The direction is set by external distraction and by verbal associations such as assonance, alliteration, rhyme, punning and **clang associations** (word choice governed by sound not meaning). Crucially, the links remain *understandable*: one can often follow, or even reverse, the train (Sims 2015). Seen in mania and hypomania.

Prolixity (ordered flight)

A milder, more ordered variant of flight of ideas seen in hypomania: the stream is over-productive and diffuse but the patient does eventually reach the goal.

Retardation / inhibition of thinking

Slowing of the stream: the train of thought is decelerated, the number of ideas reduced, and the patient experiences difficulty in thinking; seen in depression and in retarded psychomotor states.

Poverty of thought

A reduction in the *amount* of thought, reflected as poverty of speech (brief, unelaborated, monosyllabic replies) or poverty of content (adequate quantity of speech conveying little information); a negative disturbance seen in the negative syndrome of schizophrenia and in depression.

13.3 Disorders of the stream: continuity of thought

Definition. These concern *breaks and repetitions* in the continuity of the flow rather than its speed (Companion to Psychiatric Studies).

Thought block

An *abrupt, complete cessation* of the stream of thought, experienced by the patient as the mind suddenly going blank ("snapping off"), with no thought to replace it; on resuming, the patient often takes up a fresh, unrelated topic. When subjectively distressing and unexplained, it carries weight toward schizophrenia. Distinguish from the ordinary "losing one's thread", which is explicable and recoverable.

Perseveration

Senseless persistence of a word, phrase or idea *beyond the point at which it is relevant*, so that once a subject or word is begun the patient repeatedly returns to it despite a change of question. A pointer to organic brain disease, especially dementia and frontal lesions.

Circumstantiality

Speech that is over-inclusive and indirect, laden with tedious and parenthetical detail, so that reaching the goal idea is greatly delayed; but the goal *is eventually reached*. This is the key discriminator from derailment and from tangentiality, where the goal is never reached. Common in obsessional and epileptic personalities, low intelligence, and, at a non-pathological level, in normal "long-winded" people.

13.4 Disorders of the form: formal thought disorder and its concept

Definition. **Formal thought disorder** denotes a disturbance of the *form* of thought: the loss of the normal structure, logical coherence and connectedness of thinking, the "how" or mechanics of thought rather than its content, which makes conversation hard or impossible to follow and is a cardinal feature of schizophrenia (Companion to Psychiatric Studies, AIIMS 2024). Because

thinking is inferred only from language, the terms "thought disorder" and "speech disorder" are sometimes used interchangeably. Healthy thinking has been summarised by the "3 Cs": *constancy*, *clear organisation* and *continuity*; deviation in any is a formal disturbance (AIIMS 2024). Historically several theorists each proposed a core defect, summarised below.

Kraepelin: akataphasia

An early term for the disordered, ungrammatical expression of thought.

Bleuler: loosening of associations

The founding concept: a loosening of the associative threads that normally bind thoughts together, held by Bleuler to be the fundamental disturbance of schizophrenia.

Cameron: asyndesis and overinclusion

Asyndesis is a lack of adequate connections between successive thoughts (a breakdown of the "cementing" links); **overinclusion** is the inability to keep the boundaries of a concept, so that irrelevant material is drawn in.

Goldstein: concrete thinking

Loss of the abstract attitude, so the patient thinks in literal, concrete terms and cannot handle concepts; tested by proverb interpretation and similarities, and seen in schizophrenia and organic states.

Schneider: the five features

Schneider described derailment, substitution, omission, fusion and drivelling as the elementary faults underlying disordered thinking.

13.5 Disorders of the form: the descriptive signs

The named phenomena. These are the signs actually elicited at the bedside, each a way in which the connectedness of speech breaks down (Fish 2007, Sims 2015, Andreasen 1979).

Loosening of associations / derailment

The ideas slip off the track onto another that is obliquely related or wholly unrelated; the "train" of thought leaves the "rails". Meaning is lost gradually over several sentences (contrast word salad, where individual sentences are already meaningless).

Knight's move thinking

A term for a sharp, illogical, oblique transition between ideas, likened to the chess knight that never moves in a straight line; used near-synonymously with severe derailment.

Tangentiality

Replies that veer away from the point and, unlike circumstantiality, *never return* to the goal idea; the answer is obliquely related to the question but never actually answers it.

Word salad (schizophasia, incoherence)

Speech so disordered that it is essentially incomprehensible: words and phrases are strung together with the rules of grammar and syntax ignored, so that even individual sentences carry no meaning.

Neologisms

The invention of genuinely new words with no established meaning (e.g. "tarn-harn"); to be distinguished from *word approximations*, where existing words are used in an idiosyncratic, quasi-logical way ("a menu three times a day" for meals).

Verbigeration

The automatic, stereotyped repetition of words, phrases or sentences "like a scratched record", a verbal stereotypy; differs from echolalia, which repeats another person's words.

Concrete thinking

See Goldstein above: literal, non-abstract interpretation, e.g. giving the literal meaning of a proverb.

Asyndesis

See Cameron above: a lack of the connecting links between one thought and the next.

13.6 Distinguishing the three "goal" disorders

Read down the discriminator column. Circumstantiality, tangentiality and derailment are constantly confused; they separate on two axes, whether the goal is reached and whether the digressions are logically related.



Fig 6.20 Does the speech reach its goal?.

SIGN	REACHES THE GOAL IDEA?	NATURE OF DIGRESSION	TYPICAL SETTING
Circumstantiality	**Yes, eventually (after much detail)**	Over-inclusive but relevant detail	Obsessional / epileptic personality, low IQ
Tangentiality	**No, never returns**	Obliquely related, drifts off	Schizophrenia, organic states
Derailment (loosening)	**No, meaning lost over sentences**	Slips onto unrelated track	Schizophrenia (positive FTD)

The single most reliable discriminator is whether the goal idea is finally reached: only circumstantiality reaches it.

RULE **Does the patient reach the goal?** Circumstantiality reaches it after a long detour; tangentiality and derailment never do - the single cleanest discriminator in the topic.

13.7 Disorders of the content of thought

Definition. Content is *what* the person is thinking; its disorders are the abnormal ideas that dominate the mind, graded by the degree to which they are held with conviction and resisted (Sims 2015). Delusions, the most important, are taught in full in the next topic and are only listed here.

Preoccupations

Ordinary thoughts that recur with abnormal intensity or frequency (worry over illness, somatic preoccupation in depression and anxiety); ego-syntonic and not resisted.

Overvalued idea

A comprehensible, non-delusional belief that comes to dominate the person's life and is pursued with abnormal intensity, but which is not held with true delusional conviction and is not utterly beyond reason (e.g. the litigious querulant, the morbidly jealous, the dysmorphophobic). Sits between a normal belief and a delusion.

Obsessions and compulsions

Obsessions are recurrent, intrusive, unwanted thoughts, images or impulses, recognised as one's own (contrast thought insertion) and as senseless, and actively resisted, generating anxiety; **compulsions** are the repetitive mental or motor acts performed to neutralise them. Ego-dystonic, insight typically retained.

Phobias

Persistent, irrational fears of a specific object or situation, recognised as excessive, leading to avoidance.

Delusions

Fixed, false, unshakeable beliefs out of keeping with the person's culture, held with absolute conviction; the full taxonomy is in the next topic.

13.8 Disorders of the possession of thought

Definition. **Thought possession** is the normal sense that one's thoughts are *one's own* and are *under one's own control*. Its disorders are disturbances of this ownership and boundary: at one pole the obsessional experiences unwanted thoughts as intrusive yet still recognises them as self-generated; at the other, the patient with schizophrenia attributes thoughts to a foreign agency or feels them stolen or made public. This group, "thought alienation", comprises three named signs of disordered thought possession that are *Schneiderian first-rank symptoms* (cross-refer to the first-rank note): thought insertion, thought withdrawal and thought broadcast.

Thought insertion

The experience that thoughts *not one's own* have been placed into one's mind by an external agency; in thought insertion the key is the loss of the sense of *ownership*, the patient insisting the thoughts are alien, not merely unwanted (distinguishing it from an obsession).

Thought withdrawal

The experience, thought withdrawal, that one's thoughts are being *removed or extracted* from the mind by an external force, often reported together with the sudden emptiness of thought block.

Thought broadcast

In thought broadcast the experience is that one's thoughts *escape the confines of the self* and are known to, or shared with, others (broadcast, diffused), without the patient speaking them aloud; a disorder of thought, to be distinguished from the auditory hallucination of *thought echo* (hearing one's own thoughts spoken aloud).

COMMON TRAP

Do not confuse an **obsession** with **thought insertion**. Both are unwanted intrusive thoughts, but the obsessional patient *knows the thought is his own* (ego-dystonic but self-owned) and resists it, whereas in thought insertion *ownership itself is lost*: the patient is convinced the thought was put there by an outside agency. Ownership retained equals obsession; ownership lost equals thought insertion, a first-rank symptom.

HOLD THIS

Thought disorder splits four ways: stream (tempo), form (coherence), content (the ideas), possession (ownership). Two settling questions - is the goal reached? is ownership retained? - resolve most of the confusions.

13.9 Aetiological pointers and the modern caveat

Description first, then the pattern. The signs are defined descriptively, but each carries a soft aetiological steer worth holding at the bedside (Companion to Psychiatric Studies). Flight of ideas, clang associations and pressure of speech point to mania; poverty of thought and content to negative-syndrome schizophrenia or depression; perseveration, stereotypy and echolalia to organic brain disease; positive formal thought disorder (derailment, incoherence, neologisms) and the possession disorders to schizophrenia. But two cautions are decisive for the exam. First, formal thought disorder is *not specific* to any one diagnosis and overlaps heavily across stream and form. Second, the thought-possession signs, though first-rank, are *not pathognomonic* of schizophrenia: they occur in affective and organic psychoses, and the modern consensus, reflected in DSM-5 dropping the special weighting of first-rank symptoms, is that they are not diagnostically decisive. Form over content still holds as a descriptive discipline, but form alone does not fix the diagnosis.

CLINICAL ANCHOR

At the bedside the four axes map onto four bedside manoeuvres: for *stream*, listen to the rate and continuity of spontaneous speech; for *form*, ask an open question and judge whether you can follow the reply; for *content*, ask directly about worries, obsessions and beliefs; for *possession*, ask "are your thoughts your own, can others read or take them, are thoughts put into your mind?". This is descriptive triage, never a diagnosis named to the patient.

PEARL

The cleanest single discriminator in the whole topic: *does the patient reach the goal?* Circumstantiality reaches it after a long detour; tangentiality and derailment never do. And the cleanest boundary sign: *is ownership of the thought retained?* Yes in obsessions, no in thought insertion. Two questions settle most of the confusions examiners set.

MNEMONIC

"S-F-C-P": Stream, Form, Content, Possession

Four axes in order of increasing "depth" from surface tempo to the ego-boundary: **S**tream (speed and flow: flight of ideas, block, perseveration, circumstantiality), **F**orm (coherence: derailment, word salad, neologisms), **C**ontent (the ideas: overvalued ideas, obsessions, delusions), **P**ossession (ownership: insertion, withdrawal, broadcast).

GOOD TO REMEMBER

- **Disorders of thought:** classified into stream (tempo/continuity), form (coherence), content (the ideas) and possession (ownership/control).
- **Flight of ideas:** pressured accelerated stream, chance associations by rhyme, punning and clang, distractible, but links remain understandable; mania.
- **Prolixity:** ordered flight of ideas of hypomania that eventually reaches the goal.
- **Retardation of thinking:** slowed stream, fewer ideas; depression.
- **Poverty of thought:** reduced amount of thought (poverty of speech / of content); negative schizophrenia, depression.
- **Thought block:** abrupt complete cessation of the stream, mind goes blank ("snapping off"); weight toward schizophrenia.
- **Perseveration:** senseless repetition of a word/idea beyond its relevance; points to organic brain disease.
- **Circumstantiality:** over-inclusive, detour-laden speech that *does* eventually reach the goal idea.
- **Formal thought disorder:** loss of the structure and connectedness of thinking, the "how" of thought; cardinal in schizophrenia.
- **Kraepelin:** akataphasia (disordered, ungrammatical expression of thought).
- **Bleuler:** loosening of associations, the fundamental disturbance of schizophrenia.
- **Cameron:** asyndesis (lack of connecting links) and overinclusion (loss of concept boundaries).
- **Goldstein:** concrete thinking (loss of the abstract attitude).
- **Schneider:** derailment, substitution, omission, fusion, drivelling.
- **Derailment / loosening:** ideas slip off the track; meaning lost over sentences.
- **Knight's move thinking:** sharp illogical oblique transitions, like the chess knight; near-synonym of severe derailment.
- **Tangentiality:** replies that veer off and *never* return to the goal (contrast circumstantiality).
- **Word salad (schizophasia):** incomprehensible speech, syntax ignored, individual sentences meaningless.
- **Neologisms:** genuinely new invented words; distinct from word approximations.
- **Verbigeration:** automatic stereotyped repetition of phrases "like a scratched record"; differs from echolalia.
- **Overvalued idea:** comprehensible non-delusional belief dominating life, held short of delusional conviction.
- **Obsessions / compulsions:** intrusive unwanted self-owned thoughts, resisted, ego-dystonic; neutralising acts.
- **Thought possession:** the sense of owning and controlling one's thoughts; its disorders are thought alienation.
- **Thought insertion:** alien thoughts placed in the mind by an external agency; loss of *ownership* (first-rank).
- **Thought withdrawal:** thoughts extracted from the mind by an external force (first-rank).
- **Thought broadcast:** thoughts escape the self and are known to others; a disorder of thought, not thought echo (first-rank).
- **Andreasen (1979):** TLC scale; positive vs negative formal thought disorder.
- **First-rank caveat:** possession disorders are first-rank but *not* pathognomonic; DSM-5 dropped their special weighting.

14 · Understanding delusions

The delusion is the cardinal disturbance of thought content and, for the phenomenologist, the most examined sign in all of descriptive psychopathology. The exam does not want a lay

definition, it wants the Jaspersian architecture: what makes a belief delusional in **form** rather than in content, how the un-understandable **primary delusion** is separated from the merely secondary one, and how the delusion is discriminated from the **overvalued idea** and the obsession. Ground your description in Jaspers (General Psychopathology, 1913), Fish (Clinical Psychopathology) and Sims (Symptoms in the Mind), the three texts every Indian examiner reaches for.

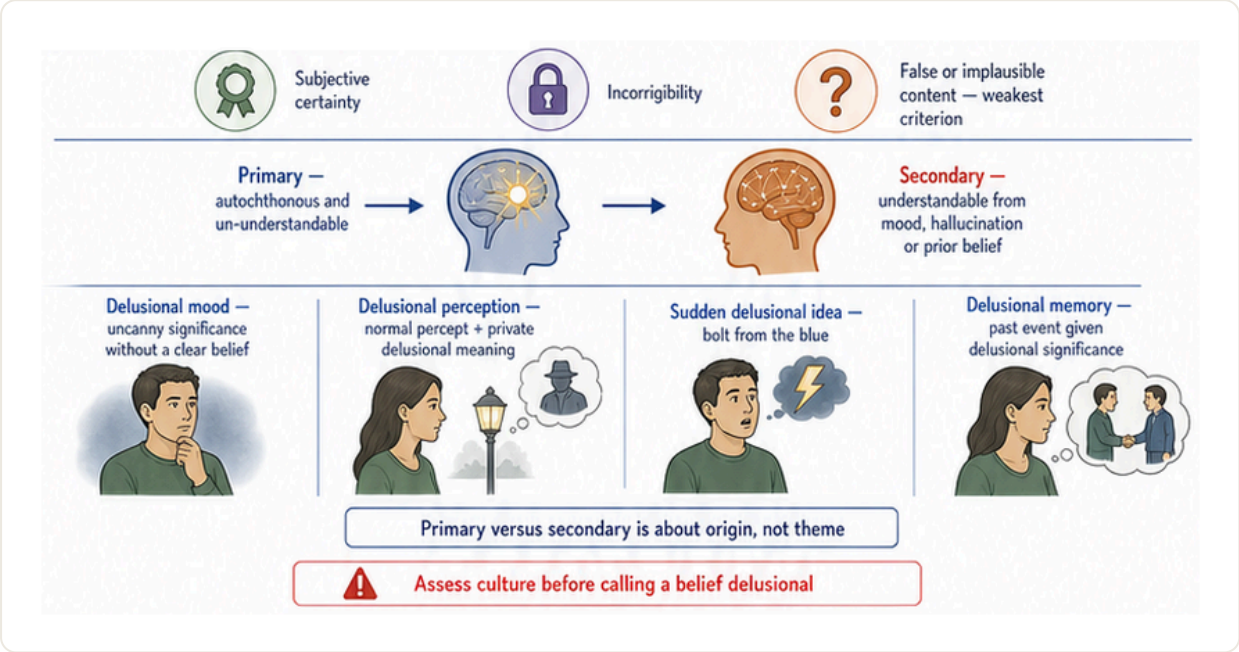


Fig 6.21 Primary delusional experience.

Describe, do not explain. Jaspers' discipline is to characterise the abnormal experience by its form (a fixed belief held with absolute certainty) and to resist the temptation to explain it by its content (why the patient believes he is persecuted). The whole classification below is a classification of form and origin, not of theme alone.

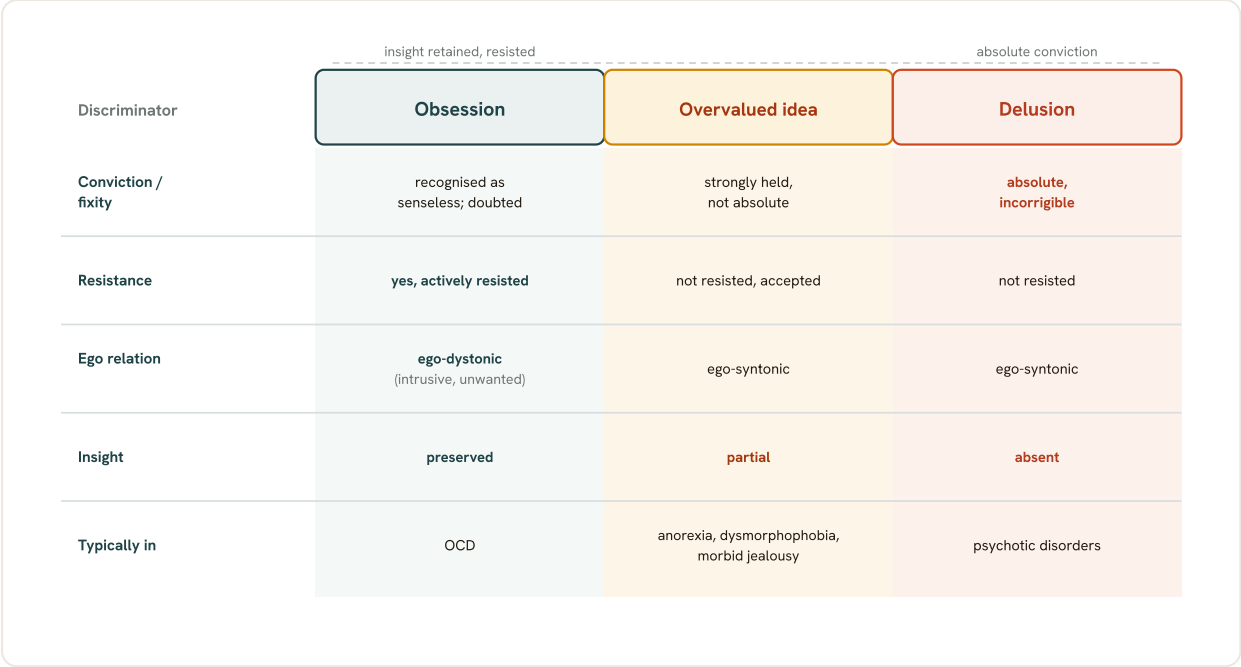


Fig 6.22 Delusion, overvalued idea and obsession compared. Read left to right as a gradient. An obsession is ego-dystonic, resisted, and held with retained insight; a delusion is ego-syntonic, unresisted, held with absolute conviction and no insight; the overvalued idea sits in between, a comprehensible belief held strongly but not with delusional fixity. Insight and resistance fall as conviction rises across the three.

14.1 Definition and the three Jaspersian criteria

Definition. A delusion is a fixed, false belief, held with absolute conviction, out of keeping with the person's social, educational and cultural background, and not amenable to reason or contrary evidence (Sims 2015, Kaplan & Sadock 2024). Jaspers gave three external criteria by which a delusion can be recognised.

Subjective certainty

Held with extraordinary, incorrigible conviction, an absolute subjective certainty far beyond ordinary belief.

Incorrigibility

Not amenable to reason, logic, argument or contrary experience; counter-evidence is re-interpreted rather than accepted.

Impossibility or falsity of content

The content is false, impossible or at least implausible; note this is the weakest criterion, since a delusion may occasionally be true (see the pitfall below).

COMMON TRAP

Falsity is NOT the defining feature. A morbidly jealous man may be delusional even if his wife happens to be unfaithful: the belief is delusional by the disordered mental process that produced it, not by whether it turns out true (Shorter Oxford). The other trap is culture: a belief widely shared within the patient's religious or cultural group is not a delusion, so always ask whether peers hold it.

14.2 The primary versus secondary split (the Jaspersian core)

The distinction is by origin, not theme. Jaspers separated delusions according to whether they can be understood as arising from something else.

primary delusion

Autochthonous (arising from within), it appears suddenly, fully formed, with full conviction and no discernible mental events leading up to it; it is un-understandable, meaning it cannot be derived from mood, personality or another experience. Given great diagnostic weight in schizophrenia.

secondary delusion

Understandable (in Jaspers' sense) as arising out of a preceding morbid experience: a mood state, a hallucination, or a pre-existing delusion. A profoundly depressed woman believes she is worthless; a man who hears accusing voices concludes he is being followed.

Secondary delusions may accumulate and interconnect into a **systematised** delusional system. Primary delusions are recorded only when certainly present, because of their diagnostic force.

RULE **The primary versus secondary split is by origin, not theme.** A primary delusion is un-understandable and autochthonous; a secondary one is understandable as arising from mood, a hallucination or a prior delusion.

14.3 The primary delusional experiences

Not all primary experiences begin as an idea. Jaspers and Schneider described four forms of primary delusional experience; the examiner wants each defined crisply.

delusional mood (Wahnstimmung)

An uncanny, uneasy sense that the world has subtly changed and that something of immense significance is about to be revealed; the patient feels "something sinister is going on but I cannot say what." This delusional atmosphere provides the context from which fully formed delusions crystallise.

delusional perception

A real, normally perceived object is given a private, unwarranted delusional meaning (a curtain drawn, leaves turning yellow, become a signal that he is the chosen one). Schneider's two-memberedness: link one is the normal percept, link two is the delusional significance. A first-rank symptom of schizophrenia.

Sudden delusional idea (autochthonous idea, delusional intuition)

A fully formed delusional belief arrives in a single stage, out of the blue, with no preceding perception, "a bolt from the blue" (distinguished from delusional perception, which has two stages: percept then meaning).

Delusional memory (delusional retrospective falsification)

A delusional significance is attached to a real past event, or an autochthonous delusion is falsely dated to the past so the memory itself is the delusion (Fish).

CLINICAL ANCHOR

A 25-year-old man saw the yellowing leaves of a tree outside his house (a true, normal percept) and was instantly and unshakeably certain this was a signal from God that he alone was the chosen one, with no prior delusional system. That is a textbook delusional perception, not a misinterpretation of a pre-existing belief.

14.4 Delusional perception as a first-rank symptom (and the modern caveat)

First-rank status. Schneider listed delusional perception among the first-rank symptoms of schizophrenia, alongside audible thoughts, voices arguing or commenting, passivity of affect, impulse and volition, somatic passivity, thought insertion, withdrawal and broadcast. It is a disorder of thought, not of perception: the percept is entirely normal, only the meaning is deluded.

PEARL

The currency point examiners reward: first-rank symptoms are NOT pathognomonic of schizophrenia (they occur in mania, psychotic depression and organic states) and neither ICD-11 nor DSM-5 gives them privileged diagnostic weight any longer. Delusional perception remains the phenomenologically purest FRS, but it is a pointer, not proof.

14.5 Delusions classified by content, part one: the affect-linked themes

By theme. Once origin is settled, delusions are catalogued by content. Content carries some diagnostic hint but is defined descriptively.

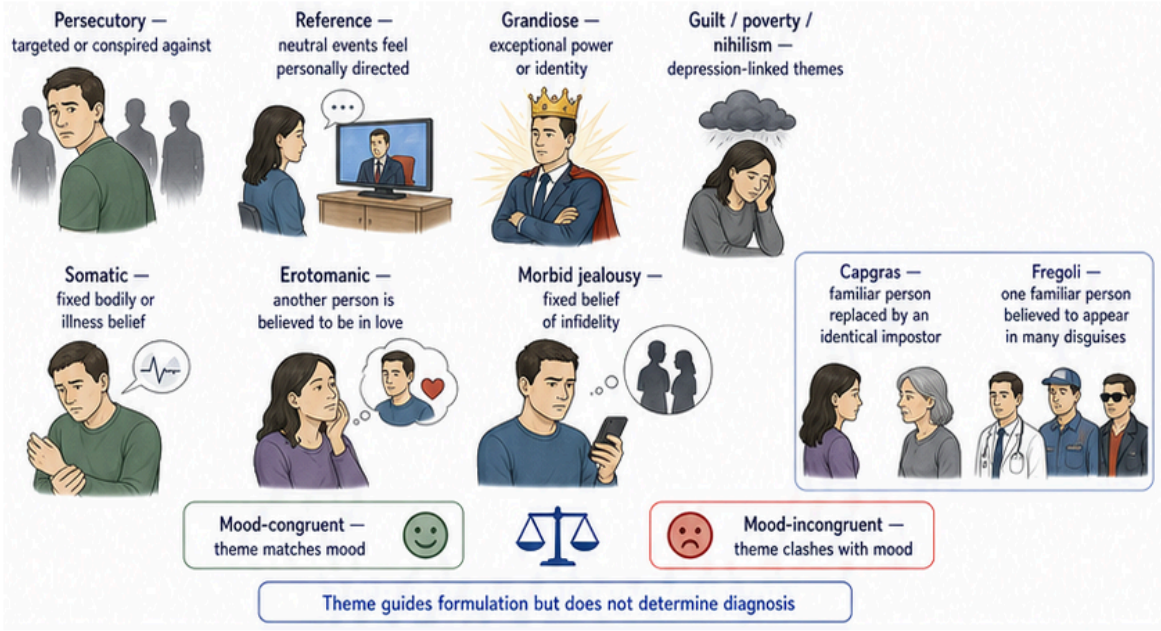


Fig 6.23 Delusions: theme, mood and misidentification.

persecutory (paranoid)

The conviction of being targeted, harassed, cheated, spied on or conspired against; the commonest theme, seen across schizophrenia, affective psychoses and organic states.

Delusion of reference

Events, objects, remarks, gestures or media items (a newspaper article, a stranger's cough) are believed to carry a special personal meaning directed at the patient.

grandiose delusion (expansive)

Inflated belief in one's own power, identity, wealth, talent or special mission; characteristic of mania and of grandiose-type delusional disorder.

Religious delusion

A delusion with religious content (being God, the chosen one, damned); judged delusional only when it exceeds the patient's faith community's shared beliefs.

Delusion of guilt (self-accusation)

Unfounded conviction of having committed a terrible sin or crime deserving punishment; a mood-congruent feature of severe depression.

Nihilistic delusion (Cotard)

Belief that oneself, a body part, others or the world has ceased to exist, is dead, rotting or has no blood or bowels; described by Cotard (1882), typically in severe depression.

14.6 Delusions classified by content, part two: body, love, jealousy, identity, control

Hypochondriacal (somatic) delusion

Fixed false belief of harbouring a serious illness (cancer, AIDS, infestation) despite reassurance; the core of monosymptomatic hypochondriacal psychosis.

Amorous delusion (erotomania, de Clerambault's syndrome)

The unshakeable conviction that another person, usually of higher status, is secretly in love with the patient.

Morbid jealousy (Othello syndrome, delusion of infidelity)

Delusional certainty that the partner is being unfaithful, driving relentless checking and interrogation; carries a real risk of violence.

Capgras delusion (illusion of doubles)

Belief that a familiar person (usually close) has been replaced by an identical impostor or double; a delusional misidentification.

Fregoli delusion

Belief that a familiar persecutor is disguising himself as, or masquerading behind, various strangers the patient meets; the mirror image of Capgras.

Delusions of control and passivity

The patient experiences his own actions, impulses, thoughts or affect as made or controlled by an external agency (passivity phenomena, first-rank symptoms).

> **COMMON TRAP**
>
> Capgras is the double (replacement of the familiar by an impostor); Fregoli is the disguise (a single persecutor hiding inside many strangers). Do not swap them. Both are delusional misidentification syndromes, phenomenological symptoms that can also present as named syndromes.

14.7 The discrimination the exam loves: delusion versus overvalued idea versus obsession

The classic viva triad. An **overvalued idea** (Wernicke 1900, reviewed by McKenna 1984) is a comprehensible, understandable, isolated belief, strongly held with intense affect and pursued beyond the bounds of reason, dominating the person's life, yet not utterly fixed and, crucially, ego-syntonic (the patient does not regard it as senseless and does not resist it). Jaspers held that the overvalued idea differs from a delusion mainly in the level of conviction, and Fish added that the patient with an overvalued idea invariably acts on it, determinedly and repeatedly. The obsession, by contrast, is intrusive, recognised as the patient's own but senseless, ego-dystonic and actively resisted.

FEATURE	DELUSION	OVERVALUED IDEA	OBSESSION
Fixity / conviction	**Absolute, incorrigible**	Strong but not utterly fixed	Doubt present, not fixed
Understandability	Un-understandable (if primary)	**Comprehensible, understandable**	Comprehensible but senseless
Resistance by patient	None	None	**Present, active resistance**
Ego relation	Ego-syntonic	**Ego-syntonic**	Ego-dystonic
Sense of intrusiveness	Absent	Absent	**Present, felt as intrusive**
Insight	Absent	Partial or absent	**Retained (thought is own, senseless)**
Prototype	Persecutory delusion	Anorexia, morbid jealousy	Contamination obsession

The three-way discrimination on fixity, understandability, resistance, ego relation and insight; the diagnostic axis examiners probe most.

HOLD THIS

A delusion is a fixed, false, incorrigible belief out of cultural keeping; falsity is its weakest criterion. The obsession is resisted and ego-dystonic with insight; the overvalued idea is comprehensible and strongly held but not absolutely fixed.

14.8 Mood-congruent versus mood-incongruent delusions

Congruence with prevailing affect. This axis matters for classifying psychotic mood disorder.

Mood-congruent

Content matches the affective state: guilt, nihilism, poverty and hypochondriasis in depression; grandiosity and special powers in mania.

Mood-incongruent

Content is at odds with the mood, for example persecutory or passivity delusions in a euphoric manic patient; their presence carries prognostic and diagnostic weight.

TRAP Mood-incongruent delusional content (a delusion whose theme clashes with the mood) is not the same as incongruity of affect (an emotional display that clashes with the topic) - one is content, the other is expressed affect.

14.9 Bizarre versus non-bizarre delusions

Physical possibility is the axis.

Bizarre delusion

Content is clearly implausible, not understandable to same-culture peers and not derived from ordinary life experience (e.g. one's organs have been removed and replaced without a scar); historically weighted toward schizophrenia.

Non-bizarre delusion

Content, though false, could conceivably occur (being followed, poisoned, deceived by a spouse); the hallmark of delusional disorder.

PEARL

DSM-5 downgraded bizarreness: it removed the old rule that a single bizarre delusion alone met Criterion A for schizophrenia. Inter-rater reliability for judging bizarreness is poor, so lean on the primary versus secondary and delusion versus overvalued idea distinctions, which the examiner scores more reliably.

MNEMONIC

"SII" for the Jaspers triad

Subjective certainty, Incorrigibility, Impossibility (or falsity) of content. For the primary delusional experiences, remember the sequence a patient may pass through: delusional Mood, delusional Perception, sudden delusional Idea, delusional Memory (M-P-I-M).

GOOD TO REMEMBER

- **Delusion (definition):** fixed, false belief, absolute conviction, out of keeping with social and cultural background, not amenable to reason (Jaspers, Sims, K&S).
- **Jaspers' three criteria:** subjective certainty, incorrigibility, impossibility or falsity of content (the last being the weakest).
- **primary delusion:** autochthonous, sudden, fully formed, un-understandable; heavy diagnostic weight in schizophrenia.
- **secondary delusion:** understandable as arising from mood, another experience (hallucination) or a pre-existing delusion; may systematise.
- **delusional mood (Wahnstimmung):** uncanny sense that something significant is about to be revealed; the atmosphere before the delusion crystallises.
- **delusional perception:** real normal percept given a private delusional meaning; Schneider's two-memberedness; a first-rank symptom.
- **Autochthonous (sudden delusional) idea:** fully formed delusion in one stage, "bolt from the blue," no preceding percept.
- **Delusional memory:** delusional meaning attached to a real past event, or delusion falsely dated to the past (Fish).
- **persecutory (paranoid):** conviction of being targeted, harassed or conspired against; commonest theme.
- **Delusion of reference:** ordinary events or remarks carry a special personal meaning aimed at the patient.
- **grandiose delusion:** inflated power, identity, wealth or mission; classic in mania.
- **Religious / guilt / nihilistic:** religious content; unfounded sin deserving punishment; Cotard (1882) belief of non-existence or being dead.
- **Hypochondriacal:** fixed false belief of serious illness despite reassurance.
- **Erotomania (de Clerambault):** conviction a higher-status other secretly loves the patient. **Othello:** delusional infidelity, violence risk.
- **Capgras:** familiar person replaced by an impostor double. **Fregoli:** a persecutor disguised as many strangers.
- **Passivity / control:** actions, impulses, thoughts or affect experienced as externally made; first-rank symptoms.
- **overvalued idea (Wernicke 1900, McKenna 1984):** comprehensible, strongly held, not utterly fixed, ego-syntonic, unresisted, dominates life (anorexia, morbid jealousy).
- **Obsession:** intrusive, recognised as own but senseless, ego-dystonic, resisted, insight retained.
- **Mood congruence:** congruent (guilt, nihilism in depression; grandiosity in mania) versus incongruent (persecution in mania).
- **Bizarre vs non-bizarre:** physically impossible versus conceivable; DSM-5 removed the single-bizarre-delusion shortcut for schizophrenia.
- **Modern caveat:** first-rank symptoms (including delusional perception) are not pathognomonic and lost privileged status in ICD-11 and DSM-5.

15 · Schneiderian first-rank symptoms

The single most examined list in descriptive psychopathology. Kurt **Schneider** (1959), working in the Jaspersian descriptive tradition, proposed a set of **first-rank** symptoms (**symptoms of the first rank**, **Symptome ersten Ranges**) not as a theory of what schizophrenia *is*, but as a pragmatic clinical shortcut: experiences that, when present in the absence of coarse brain disease, let a busy clinician make the diagnosis reliably. He explicitly ranked them above

second-rank symptoms (other hallucinations, perplexity, mood change) and above the affective disorders, so that an organic or schizophrenic picture took precedence over an unmistakable manic or melancholic one (Companion 2010; Sims 2015).

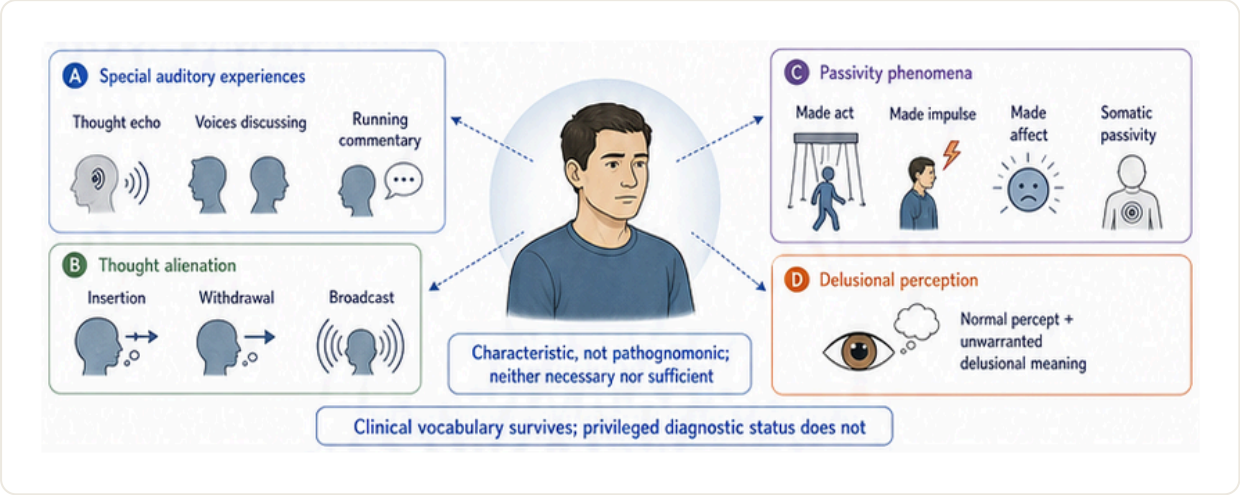


Fig 6.24 Schneiderian first-rank symptoms.

For the exam the two things that must be paired are (1) the crisp list in its classic groups, and (2) the modern caveat. Schneider called them pathognomonic of schizophrenia "except in the presence of coarse brain disease", but they are **not** pathognomonic: they occur in mania and in organic states, and up to a fifth of people with schizophrenia never show any of them (Fish 2007; Kaplan and Sadock 2024). Because of this they have lost their privileged diagnostic status: DSM-5 (2013) removed the rule that a single first-rank symptom sufficed for the A-criterion, and ICD-11 (2022) no longer grants them special weight. Learn them as the highest-yield descriptive vocabulary, not as a diagnostic test.

15.1 What Schneider actually claimed (and the exact caveat)

Pragmatic, not theoretical. Schneider (1959) built the list for reliability, not validity. He wrote that these symptoms are diagnostic of schizophrenia "provided only that there is no question of cerebral disease"; the phrase *coarse brain disease* is the escape clause every examiner wants quoted. He did not believe they revealed a mechanism, only that they were the most characteristic and easily recognised markers available to a clinician at the bedside (Kaplan and Sadock 2024). The three ranks form a hierarchy: first-rank symptoms outrank second-rank symptoms, and both outrank affective symptoms, which is why a Schneiderian diagnostician diagnosed schizophrenia even when florid mood symptoms were present.

RULE **Quote the escape clause: first-rank symptoms point to schizophrenia only "in the absence of coarse brain disease".** Schneider built them for reliability at the bedside, not as a theory of what schizophrenia is.

15.2 Group (a): auditory hallucinations of a special kind

Three specific forms, all auditory. Schneider singled out three verbal auditory hallucinations. These are the ones to define precisely, because "voices" alone is not first-rank.

Thought echo (audible thoughts, Gedankenlautwerden, echo de la pensee)

The patient hears their own thoughts spoken aloud, just before, at the same time as, or immediately after they occur. Example: while washing up, "I thought I must fetch washing powder, and instantly a voice said, I shall go to the market to buy washing powder" (Clinical Methods AIIMS 2024).

Voices arguing or discussing (third person)

Two or more hallucinatory voices discuss or argue about the patient, referring to them in the third person ("he", "she"), as though the patient were absent.

Running commentary

A voice (or voices) gives a running commentary on the patient's actions as they happen: "she is putting salt in excess, she is leaving the food unattended" (Clinical Methods AIIMS 2024).

The discriminator. The form, not the content, is what matters. Third-person and running-commentary voices are first-rank; second-person command hallucinations ("get up and run away") are *not* first-rank, however distressing.

15.3 Group (b): thought alienation

The self-boundary is breached. The unifying experience is loss of the normal sense that one's own thoughts are private and one's own. Cross-refer the thought-disorder topic for fuller treatment; here are the three first-rank members.

Thought insertion

Thoughts that are not the patient's own are experienced as put into their mind by an external agent. The alienness of ownership, not merely the content, is the sign.

Thought withdrawal

The patient experiences thoughts being actively removed or extracted from their mind by an outside force, often felt as a sudden emptying.

Thought broadcast

The patient's thoughts escape and are experienced as accessible to others, as if spoken aloud or transmitted, without any act of speaking. Distinguish from thought echo, which is a hallucination of hearing one's own thoughts, not a leakage to others (Clinical Methods AIIMS 2024).

15.4 Group (c): passivity phenomena (made or influenced experiences)

Volition, impulse, affect and body are hijacked. In **passivity** phenomena the patient experiences their own actions, urges, feelings or bodily sensations as made, imposed or controlled by an external agency: the sense of personal agency (the feeling that "I am the author of this") is lost while the act still occurs. The key words examiners look for are "made" and "as if controlled".

Made act (made volition)

The patient carries out an action but experiences it as not their own; some external agent is felt to be moving them, and they are a passive participant in their own behaviour.

Made impulse (made drive)

An impulse or drive to act is experienced as imposed from outside, so the urge itself is felt to be alien and controlled.

Made affect (made feeling)

Emotions the patient does not own are felt to be produced in them by an external agent: "the feelings are not mine, they are put into me".

Somatic passivity

Bodily sensations (tactile or visceral) are experienced as imposed on the patient by an outside agency, for example a sensation of being irradiated or manipulated from without.

15.5 Group (d): delusional perception

A real percept, an unwarranted delusional meaning. In **delusional perception** a normal, correctly perceived object or event is invested, in a single step, with a highly personal delusional significance that is not logically connected to it: seeing the traffic light turn red and knowing instantly "that means I am the chosen one". Schneider stressed its *two-memberedness* (link one the real perception, link two the abnormal meaning), and Jaspers held it to be *un-understandable*, arising without any mediating inference (Schneider 1959; Jaspers 1913; Sims 2015). It is the only first-rank symptom that is a delusion rather than a hallucination or passivity experience.

15.6 The classic list at a glance

GROUP	FIRST-RANK SYMPTOM	ONE-LINE DESCRIPTION
(a) Special auditory hallucinations	**Thought echo**	Own thoughts heard spoken aloud (audible thoughts, Gedankenlautwerden)
	Voices arguing / discussing	Two or more voices discuss the patient in the third person
	Running commentary	A voice narrates the patient's actions as they happen
(b) Thought alienation	Thought insertion	Alien thoughts put into the mind by an external agent
	Thought withdrawal	Thoughts extracted from the mind by an outside force
	Thought broadcast	Thoughts leak out and are shared with others without speech
(c) Passivity (made) phenomena	**Made act**	Actions experienced as controlled by an external agent
	Made impulse	Urge to act imposed from outside
	Made affect	Emotions felt to be produced by an external agent
	Somatic passivity	Bodily sensations imposed by an outside agency
(d) Delusional perception	Delusional perception	Real percept given an instant, unwarranted delusional meaning

The eleven classic first-rank symptoms in Schneider's four groups; three hallucinatory forms, three thought-alienation experiences, four passivity phenomena, and delusional perception.

HOLD THIS

First-rank symptoms are highly characteristic but not pathognomonic; they are neither necessary nor sufficient for schizophrenia. DSM-5 and ICD-11 removed the single-symptom rule, so learn them as vocabulary, not a diagnostic test.

15.7 Why they are not pathognomonic

They cross diagnostic boundaries. The single most important teaching point. First-rank symptoms are neither necessary nor sufficient for schizophrenia. They occur in affective psychosis: Schneiderian first-rank symptoms have been reported in around 10 to 20% of manic patients, where they are usually short-lived, changing in content within days (Shorter Oxford 2012). They occur in organic states, in psychotic depression, in substance-induced psychosis and in temporal lobe epilepsy. Conversely, up to a fifth of people with schizophrenia never manifest any first-rank symptom (Fish 2007). The International Pilot Study of Schizophrenia (WHO) confirmed they appear cross-culturally but did not establish specificity (Kaplan and Sadock 2024).

10-20%	~20%
OF MANIC PATIENTS SHOW FRS	OF SCHIZOPHRENIA SHOW NONE

15.8 Loss of special status in DSM-5 and ICD-11

The one-symptom rule is gone. Earlier systems (DSM-III onward, ICD-10) gave first-rank symptoms extra diagnostic weight; ICD-10 allowed a single clear first-rank symptom to satisfy criterion. DSM-5 (2013) abolished this: bizarre delusions and first-rank auditory hallucinations no longer count double, and at least two criterion-A symptoms are now required, one of which must be delusions, hallucinations or disorganised speech. ICD-11 (2022) similarly dropped their privileged position, treating them as one class of core symptom among several. The clinical vocabulary survives; the diagnostic shortcut does not.

COMMON TRAP

First-rank symptoms do not equal schizophrenia. The exam favourite: a manic patient with thought insertion and delusional perception is *not* thereby schizophrenic, because around 10 to 20% of manic patients show first-rank symptoms and up to a fifth of people with schizophrenia show none. First-rank symptoms are highly characteristic descriptive markers, but they are not necessary, not sufficient, and not pathognomonic; the diagnosis rests on the whole picture and course, not on ticking a Schneiderian box. Also do not confuse second-person command hallucinations ("run away") with first-rank third-person or running-commentary voices; commands are not first-rank.

MNEMONIC

A B C D: Auditory, Broadcast-of-thought, Controlled (passivity), Delusional perception

The four Schneiderian groups map to A (the three special auditory hallucinations), B (thought alienation, of which broadcast is the memorable member alongside insertion and withdrawal), C (Controlled = the made or passivity phenomena), and D (delusional perception). Within C, remember the four "made" experiences: made act, made impulse, made affect, and somatic passivity.

GOOD TO REMEMBER

- **Kurt Schneider (1959):** proposed first-rank symptoms as pragmatic, reliable markers of schizophrenia "except in the presence of coarse brain disease"; ranked above second-rank and above affective symptoms.
- **Thought echo (Gedankenlautwerden, audible thoughts):** hearing one's own thoughts spoken aloud, just before, during or after thinking them.
- **Voices arguing / discussing:** two or more voices talk about the patient in the third person.
- **Running commentary:** a voice narrates the patient's actions as they occur.
- **Thought insertion:** alien thoughts placed into the mind by an external agent.
- **Thought withdrawal:** thoughts felt to be removed from the mind by an outside force.
- **Thought broadcast:** one's thoughts escape and become accessible to others without speech.
- **Made act (made volition):** passivity of action, experienced as externally controlled.
- **Made impulse:** an urge to act imposed from outside.
- **Made affect:** emotions felt to be produced by an external agent.
- **Somatic passivity:** bodily sensations imposed by an outside agency.
- **Delusional perception:** a real percept given an instant, unwarranted personal delusional meaning (the only first-rank delusion; Jaspers' two-member analysis).
- **Not pathognomonic:** present in around 10 to 20% of manic patients and in organic states; absent in up to a fifth of people with schizophrenia.
- **DSM-5 (2013) and ICD-11 (2022):** removed the single-first-rank-symptom rule; first-rank symptoms lost their special diagnostic weight.

16 · Disorders of the experience of self

The disorders of self are the psychopathology of the "I". The **disorders of self** (the ego disorders, the **Ich-Storungen**) concern not *what* the patient perceives or believes but the very awareness that experience belongs to a self and that this self is bounded off from the world. Every normal act of consciousness carries an implicit sense of ownership: *I* am thinking this thought, *I* am doing this act, *I* am a single person now and the same person I was yesterday, and there is a boundary between what is inside me and what is outside. Jaspers (1913) in *General Psychopathology* and later Scharfetter (1980) analysed this awareness of the self into distinct dimensions; their disorder gives the ego disorders their exam-relevant structure (Sims 2015; Fish 2007).

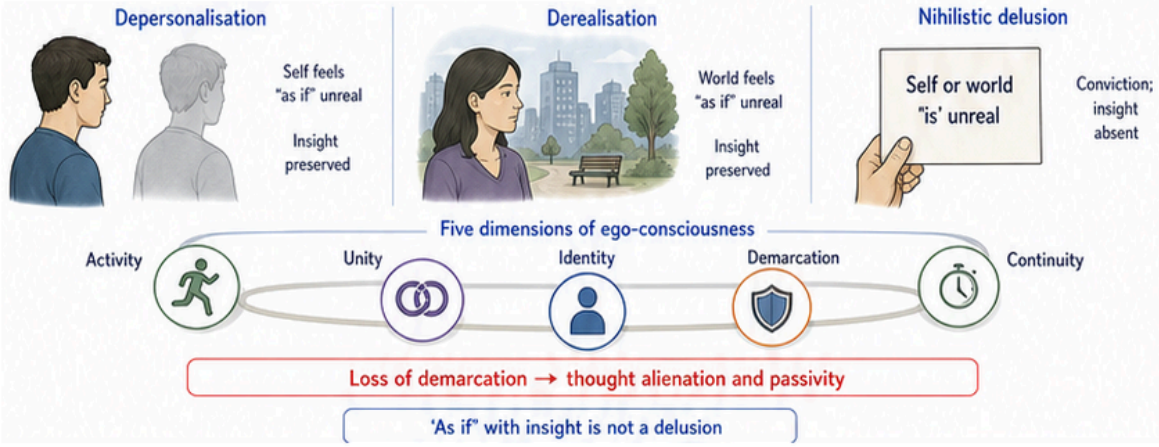


Fig 6.25 Experience of self: 'as if' versus 'is'.

For the exam, three things must be held together. First, the definition of the **ego boundary** and its loss as the substrate of passivity and thought alienation. Second, depersonalisation and derealisation as changes in the *quality* of self-awareness that keep their "as if" character and therefore preserve insight, unlike delusion. Third, the Jaspers to Scharfetter dimensions of ego-consciousness with the disorder that maps onto each. Ground the description, not the explanation: as always in descriptive psychopathology it is the form of the experience that is the sign (Jaspers 1913; Sims 2015).

16.1 Awareness of the self and its boundary with the world

The self is normally felt, not inferred. Healthy self-experience has a taken-for-granted, pre-reflective quality: I do not have to work out that a thought is mine or that my body is me, it is simply given. Jaspers (1913) described this immediate ego-consciousness as the background against which all other experience is set, and Scharfetter (1980) called it the awareness of one's own being (*Ich-Bewusstsein*). The self is also demarcated: there is an experienced membrane between the inner world (thoughts, feelings, will, body) and the outer world of objects and other people. Disorders of self are disturbances of this immediate awareness and of this membrane, and they range from the mild and neurotic (depersonalisation) to the psychotic dissolution of the boundary in schizophrenia (Sims 2015).

16.2 The ego boundary and its loss

The membrane between self and not-self. The **ego boundary** is the experienced line that separates what is self from what is not-self, that marks internal mental events as belonging to me and external percepts as belonging to the world. Paul Federn introduced the concept in the psychoanalytic theory of psychosis, holding that in schizophrenia the ego boundary that ordinarily separates thoughts and feelings from perceptions becomes faulty, so that inner mental content is no longer marked with "ego feeling" as one's own and is experienced instead as external reality (Kaplan and Sadock 2024). When the ego boundary fails, the patient can no longer reliably tell whether an experience arises from within or is imposed from without: this is the common root of thought alienation (insertion, withdrawal, broadcast) and of the passivity phenomena. Schneider spoke of the same clinical picture as a "loss of ego boundaries" (Companion 2010). The

loss of the ego boundary is therefore the descriptive substrate that unifies the most characteristic first-rank experiences of schizophrenia.

16.3 Depersonalisation

A change in the awareness of one's own self. **Depersonalisation** (also spelt **depersonalization** in American texts) is an altered, uncanny change in the quality of self-awareness: the patient feels unreal, detached, cut off from their own experience, as though watching themselves from outside or acting like an automaton or robot going through the motions. Feelings feel deadened or absent, actions feel mechanical, the self feels strange and unfamiliar (Sims 2015). The defining feature is the *"as if"* quality: the patient says they feel *as if* they were unreal, *as if* in a dream, *as if* watching themselves, and they retain full insight that this is a subjective change and not literally true. That preserved "as if" awareness is exactly what separates depersonalisation from a nihilistic delusion, in which the patient believes with delusional conviction that they truly do not exist or have no self (Fish 2007).

Depersonalisation (depersonalization)

An "as if" change in the awareness of one's own self: feeling unreal, detached, watching oneself, emotionally deadened, an automaton, with insight preserved.

Emotional numbing (de-affectualisation)

The component in which affect feels flattened or absent, so the patient complains of feeling nothing, not even grief they know they should feel.

Anaesthesia dolorosa psychica

The painful awareness of the loss of feeling itself: distress precisely because emotions cannot be felt.

16.4 Derealisation

The outer world, not the self, feels unreal. **Derealisation** (also spelt **derealization**) is the outward-facing counterpart: the surrounding world feels unreal, flat, two-dimensional, lifeless, artificial or stage-managed, as if made of cardboard or seen through glass. People may look like actors or automata, familiar places feel strange, colours seem dull and the world seems drained of vitality (Sims 2015). Depersonalisation and derealisation are together classically described as the "as-if" phenomena: they very frequently co-occur, both share the preserved "as if" quality and preserved insight, and both are grouped in DSM-5 as depersonalisation-derealisation disorder. They are non-specific, appearing in anxiety and panic (Roth's phobic-anxiety-depersonalisation syndrome), depression, temporal lobe epilepsy, migraine, fatigue and sleep deprivation, dissociative states, and as an SSRI or benzodiazepine withdrawal symptom, and can occur transiently in healthy people (Kaplan and Sadock 2024).

Derealisation (derealization)

An "as if" change in the awareness of the surrounding world: it feels unreal, flat, lifeless, artificial or stage-set, with insight preserved.

Deja vu / jamais vu (adjacent)

Familiarity phenomena often reported alongside derealisation: the unfamiliar felt as familiar (deja vu) or the familiar felt as strange (jamais vu).

16.5 Depersonalisation versus derealisation versus delusion

FEATURE	DEPERSONALISATION	DEREALISATION	NIHILISTIC DELUSION
What feels unreal	The self ("I feel unreal")	The outer world ("the world feels unreal")	Self or world (asserted as fact)
Quality of experience	**"As if" unreal**	**"As if" unreal**	**"Is" unreal (conviction)**
Insight	Preserved	Preserved	Absent
Reality testing	Intact	Intact	Lost
Typical setting	Anxiety, depression, dissociation, fatigue	Same, often with depersonalisation	Psychotic (Cotard's) depression, schizophrenia

The "as if" quality with preserved insight is the single discriminator that separates depersonalisation and derealisation from a nihilistic (Cotard) delusion, in which unreality is asserted as fact with delusional conviction.

RULE **The "as if" quality with preserved insight is what keeps depersonalisation and derealisation from being delusions.** "I feel as if I am unreal" (insight kept) is not "I do not exist" (Cotard, insight lost).

16.6 The five dimensions of ego-consciousness (Jaspers and Scharfetter)

Jaspers' four formal characteristics, and Scharfetter's fifth. Jaspers (1913) held that immediate ego-consciousness has *four* formal characteristics: activity, unity at any one moment, continuity of identity over time, and demarcation from the environment. Scharfetter then *added a fifth*, **ego vitality**, the awareness of simply being or existing, which Jaspers had folded inside the awareness of activity. The resulting five, each with a characteristic disorder, are the most examinable single frame for the disorders of self. Note the exam trap: the fifth dimension is vitality, not a separate "continuity", because continuity of identity over time is already Jaspers' identity aspect (Sims 2015; Fish 2007).

Awareness of vitality (ego-vitality; Scharfetter's addition)

The awareness of simply being alive and existing. Disorder: the conviction of not existing, of being dead or having no body, which is the core experience of the nihilistic (Cotard) delusion, and the deadened quality of severe depersonalisation.

Awareness of activity (ego-activity)

The sense that I am an active agent, that my mental acts and perceptions are my own doing. Disorder: loss of the sense of agency, and the "acting as an automaton" quality of depersonalisation.

Awareness of unity (ego-consistency, coherence)

The awareness that at any one moment I am a single, undivided person. Disorder: the experience of being split or divided, of two selves or a self fragmenting.

Awareness of identity (ego-identity, continuity of identity over time)

The awareness that I am the same person now that I have always been, persisting as one and the same self from moment to moment and across the lifespan. Disorder: the conviction of having become someone or something else, as in metamorphosis or delusional misidentification of the self, and the sense of being a different self before and after a point.

Awareness of demarcation (ego-boundary)

The awareness of a boundary between self and not-self, between inner and outer world. Disorder: loss of the boundary, giving thought insertion, withdrawal, broadcast and the passivity (made) phenomena.

The bridge to the earlier sections. Depersonalisation is chiefly a disorder of the awareness of activity, shading into vitality when the patient feels dead rather than merely unreal; the nihilistic delusion is the full disorder of vitality; and the loss of the ego boundary is the disorder of the awareness of demarcation and is the substrate of passivity and thought alienation. The scheme thus ties the whole topic together.

HOLD THIS

Loss of the ego boundary (the awareness of demarcation) is the descriptive substrate of passivity and thought alienation. Scharfetter's five dimensions - activity, unity, identity, demarcation, continuity - each carry their own disorder.

16.7 Passivity experiences as loss of the self's demarcation

Agency is retained by the act but lost by the self. In **passivity** experiences the patient carries out an action, feels an emotion, has an impulse or registers a bodily sensation, but experiences it as made, imposed or controlled by an external agency: the act still occurs, yet the sense of being its author is gone. Descriptively this is precisely a failure of the awareness of demarcation, a breach of the ego boundary that no longer walls off the self's own volition, affect and body from outside control (Sims 2015; Fish 2007). The passivity phenomena are Schneiderian first-rank symptoms; cross-refer the first-rank topic for their diagnostic weight and the modern caveat that they are not pathognomonic.

Made act (made volition)

An action is performed but experienced as controlled by an external agent; the patient is a passive vehicle of their own behaviour.

Made impulse (made drive)

The urge or drive to act is felt to be imposed from outside and alien to the self.

Made affect (made feeling)

Emotions are experienced as produced in the patient by an external agency: "these feelings are not mine, they are put into me".

Somatic passivity

Bodily or visceral sensations are experienced as imposed by an outside force, for example being irradiated or manipulated from without.

16.8 Where the ego disorders sit clinically

A spectrum from neurotic to psychotic. The disorders of self span a range. At the mild end, depersonalisation and derealisation are non-psychotic, keep their "as if" quality and preserved insight, and occur in anxiety, depression, dissociation, fatigue and healthy people. At the severe end, loss of the ego boundary, the passivity phenomena and thought alienation are psychotic disorders of the awareness of demarcation and are highly characteristic of schizophrenia. Between them, disorders of the awareness of unity, identity and continuity shade from the

depersonalised "as if I were two people" into frank delusions of being split, transformed or replaced. Reading a report of unreality, the crucial clinical question is always whether the "as if" quality and insight are preserved (depersonalisation or derealisation) or lost (delusion) (Sims 2015; Fish 2007).

CLINICAL ANCHOR

A young woman with panic attacks says: "During the attacks I feel as if I'm not really here, like I'm watching myself from behind a glass wall, and the room looks flat and fake, like a film set." Two signs are present: depersonalisation (watching herself, feeling unreal) and derealisation (the room flat and fake). Both carry the "as if" quality and she knows the change is in her, not in reality, so insight is intact. This is not psychosis; it is the classic anxiety-linked depersonalisation-derealisation picture, and naming it correctly steers you to anxiety management rather than antipsychotics.

COMMON TRAP

Do not confuse depersonalisation with a nihilistic delusion. The patient who says "I feel *as if* I have no self" and knows it is a feeling has depersonalisation with insight; the patient who states as fact "I have no head, I do not exist, my organs have rotted away" and is convinced of it has a nihilistic (Cotard) delusion. The word "unreal" appears in both; the discriminator is the preserved "as if" quality and insight, not the content. Equally, do not label ordinary loss of the ego boundary as merely "poor concentration": thought insertion, withdrawal and broadcast are disorders of the awareness of demarcation, not of attention.

MNEMONIC

V A C I D: Vitality, Activity, Consistency (unity), Identity, Demarcation

The five dimensions of ego-consciousness, Jaspers' four plus Scharfetter's fifth: awareness of Vitality (being alive at all, Scharfetter's addition), Activity (agency), Consistency or unity (single person now), Identity (same person as always, continuous through time), and Demarcation (the ego boundary). Their disorders, respectively: the nihilistic delusion of not existing; depersonalisation of agency; feeling split; feeling transformed into another; and loss of the boundary giving passivity and thought alienation.

GOOD TO REMEMBER

- **Disorders of self (ego disorders, Ich-Storungen):** disturbances of the immediate awareness that experience belongs to a self and that the self is bounded from the world (Jaspers 1913; Scharfetter 1980).
- **Ego boundary (Federn):** the experienced membrane between self and not-self; its loss un-marks inner events as one's own and is the substrate of passivity and thought alienation (Kaplan and Sadock 2024; Schneider's "loss of ego boundaries").
- **Depersonalisation (depersonalization):** an "as if" change in awareness of one's own self, feeling unreal, detached, watching oneself, an automaton, with insight preserved.
- **Derealisation (derealization):** an "as if" change in awareness of the surrounding world, which feels unreal, flat, lifeless or artificial, with insight preserved.
- **"As if" quality:** the defining feature of depersonalisation and derealisation; preserves insight and separates them from nihilistic (Cotard) delusion, where unreality is asserted as fact.
- **Jaspers (1913):** formal analysis of immediate ego-consciousness in General Psychopathology.
- **Scharfetter (1980) five dimensions:** awareness of activity, of unity, of identity, of demarcation (the boundary), and of continuity of the self, each with its own disorder.
- **Awareness of activity:** sense of agency and vitality; disorder = depersonalisation, the automaton quality.
- **Awareness of unity:** being one person at a moment; disorder = feeling split or divided.
- **Awareness of identity:** being the same person one has always been; disorder = feeling transformed into another.
- **Awareness of demarcation:** the self-world boundary (the ego boundary); disorder = thought insertion, withdrawal, broadcast and passivity.
- **Awareness of continuity:** the self persisting through time; disorder = feeling discontinuous, a broken self.
- **Passivity (made) phenomena:** made act, made impulse, made affect and somatic passivity; loss of the self's demarcation; Schneiderian first-rank but not pathognomonic (cross-refer first-rank).
- **Depersonalisation-derealisation:** the classic "as-if" phenomena; non-specific, seen in anxiety, depression, dissociation, epilepsy, migraine, fatigue and SSRI or benzodiazepine withdrawal; grouped as one disorder in DSM-5.

17 · Disorders of emotion and affect

The **disorders of emotion** are the descriptive psychopathology of feeling: how the range, quality, tone, congruity and stability of a person's emotional life go wrong, read purely at the level of what is observed and reported. This is a genuine Paper I long-essay topic in its own right, distinct from the *theories* of emotion (James-Lange, Cannon-Bard, Schachter-Singer), which belong to the General and Developmental Psychology notes and explain the *mechanism* of normal emotion. Here the task is Jaspers, Fish and Sims phenomenology: name the abnormality, define it crisply, and give a clinical example, form over content (Jaspers 1913, Fish 2007, Sims 2015).

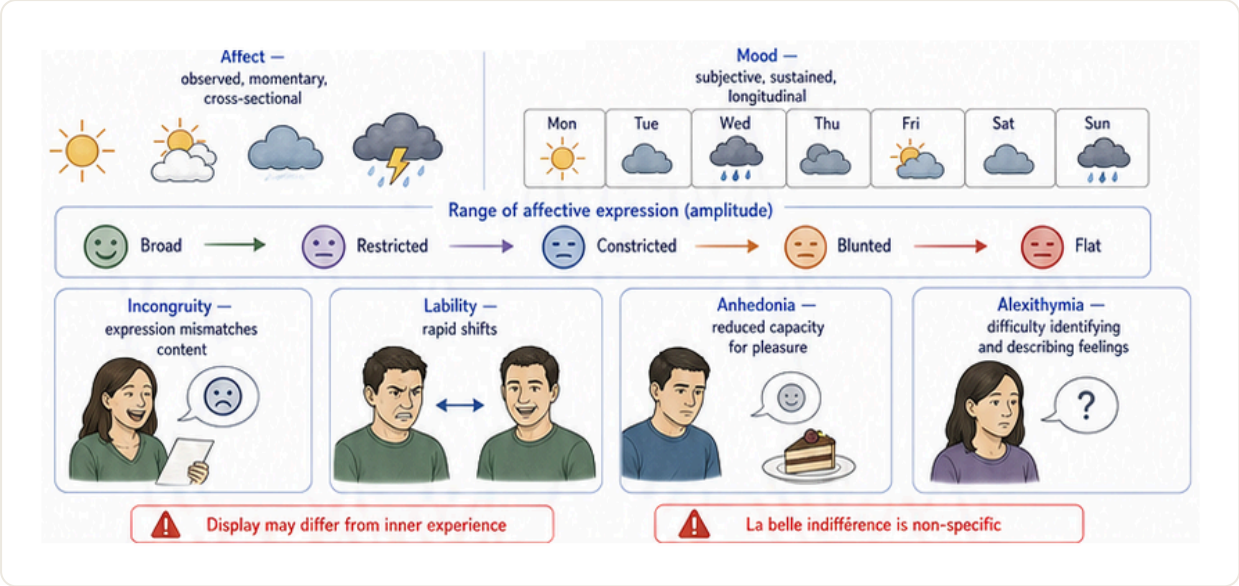


Fig 6.26 Mood, affect and emotional experience.

Exam framing. Examiners reward three things kept clean. First, the vocabulary: **affect** versus **mood** versus emotion, a distinction that anchors the whole answer. Second, the disorders of the *tone or quality* of mood (depression, elation, anxiety, irritability, perplexity, apathy). Third, the disorders of the *expression, congruity and stability* of affect (blunting and flattening, incongruity, lability, and the special signs anhedonia and alexithymia). Weave in the caveat that blunting and incongruity, though characteristic of schizophrenia, are not by themselves pathognomonic and must be judged over the whole interview, not spot-diagnosed (Companion to Psychiatric Studies).

17.1 The vocabulary: affect, mood and emotion

Get the three terms exactly right; the whole answer rests on them. The standard convention (Kaplan & Sadock 2024, Sims 2015) separates the momentary observed expression from the sustained subjective state.

Emotion

The generic term for a complex feeling state with psychic, somatic and behavioural components; a stirred-up condition of the organism. Affect and mood are the two clinical ways of sampling it.

Affect

The *momentary, observed, cross-sectional* emotional expression: the outward, moment-to-moment tone the clinician sees, inferred from face, voice, posture and reactivity during the interview. It is to mood as weather is to climate. Described by quality, range, appropriateness (congruity) and reactivity.

Mood

The *sustained, pervasive, subjective* emotional state, coloured over time and reported by the patient; the emotional climate that persists and biases perception, as against the transient affect. Rated by quality, stability and congruity with thought.

PEARL

Affect is weather (what you see now, cross-sectional, observed); **mood** is climate (what is felt over time, sustained, subjective). The examiner's shorthand test: mood is what the patient tells you, affect is what you observe.

HOLD THIS

Affect is the momentary observed expression; mood is the sustained subjective state; the range runs broad to restricted or constricted to blunted to flat. Blunting and incongruity point to schizophrenia but are never a spot diagnosis.

17.2 Disorders of the quality or tone of mood

Abnormal tone. The commonest disorders are of the *quality* of the prevailing mood: it is pathologically lowered, raised, fearful, irritable, bewildered or empty. Each has a phenomenological signature beyond ordinary sadness or happiness.

Depression (lowering of mood)

A sustained lowering of mood below the normal range, often described by the patient as qualitatively distinct from ordinary unhappiness, with a peculiarly painful quality, and accompanied by pessimism, guilt and loss of drive (Companion to Psychiatric Studies).

Dysphoria

An unpleasant, discontented, low-tinged mood, not amounting to full depression; often mixed with irritability and tension.

Elation and euphoria

Elation is an exaggerated feeling of well-being, cheerfulness and expansiveness, classically in mania, felt by the patient as heightened vitality. **Euphoria** is a milder, more static state of contented well-being out of keeping with circumstances; when neurologically driven and shallow it shades into the fatuous cheerfulness (*moria*) of frontal lesions.

Ecstasy

An intense, exalted feeling of rapture, awe or oceanic bliss, often with a sense of union with the world; seen in temporal-lobe epilepsy and some acute psychoses.

Anxiety and fear

Anxiety is an unpleasant affect of apprehensive expectation, an anticipation of threat without a defined object, with somatic accompaniments (palpitation, tremor, restlessness). **Fear** is the same affect directed at a specific, identified danger. Free-floating anxiety is anxiety unattached to any object.

Irritability

A lowered threshold for anger and annoyance, a readiness to react with hostility to minor provocation; prominent in mania, mixed affective states, depression, organic and personality disorders.

Perplexity

A bewildered, puzzled affect in which the patient feels something strange is happening but cannot grasp what, with lowered brows, slowed gaze and a partly open mouth; seen par excellence in puerperal psychosis and in any acute psychotic or organic state (Companion to Psychiatric Studies).

Apathy

A loss of feeling tone, an emotional indifference and absence of concern in which nothing seems to matter; reduced spontaneous action and speech accompany it. Seen in chronic schizophrenia, frontal and subcortical disease, and severe depression; it shades into avolition.

17.3 Blunting and flattening of affect

Loss of the normal range and depth of emotional expression, characteristic of schizophrenia. This is the single most important negative-symptom disturbance of affect, and the exam prizes the flattening-versus-**blunting** distinction, though the two are often used loosely as synonyms (Companion to Psychiatric Studies, Kaplan & Sadock 2024).

Flattening of affect

A reduction in the *range and depth* of emotional expression, with loss of the subtlety and nuance of moment-to-moment emotional interaction; the face is immobile, the voice monotonous, gestures few. Note that such patients may still be highly aroused physiologically despite the flat display.

Blunting of affect

A *coarsening* of emotion with insensitivity to social context, Kraepelin's loss of the delicacy of emotion. Sims described a woman with schizophrenia who, with obvious relish for the sensational effect, took her visitors upstairs to view her mother's corpse, dead two days (Sims 2015).

> COMMON TRAP
>
> **Blunting** and flattening carry a strong diagnostic inference (schizophrenia), so the terms must not be used loosely. They should never be a spot diagnosis: judge them across the whole interview, and exclude cultural emotional reserve, a habitually dead-pan personality, dissocial indifference, and above all drug-induced bradykinesia or parkinsonian masking, which mimic flattening (Companion to Psychiatric Studies).

17.4 Restricted and constricted affect

The milder gradations on the range-of-affect spectrum. Below full flattening lie two intermediate degrees, which the examiner expects graded correctly against the normal *broad* or full range (Kaplan & Sadock 2024).

Restricted (constricted) affect

A reduction in the range and intensity of emotional expression that is *less severe than blunting or flattening*: emotion is present and modulated but the amplitude is dampened, the display muted. Kaplan & Sadock define the two terms identically and cross-reference one to the other, so treat them as a single construct and do not grade one as milder than the other.

Broad (full) affect

The normal reference state: a full, appropriately modulated range of emotional expression across the interview. Named only to sit the abnormalities against it.

The full continuum runs: broad (normal) to restricted or constricted to blunted to flat, in order of decreasing range and depth of expression.

17.5 Incongruity of affect

A mismatch between expressed emotion and thought content. This is a discrete sign, not merely reduced affect, and one of the most examined single terms in the topic.

Incongruity of affect

The expressed emotion does not match the thought content or the setting, for example laughing while describing a bereavement, or a patient who, asked about the bandage on her wrist, replied that she had

tried to kill herself that morning and burst out laughing (Fish 2007, Companion to Psychiatric Studies). Also called inappropriate or parathymia. Sudden causeless giggling in chronic schizophrenia is the classic instance.

COMMON TRAP

Do not confuse **incongruity of affect** (form) with mood-incongruent *content* of delusions or hallucinations. Incongruity of affect is a mismatch of the emotional *display* with the topic; mood-incongruent psychotic content is a delusion whose theme is out of keeping with the mood (for example grandiose delusions in depression). Assess incongruity circumspectly: inappropriate laughter may equally signal social awkwardness or embarrassment (Companion to Psychiatric Studies).

17.6 Lability of affect, emotional incontinence and la belle indifference

Disorders of the stability and control of affect. Here the fault is not the tone or congruity but the *regulation*: emotion shifts too readily, discharges without control, or is conspicuously absent where it should be present.

Lability of affect

An abnormal instability of affect with rapid, exaggerated shifts from one emotional state to another (for example tears to laughter within minutes), the swings often shallow and readily provoked. Seen in mania, organic and frontal disorders, and delirium. The exact string **lability** denotes this rapid shifting.

Emotional incontinence

A severe, pathological loss of control over emotional *expression*: the patient weeps or laughs uncontrollably with little or no provoking stimulus and cannot check it, the outburst out of proportion to any felt emotion. The hallmark of pseudobulbar palsy and other organic (vascular, degenerative) states; sometimes called pathological (forced) crying or laughing.

La belle indifference

A striking, inappropriate *lack of concern* about a serious symptom or disability, classically described with conversion (functional neurological) disorder: the patient reports a dramatic deficit such as paralysis or blindness with bland unconcern. Its diagnostic value is now regarded as limited and non-specific.

TRAP La belle indifference is not diagnostic of conversion disorder; its specificity is now regarded as limited, so do not use bland unconcern to clinch a functional label.

17.7 Anhedonia

The loss of the capacity to experience pleasure. A cardinal, high-yield sign that straddles the mood disorders and the negative syndrome of schizophrenia.

Anhedonia

The loss or marked decrease of the capacity to experience pleasure, so that activities once enjoyed no longer give satisfaction (DSM-5-TR 2022, Sims 2015). A core symptom of a major depressive episode (loss of interest or pleasure) and one of the recognised negative symptoms of schizophrenia.

Consummatory anhedonia

Reduced pleasure experienced *in* the moment (in-the-moment liking).

Anticipatory anhedonia

Reduced pleasure *anticipated from* a future reward (wanting); research suggests it is anticipatory more than consummatory pleasure that is chiefly impaired in schizophrenia, where the patient may still enjoy an activity in the moment yet fail to seek it out.

CLINICAL ANCHOR

Anhedonia is one of the two gateway symptoms of a major depressive episode (with depressed mood) and one of the five negative-symptom domains of schizophrenia alongside avolition, asociality, affective blunting and alogia (Kaplan & Sadock 2024). Distinguish it from apathy (loss of feeling and motivation broadly) and from alexithymia (difficulty naming feelings): anhedonia is specifically the failure of *pleasure*.

17.8 Alexithymia

A difficulty identifying and describing one's own feelings. Not a psychotic sign but a trait-like disturbance of emotional awareness, coined by Sifneos (1973), that recurs in psychosomatic and personality contexts.

Alexithymia

A difficulty in identifying and describing one's own feelings, distinguishing feelings from bodily sensations of emotional arousal, coupled with an externally oriented, concrete cognitive style and impoverished fantasy life (Sifneos 1973). Literally "no words for mood".

It is associated with somatoform and psychosomatic presentations, substance use, eating disorders and cluster B personality disorders, and is measured by the Toronto Alexithymia Scale. It is a disorder of emotional *insight and articulation*, not of the experience of pleasure (contrast anhedonia) nor of expressed range (contrast blunting).

17.9 Discriminating the negative-affect signs

The exam's favourite confusion set. Four flat-looking or empty-looking states are constantly conflated. Keep the discriminator column in mind.

SIGN	WHAT IS LOST	DOMAIN OF FAULT	CLASSIC SETTING
Blunting / flattening	**Range and depth of emotional *expression***	Affect (display)	Schizophrenia (negative)
Anhedonia	**Capacity to feel *pleasure***	Hedonic experience	Depression; schizophrenia
Apathy	**Feeling tone and *motivation*; nothing matters**	Drive and feeling	Frontal, chronic schizophrenia
Alexithymia	**Ability to *identify and name* feelings**	Emotional insight	Psychosomatic, cluster B

Ask what is lost: expression (blunting), pleasure (anhedonia), motivation and feeling tone (apathy), or the words for feeling (alexithymia).

RULE **For the flat-looking states, ask what is lost.** Expression is blunting, pleasure is anhedonia, motivation and feeling tone is apathy, and the words for feeling is alexithymia.

MNEMONIC

"A FIB LIkes CAKE"

The core affect abnormalities: **A**ffect vs mood, **F**lattening, **I**ncongruity, **B**lunting; **L**ability, **I**ncontinence (emotional); **C**onstriction/restriction, **A**nhedonia, **K**eeps-calm belle indifference, al**E**xithymia. A memory hook, not a classification.

GOOD TO REMEMBER

- **Emotion:** generic stirred-up feeling state with psychic, somatic and behavioural parts.
- **Affect:** the momentary, observed, cross-sectional emotional expression (weather; what you see).
- **Mood:** the sustained, pervasive, subjective emotional state (climate; what the patient reports).
- **Depression:** sustained lowering of mood, often qualitatively distinct from ordinary sadness.
- **Elation / euphoria:** exaggerated well-being and expansiveness (mania) / milder static contentment out of keeping with circumstances.
- **Anxiety vs fear:** apprehension without an object vs apprehension at a specific identified danger.
- **Irritability:** lowered threshold for anger; prominent in mania, mixed states, depression, organic disease.
- **Perplexity:** bewildered puzzled affect, feels something strange is happening; par excellence in puerperal psychosis.
- **Apathy:** loss of feeling tone and concern, nothing matters; frontal and chronic schizophrenia, severe depression.
- **Flattening of affect:** reduced range and depth of emotional expression; schizophrenia (may be aroused underneath).
- **Blunting of affect:** coarsening of emotion and insensitivity to social context (Kraepelin's loss of delicacy).
- **Restricted / constricted affect:** dampened range milder than flattening; continuum broad to restricted or constricted to blunted to flat.
- **Incongruity of affect:** expressed emotion does not match thought content, e.g. laughing while describing a bereavement.
- **Lability of affect:** rapid, exaggerated, shallow shifts between emotional states; mania, organic, delirium.
- **Emotional incontinence:** uncontrollable weeping or laughing with little stimulus; hallmark of pseudobulbar palsy.
- **La belle indifference:** bland unconcern about a serious deficit; classically conversion disorder (low specificity now).
- **Anhedonia:** loss of the capacity to experience pleasure; core to major depression and a schizophrenia negative symptom.
- **Alexithymia:** difficulty identifying and describing one's own feelings (Sifneos 1973); Toronto Alexithymia Scale.
- **Caveat:** blunting and incongruity are characteristic of schizophrenia but not pathognomonic; judge over the whole interview, not by a single glance.

18 · Disorders of memory and of consciousness

This note teaches two neighbouring domains of descriptive psychopathology that examiners love to pair. The **disorders of memory** classify the ways in which registration, retention and recall break down, and the ways in which the *content* of what is recalled becomes distorted. The **disorders of consciousness** classify the ways in which the clear, alert awareness of self and environment is dimmed, narrowed or fragmented. Both reward the Jasperian discipline of describing form over explanation (Jaspers 1913, Fish 2007, Sims 2015): the task is to name the sign and define it crisply, ideally with a one-line clinical example, not to theorise about mechanism.

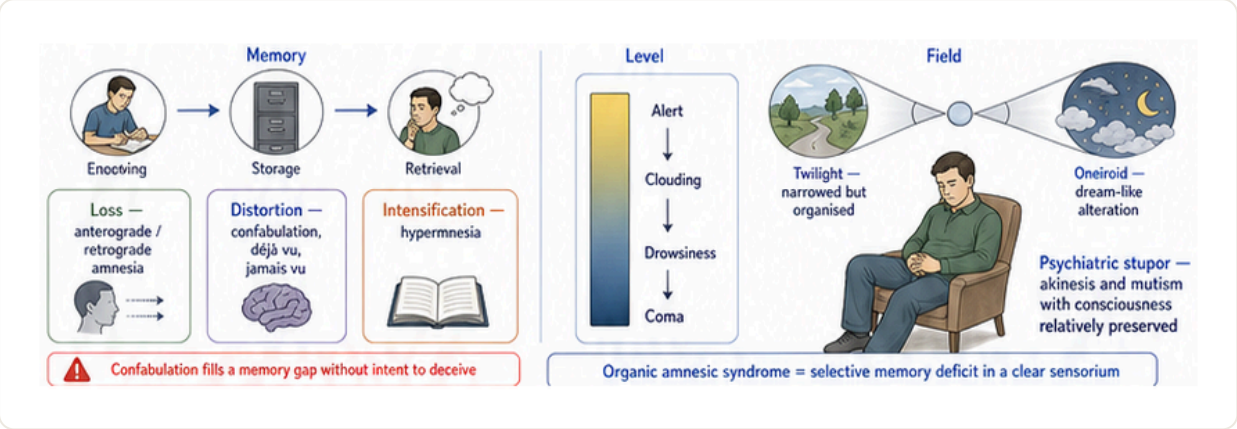


Fig 6.27 Memory and consciousness: loss, distortion, level, field.

Exam framing. Keep the two halves architecturally separate. Under memory, hold apart the loss of memory (the **amnesia**s and the organic amnesic syndrome) from the distortions of recall (the **paramnesia**s, of which **confabulation** is the flagship) and from the rare intensification, **hypermnesia**. Under consciousness, hold apart a change in the *level* of consciousness on the wakefulness continuum (**clouding**, **delirium**, drowsiness, **stupor**, coma) from a change in the *field* of consciousness (the **twilight state** and the **oneiroid** state). The neural basis of memory is developed in the Functional Neuroanatomy & Neurophysiology notes and cross-referred there; Wernicke encephalopathy and the Korsakoff syndrome are developed in full on the organic psychiatry chapter; the acute management of delirium belongs to the emergency psychiatry notes. Here we describe.

18.1 The disorders of memory: the working model

Three processes, three vulnerabilities. Memory is conventionally split into *registration* (encoding of new material), *retention* (storage), and *recall* (retrieval), layered by time-scale into immediate (working) memory, recent (short-term) memory, and remote (long-term) memory (Sims 2015). Bedside testing maps onto this: digit span probes immediate registration, a name-and-address or three-object recall at five minutes probes recent memory and new learning, and autobiographical or general-knowledge questioning probes remote memory. The classic organic profile is a severe deficit of *recent* memory and new learning with immediate memory and, initially, remote memory relatively spared, which is exactly the fingerprint of the organic amnesic syndrome below.

18.2 Amnesia: anterograde and retrograde

Definition. An **amnesia** is a pathological loss of, or gap in, memory. The single most useful division is by the temporal relation of the gap to a causative event, typically a head injury, seizure or other insult (Fish 2007, Sims 2015).

Anterograde amnesia

Loss of memory for events *after* the causative insult: the inability to lay down new memories going forward. In head injury the duration of post-traumatic amnesia (from injury to the return of continuous memory) is a rough index of severity.

Retrograde amnesia

Loss of memory for events *before* the insult, extending back from it. It typically shrinks over time and characteristically obeys Ribot's law, older and better-consolidated memories being the last to go and the first to return.

Lacunar (circumscribed) amnesia

A discrete gap for a bounded period of time, with intact memory on either side; seen after delirium, complex partial seizures and some dissociative states.

18.3 The organic amnesic syndrome (and Korsakoff)

Definition. The *organic amnesic (amnestic) syndrome* is a selective, enduring impairment of recent memory and new learning caused by identifiable brain disease, in *clear consciousness* and without global intellectual decline (ICD-10). The ICD-10 requirements are worth carrying verbatim: recent-memory impairment (anterograde and retrograde amnesia) with defective new learning; preserved immediate recall (normal digit span), attention and consciousness; preserved other intellectual function; and objective evidence of a relevant brain lesion, characteristically of the diencephalic and medial temporal structures (mammillary bodies, fornix, hippocampus, dorsomedial thalamus).

Korsakoff as the prototype. The commonest cause is thiamine deficiency in chronic alcohol dependence: Wernicke encephalopathy is the acute phase and the Korsakoff syndrome the chronic amnesic residue, together the Wernicke-Korsakoff syndrome. Its bedside signature is a dense anterograde amnesia with disorientation to time, relative sparing of remote memory, absent insight, and, in the early phase, **confabulation** filling the memory gap; confabulation tends to fade as the syndrome becomes chronic (Companion to Psychiatric Studies). The neural basis of memory and the full Wernicke-Korsakoff picture are cross-referred to the Functional Neuroanatomy & Neurophysiology notes and the organic psychiatry chapter respectively.

> **COMMON TRAP**
>
> The organic amnesic syndrome is *not* delirium and *not* dementia. It differs from **delirium** by the absence of any disturbance of consciousness or attention, and from dementia by the absence of global intellectual and personality decline. The discriminator to state in the viva is: an isolated, selective memory deficit in a clear sensorium.

HOLD THIS

Split memory into loss (amnesias), distortion (paramnesias, confabulation the flagship) and intensification (hypermnesia); split consciousness into level (clouding to coma) and field (twilight, oneiroid). The organic amnesic syndrome is a selective memory deficit in a clear sensorium.

18.4 Transient global amnesia and psychogenic amnesia

Two abrupt-onset amnesias to contrast. One is organic and self-limiting; one is dissociative and content-selective.

Transient global amnesia

An abrupt, isolated dense anterograde amnesia lasting some hours, in a fully alert middle-aged or older person who remains able to converse and perform complex tasks but repeatedly asks the same orienting questions ("where am I?"). Attributed to transient ischaemia or a spreading-depression-like event in the medial temporal lobes; it resolves within about 24 hours leaving only a permanent gap for the episode, and personal identity is retained throughout (Kaplan & Sadock 2024).

Psychogenic (dissociative) amnesia

A loss of memory, usually retrograde and for emotionally significant autobiographical material, that exceeds ordinary forgetting and is not due to organic disease; classically it spares neutral information and impersonal skills. Onset follows psychological stress or trauma.

Dissociative fugue

Dissociative amnesia *plus* a purposeful journey away from home or work, often with loss of personal identity and sometimes the assumption of a new one; the person appears outwardly normal to observers during the wandering, with a dense amnesic gap for the episode afterwards (Sims 2015).

CLINICAL ANCHOR

Loss of memory for *personal identity* (one's own name) with preserved capacity to lay down new memories points toward a psychogenic or dissociative amnesia; the organic amnesias, by contrast, spare identity and hit new learning. This is the fastest bedside organic-versus-psychogenic discriminator, though it must be held loosely and corroborated.

18.5 The paramnesias I: confabulation and deja vu / jamais vu

Definition. A *paramnesia* is a distortion of recall in which memory is falsified, rather than simply lost; the material recalled is altered, misplaced in time, or fabricated (Fish 2007, Sims 2015).

Confabulation

The filling of a gap in memory with fabricated or misplaced material that the patient accepts as genuine recollection, without intent to deceive; classically in the Korsakoff syndrome. Fish distinguishes *momentary (provoked)* confabulation, elicited by questioning and drawn from real but displaced memories, from *fantastic (spontaneous)* confabulation, an unprompted flow of grandiose or improbable false memories seen with basal-forebrain and frontal involvement.

Deja vu

A false sense of familiarity: the conviction that a genuinely novel experience has been encountered before ("I have been here already"). A common benign experience in the healthy; when frequent,

intense or stereotyped it points toward temporal lobe epilepsy (Kaplan & Sadock 2024). Related variants include deja vecu (already lived through) and deja pense (already thought).

Jamais vu

The converse: a false sense of *un*familiarity, in which a genuinely familiar situation, place or person feels strange and never before encountered. Likewise seen in temporal lobe epilepsy and in dissociative states.

18.6 The paramnesias II: retrospective falsification and delusional memory

Retrospective falsification

The unwitting distortion of a genuine memory as it is recalled, coloured by the person's present mood or beliefs, e.g. a depressed patient recalling a happy past as uniformly bleak, or an anxious one exaggerating past dangers. The event is real; its remembered emotional colouring is falsified.

Delusional memory (retrospective delusion)

The "recollection" of an event that is itself clearly delusional, or a real memory retrospectively invested with delusional significance, e.g. a patient who "remembers" that a teacher slipped LSD into his juice, the memory serving to explain his psychosis (Kaplan & Sadock 2024). A disorder of the content of thought expressed through memory, not a simple mnestic error.

18.7 Hypermnesia

Definition. **Hypermnesia** is an abnormal intensification or exaggeration of the capacity to recall, in which memories are retrieved with unusual vividness, detail or completeness (Sims 2015). It is described in the heightened arousal of mania and some anxiety states, under hypnosis, in eidetic ("photographic") imagery, in certain savant abilities, and around intensely emotionally charged experiences (the vividness of traumatic and flashbulb memories). It is the mirror image of amnesia and, unlike the paramnesias, is a change in quantity rather than accuracy of recall.

18.8 The disorders of consciousness: level on the wakefulness continuum

Definition. **Consciousness** is the awareness of the self and of the environment; the disorders of consciousness are described first as a fall in the *level* of that awareness along a continuum from full alertness to coma (Sims 2015, Fish 2007). The states below are graded points on that single dimension.

Clouding of consciousness

The mildest, most important grade: a state ranging from barely perceptible impairment to definite drowsiness, in which the person reacts incompletely to stimuli, with attention, concentration, memory and orientation impaired to varying degrees and thinking muddled, so that events may be misinterpreted. Clouding of consciousness is the *defining feature of delirium* (Shorter Oxford Textbook of Psychiatry).

Delirium

The acute confusional state: an acute, fluctuating disturbance of consciousness and attention with global cognitive impairment, disorientation, perceptual disturbance (illusions, misinterpretations, visual hallucinations), a disturbed sleep-wake cycle and altered psychomotor activity, on an organic basis. Its management is cross-referred to the emergency psychiatry notes.

Drowsiness and somnolence

Pathological sleepiness in which the patient readily lapses into sleep but is rousable to a degree; the related state Fish terms *torpor* couples drowsiness with slow thinking and a narrowed range of perception.

Coma

The deepest grade: unrousable unresponsiveness with no purposeful reaction even to strong (painful) stimuli, gradable by remaining reflex responses and EEG activity (Shorter Oxford Textbook of Psychiatry).

18.9 Stupor: the special case

Definition (the psychiatric usage). In psychiatry, **stupor** is a state of akinesis and mutism, the patient immobile, silent and unresponsive, yet with *relative preservation of consciousness*: the eyes are typically open and follow objects, or if closed are held shut against opening, reflexes are normal and posture is maintained (Shorter Oxford Textbook of Psychiatry). This is a critical and examinable divergence from neurological usage, where "stupor" implies an actual impairment of consciousness intermediate between drowsiness and coma. The psychiatric stupor is a disorder of the expression of consciousness, not necessarily of its level.

TYPE OF STUPOR	SETTING / CAUSE	DISCRIMINATING FEATURES
Organic stupor	Structural or metabolic brain disease (e.g. diencephalic or brainstem lesion, hepatic, hypoglycaemic)	**Consciousness genuinely impaired; neurological signs, abnormal EEG**
Catatonic stupor	Schizophrenia, mood disorder, organic catatonia	**Waxy flexibility, negativism, mutism, posturing; may alternate with excitement**
Depressive stupor	Severe (psychotic) depression, the extreme of retardation	**Preceded by profound retardation and low mood; recall of the period afterwards**
Dissociative stupor	Psychological trauma or conflict	**Follows stress; normal muscle tone and reflexes; no organic cause found**

Four stupors to separate: only organic stupor carries a true impairment of consciousness; the psychiatric stupors preserve it, and the discriminator is context plus the accompanying signs.

CLASSIC TRAP In psychiatry, stupor is akinesis and mutism with consciousness relatively preserved (eyes open, follow objects); in neurology it implies impaired consciousness between drowsiness and coma - the same word, opposite implication for the sensorium.

18.10 The disorders of consciousness: changes in the field

Definition. Beyond a simple dimming of level, consciousness may be *narrowed* or *qualitatively altered*, a change in the *field* rather than the level of awareness (Fish 2007, Sims 2015).

Twilight state

An abnormal state of narrowed but relatively *coherent* consciousness: awareness is constricted to a limited set of ideas and affects, yet the patient may still perform complex, apparently purposeful

actions, of which there is subsequent amnesia. Classically seen in epilepsy (postictal and complex partial states), and in dissociative and organic (e.g. anticholinergic) conditions. Emotional outbursts or violent acts may occur during a twilight state (Kaplan & Sadock 2024; Clinical Methods in Psychiatry, AIIMS 2024).

Oneiroid state

A dream-like alteration of consciousness in which vivid, often fantastic scenic (dream-like) imagery unfolds and the patient is partly detached from the real environment while not asleep; primary and secondary process thinking intermingle. If prolonged, an oneiroid state may merge into a twilight state (Shorter Oxford Textbook of Psychiatry; Kaplan & Sadock 2024). Described in catatonic and cycloid psychoses and in some organic and toxic states.

PEARL

Distinguish a change in *level* from a change in *field*. Clouding, drowsiness and coma dim the overall brightness of consciousness; the **twilight state** and the **oneiroid** state leave a preserved brightness but distort its *content and range*, narrowing the field (twilight) or filling it with dream-imagery (oneiroid). The historical Ganser syndrome, with its twilight state, approximate answers (vorbeireden) and clouded consciousness, sits at the boundary of the two (Kaplan & Sadock 2024).

MNEMONIC

Level = "CD-DS-C"; Field = "TO"

The *level* continuum in order of deepening: **C**louding, **D**rowsiness, **D**elirium (as the clinical syndrome of clouding), **S**tupor (psychiatric sense, level preserved), **C**oma. The *field* changes: **T**wilight (narrowed, coherent) and **O**neiroid (dream-like).

GOOD TO REMEMBER

- **Disorders of memory:** split into loss of memory (amnesias, organic amnesic syndrome), distortions of recall (paramnesias), and intensification (hypermnesia).
- **Anterograde amnesia:** loss of memory for events *after* the insult (failure of new learning); post-traumatic amnesia duration indexes head-injury severity.
- **Retrograde amnesia:** loss of memory for events *before* the insult; shrinks with time, obeys Ribot's law (recent memories most vulnerable).
- **Organic amnesic syndrome:** selective recent-memory and new-learning deficit in clear consciousness, no global intellectual loss (ICD-10); diencephalic / medial-temporal lesions.
- **Korsakoff syndrome:** chronic amnesic residue of thiamine deficiency in alcohol dependence; dense anterograde amnesia, disorientation, absent insight, early confabulation (cross-refer the Functional Neuroanatomy & Neurophysiology notes and the organic psychiatry chapter).
- **Transient global amnesia:** abrupt isolated anterograde amnesia for hours in an alert older person, repeated questioning, identity retained, resolves in ~24 h.
- **Psychogenic (dissociative) amnesia:** retrograde loss of emotionally significant autobiographical memory after stress; spares neutral facts and skills.
- **Dissociative fugue:** dissociative amnesia plus purposeful travel and loss of / new personal identity, with amnesia for the episode.
- **Paramnesia:** a distortion (falsification) of recall rather than a loss.
- **Confabulation:** filling a memory gap with fabricated / misplaced material accepted as true, without intent to deceive; classic in Korsakoff; momentary (provoked) vs fantastic (spontaneous) types.
- **Deja vu:** false sense of familiarity with a novel experience; frequent/stereotyped forms suggest temporal lobe epilepsy.
- **Jamais vu:** false sense of unfamiliarity with a genuinely familiar situation; temporal lobe epilepsy, dissociation.
- **Retrospective falsification:** a real memory unwittingly distorted by present mood or belief.
- **Delusional memory:** recollection of a clearly delusional event, or a real memory invested with delusional meaning; a content-of-thought disorder.
- **Hypermnesia:** abnormal intensification of recall (mania, hypnosis, eidetic imagery, flashbulb / traumatic memories); the mirror of amnesia.
- **Disorders of consciousness:** split into change of *level* (wakefulness continuum) and change of *field* (narrowing / qualitative alteration).
- **Clouding of consciousness:** incomplete reaction to stimuli with impaired attention, memory and orientation; the defining feature of delirium.
- **Delirium:** acute, fluctuating clouding with global cognitive impairment and perceptual disturbance on an organic basis (management cross-referred to the delirium and neurocognitive notes).
- **Drowsiness / somnolence (torpor):** pathological rousable sleepiness with slow thinking and narrowed perception.
- **Coma:** unrousable unresponsiveness with no purposeful response to strong stimuli; graded by reflexes and EEG.
- **Stupor (psychiatric):** akinesis and mutism with *relative preservation of consciousness* (eyes open, follow objects); differs from neurological usage (which implies impaired consciousness). Types: organic, catatonic, depressive, dissociative.
- **Twilight state:** narrowed but relatively coherent consciousness with complex purposeful acts and later amnesia; epilepsy, dissociation, organic states.
- **Oneiroid state:** dream-like consciousness with vivid scenic imagery while awake; catatonic / cycloid psychoses, organic-toxic states; may merge into a twilight state if prolonged.

19 · Disorders of movement, and attention, orientation and insight

This note closes the phenomenology by teaching two remaining domains. The **disorders of motor** function are the abnormalities of movement and behaviour that arise from a disordered mind rather than from a primary neurological lesion, with the catatonic syndrome at their centre. Then come the cognitive domains that complete the mental state examination: attention, orientation, insight and judgement. As throughout descriptive psychopathology, the discipline is to name the sign and define it crisply (Fish 2007; Sims 2015).

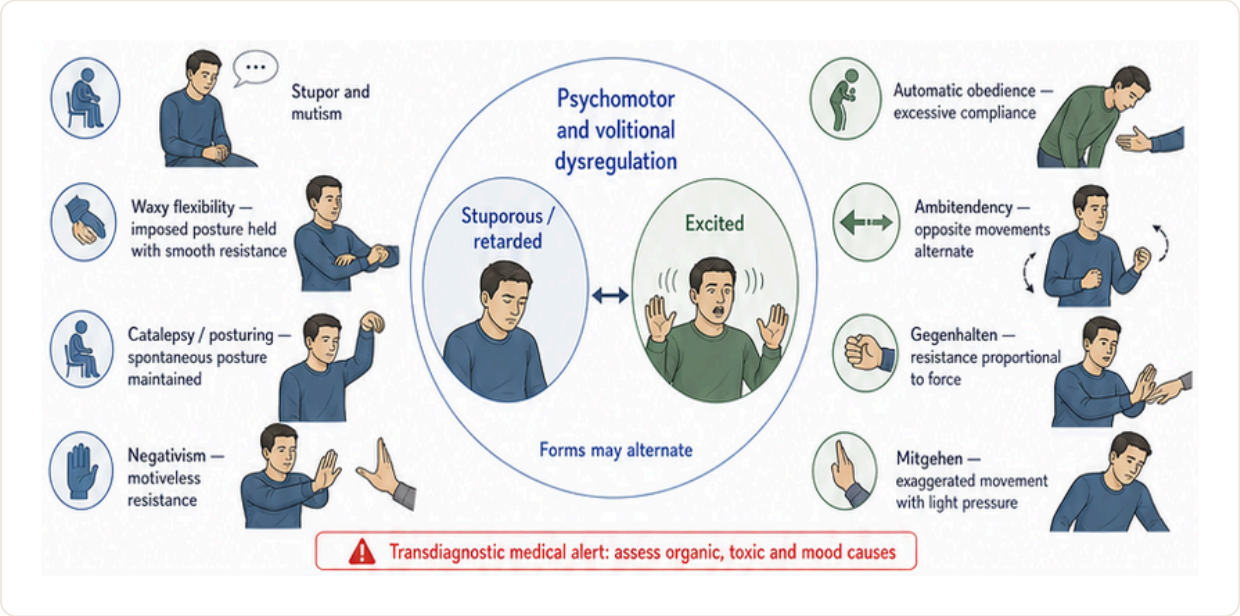


Fig 6.28 Catatonia: dysregulation of will and movement.

Exam framing. Catatonia is high-yield and returns as a short note (its clinical features), so learn the signs precisely and be able to separate the abnormal movements from one another. The cognitive close of the mental state, attention, orientation, insight and judgement, is where a candidate loses easy marks by treating insight as all-or-none; the examiner wants it graded. The acute treatment of catatonia (benzodiazepines, ECT) belongs to the emergency psychiatry notes and is cross-referred.

19.1 Catatonia: the syndrome

Definition. **Catatonia** is a syndrome of psychomotor dysregulation in which the normal relationship between will and movement is disturbed, producing a striking combination of motor, volitional and behavioural signs (Kahlbaum 1874; Fish 2007). It was long tied to schizophrenia but is now recognised as transdiagnostic: it complicates mood disorders (especially severe depression and mania) more often than schizophrenia, and it arises from many organic and toxic causes (encephalitis, metabolic derangement, autoimmune disease). It can present as a retarded/stuporous form or an excited form, and the two may alternate. Modern operationalised criteria (DSM-5, and rating instruments such as the Bush-Francis catatonia rating scale) require a threshold number of signs from the list below (Bush and colleagues 1996).

19.2 The catatonic signs

The named signs, each defined. The examiner rewards the ability to define each sign in a line, so hold the list precisely (Fish 2007; Sims 2015).

Stupor

Akinesis and mutism with relative preservation of consciousness (the catatonic stupor; cross-refer the consciousness topic).

Waxy flexibility (cerea flexibilitas)

The limbs, when moved by the examiner, hold their new posture with a smooth, even, plastic resistance, like bending a wax rod; the imposed posture is then maintained.

Catalepsy and posturing

The spontaneous maintenance of an abnormal, often uncomfortable posture for long periods; psychological pillow, in which the head is held raised off the bed as if on a pillow, is the classic example.

Negativism

A motiveless resistance to all instructions or attempts to be moved, and the doing of the opposite of what is asked; a disorder of the will, not simple non-cooperation.

Mutism and automatic obedience

Mutism is a verbal near-absence with no organic cause. Automatic obedience is the opposite pole to negativism: the patient carries out every instruction like an automaton, even harmful ones.

Ambitendency

An alternation between opposite movements arising from a conflict of will, for example repeatedly half-extending and withdrawing the hand when asked to shake hands.

Gegenhalten and mitgehen

Gegenhalten (opposition) is a resistance to passive movement proportional to the force applied; mitgehen (going along) is an excessive, exaggerated movement of a body part in response to the lightest pressure ("anglepoise lamp" sign).

Excitement

The excited form: purposeless, frenzied, agitated motor activity not influenced by external stimuli, which may become a life-threatening malignant catatonia.

> **COMMON TRAP**
>
> Waxy flexibility, negativism and automatic obedience look contradictory but coexist in the same syndrome because all three are disorders of the *will*: catatonia is a dysregulation of volition, so a patient may resist one instruction (negativism) yet passively hold an imposed posture (waxy flexibility) minutes later. Do not expect internal consistency.

19.3 Abnormal movements and behaviours

The repetitive and imitative signs. Beyond the catatonic core, descriptive psychopathology names several disorders of purposeful movement, and the exam turns on telling them apart (Fish 2007; Sims 2015).

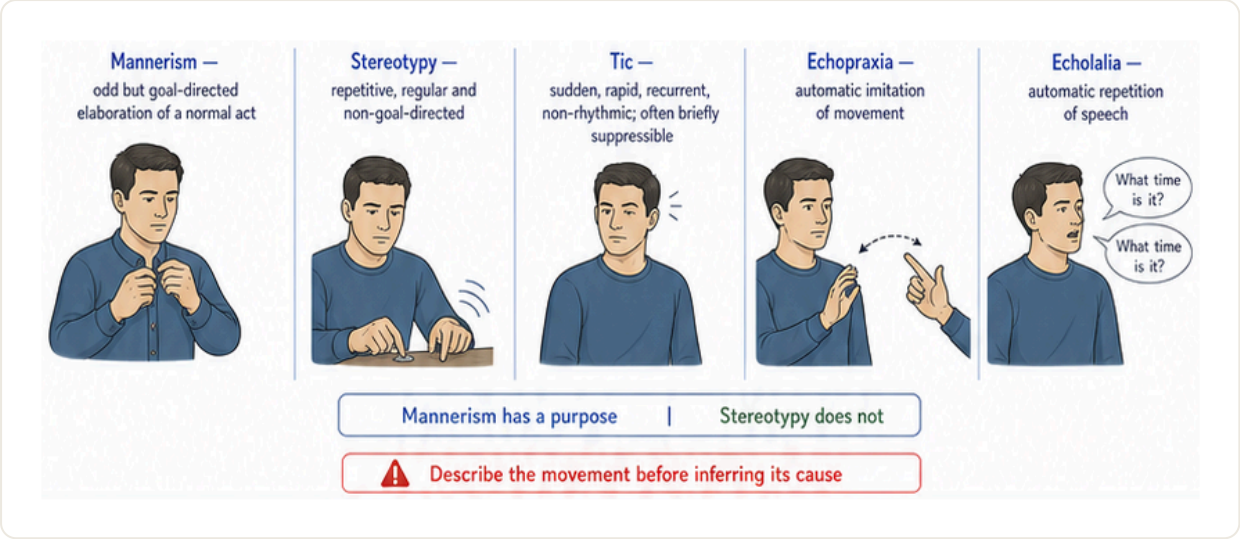


Fig 6.29 Abnormal movements: purpose is the discriminator.

Mannerism

An odd, stilted or bizarre *goal-directed* movement or elaboration of a normal action: a stereotyped, theatrical salute instead of an ordinary greeting. The movement has a purpose, but it is performed strangely.

Stereotypy

A repetitive, regular, *non-goal-directed* movement (rocking, rubbing, repeatedly touching an object) carried out uniformly and without evident purpose. Purposelessness is the discriminator from mannerism.

Tic

A sudden, involuntary, rapid, recurrent, non-rhythmic movement or vocalisation, often briefly suppressible, distinct from the catatonic and stereotyped signs.

Echopraxia

The automatic, senseless imitation of another person's *movements*, even when asked not to; its verbal counterpart is echolalia, the imitation of another's speech.

CLINICAL ANCHOR

Catatonic signs are a medical alert, not just a description. Recognising waxy flexibility, mutism, negativism or posturing should prompt a lorazepam challenge and a search for an organic cause, because untreated catatonia risks dehydration, venous thromboembolism and malignant catatonia. The phenomenology is the entry point to a treatable emergency; the acute management is developed on the emergency psychiatry notes.

RULE **Purpose separates mannerism from stereotypy.** A mannerism is an odd but goal-directed movement; a stereotypy is repetitive and non-goal-directed.

19.4 Attention and concentration

Definition. **Attention** is the active direction of consciousness onto a target, and concentration is its sustained maintenance over time (Sims 2015). Disorders include distractibility (attention captured by every passing stimulus, as in mania and delirium), impersistence (inability to sustain

attention), and the narrowed, poorly shifted attention of clouded consciousness. At the bedside attention and concentration are tested by digit span (registration and immediate attention), serial sevens or serial threes, and reciting the months of the year in reverse.

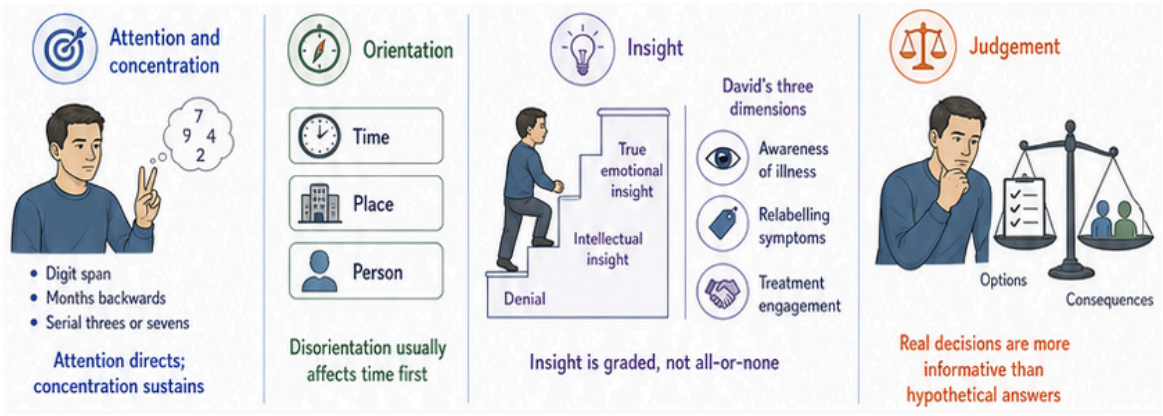


Fig 6.30 The cognitive close of the mental state examination.

19.5 Orientation

Definition. Orientation is the awareness of oneself in relation to time, place and person: knowing the date and time, the current location, and the identity of oneself and others. Disorientation, a loss of this awareness, is a cardinal sign of an *organic* disturbance of consciousness (delirium and dementia) and characteristically affects time first, then place, then person. Orientation is closely tied to attention and memory: a patient cannot be oriented if attention or new learning is grossly impaired. Preserved orientation in a floridly psychotic patient points away from an organic confusional state.

19.6 Insight

Definition, and why it is graded. Insight is the patient's awareness of their own mental state: that they are ill, that the illness is psychiatric, and that treatment is needed. The examinable point is that insight is not all-or-none but a graded, multidimensional phenomenon. A useful clinical grading runs: complete denial of illness; slight awareness of being ill and needing help but denying it at the same time; awareness of being ill but attributing it to external or physical causes; awareness that the illness is due to something unknown in the self; intellectual insight (admitting illness and that symptoms are due to a disturbance in the self, but without applying this knowledge); and true (emotional) insight, in which the awareness leads to changed behaviour and adherence. David's three-dimensional model (awareness of illness, correct relabelling of symptoms as pathological, and treatment adherence) is the modern operationalisation. Insight has prognostic and medico-legal weight (it bears on capacity and on adherence).

HOLD THIS

Catatonia is a transdiagnostic dysregulation of the will (commoner in mood disorders than schizophrenia), and insight is graded, not all-or-none. David's three dimensions: awareness of illness, relabelling of symptoms, and treatment adherence.

19.7 Judgement

Definition. **Judgement** (also spelt **judgment**) is the capacity to assess a situation correctly and to act sensibly within it, weighing options and consequences. It is assessed by observing the patient's real decisions (social, financial, personal) and, historically, by hypothetical test questions, though these are unreliable. Impaired judgement is prominent in mania (reckless spending, disinhibition), in the frontal-executive syndromes, in intoxication, and in psychosis when actions follow delusional beliefs. Judgement and insight together complete the cognitive close of the mental state examination.

PEARL

Orientation is the fastest bedside organic screen. A patient who is disoriented to time and place, especially with fluctuation and inattention, has an organic disturbance of consciousness (delirium) until proven otherwise, whatever the psychiatric content; a patient with florid hallucinations and delusions but intact orientation and attention is more likely in a primary psychotic state. Test orientation early.

MNEMONIC

Movement: "MSET" and "WooNBAG"

The abnormal movements to separate: **M**annerism (goal-directed, odd), **S**tereotypy (non-goal-directed, repetitive), **E**chopraxia (imitates movement), **T**ic. The catatonic core: **W**axy flexibility, autOmatic obedience, **N**egativism, **B**izarre posturing/catalepsy, **A**mbitendency, **G**egenhalten (with mutism and stupor).

GOOD TO REMEMBER

- **Disorders of motor function:** abnormalities of movement and behaviour of psychological origin; the catatonic syndrome is the core.
- **Catatonia:** a transdiagnostic syndrome of psychomotor and volitional dysregulation (Kahlbaum); commoner in mood disorders than schizophrenia; retarded/stuporous and excited forms.
- **Waxy flexibility (cerea flexibilitas):** limbs hold an imposed posture with smooth plastic resistance.
- **Negativism:** motiveless resistance to instruction, doing the opposite; a disorder of will.
- **Automatic obedience and ambitendency:** automaton-like compliance; alternation between opposite movements from conflict of will.
- **Catalepsy / posturing, gegenhalten, mitgehen:** maintained abnormal posture; force-proportional opposition; exaggerated go-along movement.
- **Mannerism:** odd but *goal-directed* movement; **stereotypy:** repetitive *non-goal-directed* movement (the discriminator is purpose).
- **Echopraxia:** automatic imitation of movement (echolalia = imitation of speech).
- **Attention:** active direction of consciousness (concentration = its maintenance); tested by digit span and serial sevens; distractibility in mania and delirium.
- **Orientation:** awareness of time, place and person; lost first for time; disorientation is a cardinal organic sign.
- **Insight:** awareness of being ill, of the illness being psychiatric, and of needing treatment; graded, not all-or-none (David's three dimensions: awareness, relabelling, adherence).
- **Judgement (judgment):** capacity to assess a situation and act sensibly; impaired in mania, frontal syndromes, intoxication and psychosis.

Discriminate

20 · Discriminate: pick the test, name the sign

The two bands of these notes are examined most often as acts of discrimination: choosing the right instrument for a clinical problem, and separating one phenomenological sign from its near-neighbour. This is the step that turns a catalogue into a usable skill. Read the tables below as decision aids, not lists.

20.1 Band A: choosing the right test for the clinical question

Match the tool to the referral question. A psychological test is chosen to answer a specific **clinical question**, and good **test selection** starts from the **referral question** rather than from a favourite instrument. The table pairs the common questions with the answer to "**which test**", so you can **choose the test** that the problem actually needs.

THE CLINICAL / REFERRAL QUESTION	CHOOSE THE TEST	WHY
Is there intellectual disability, and how severe?	**A Wechsler (WAIS/WISC) or Binet-Kamat intelligence test plus a Vineland/VSMS adaptive measure**	ID needs both a low IQ and a deficit in adaptive behaviour; measure both
Which cognitive domains are impaired after this head injury or in this dementia?	**A neuropsychological battery (Halstead-Reitan or a flexible battery; NIMHANS battery in India)**	Profiles attention, memory, language, visuospatial and executive function domain by domain
What is the personality structure, or is the presentation being feigned?	**The MMPI (with its validity scales) and, for depth, the projectives**	The MMPI validity scales detect faking; the projectives add a dynamic picture
Is this child developing normally?	**A developmental screen (DST, Denver) or a Bayley / Gesell assessment**	Yields a developmental quotient against age norms
How severe is this depression, and is it responding to treatment?	**A symptom rating scale: HAM-D or MADRS (mania YMRS; psychosis PANSS; OCD Y-BOCS)**	Quantifies severity and tracks change over time

Test selection is driven by the referral question: ability, cognitive profile, personality, development or symptom severity each point to a different family of instrument.

20.2 Band B: illusion versus hallucination versus pseudohallucination

The perception triad. The single most tested discrimination in phenomenology separates the **illusion** (a real stimulus misperceived) from the **hallucination** (a percept with no stimulus, in outer objective space, full reality, insight lost) and from the **pseudohallucination** (a percept in inner subjective space, lacking full substantiality, insight relatively preserved). The two discriminators that do most of the work are the presence of a real stimulus and the locus (outer versus inner space).

DISCRIMINATOR	ILLUSION	HALLUCINATION	PSEUDOHALLUCINATION
Real external stimulus	Yes, misperceived	**No**	**No**
Locus	Outer space	Outer objective space	**Inner subjective space**
Reality status	Real object transformed	Full force of a true percept	**Lacks full substantiality**
Insight	Corrects on attention	Absent	**Relatively preserved**

Real stimulus separates the illusion from the other two; the outer-versus-inner locus separates the hallucination from the pseudohallucination.

20.3 Band B: obsession versus overvalued idea versus delusion

The belief triad. The second high-yield discrimination separates the **obsession** (ego-dystonic, resisted, insight retained) from the **overvalued idea** (a comprehensible belief held strongly but not with absolute fixity) from the **delusion** (ego-syntonic, unresisted, held with absolute

conviction and no insight). Read the row for insight and resistance and the answer usually falls out.

DISCRIMINATOR	OBSESSION	OVERVALUED IDEA	DELUSION
Conviction / fixity	Recognised as senseless, doubted	Strong, not absolute	**Absolute, incorrigible**
Resistance	**Actively resisted**	Not resisted	Not resisted
Ego relation	**Ego-dystonic (intrusive)**	Ego-syntonic	Ego-syntonic
Insight	Preserved	Partial	**Absent**
Typically in	OCD	Anorexia, dysmorphophobia, morbid jealousy	Psychotic disorders

Resistance and retained insight mark the obsession; absolute conviction with no insight marks the delusion; the overvalued idea sits in between.

HOLD THIS

Band A discriminates by the referral question; Band B by two triads. Perception: real stimulus and locus separate illusion, hallucination and pseudohallucination. Belief: resistance and insight separate obsession, overvalued idea and delusion.

20.4 The other near-misses worth pre-empting

Three more pairs the exam rewards. A few further discriminations recur across the phenomenology and are worth rehearsing together.

Blunting versus incongruity of affect

Blunting is a *loss of range and depth* of emotional expression; incongruity is emotion that is present but *does not match* the thought content (laughing while describing a bereavement). Both occur in schizophrenia; one is reduced affect, the other mismatched affect.

Delirium versus dementia

Delirium is acute, fluctuating, with clouded consciousness and impaired attention; dementia is chronic, stable or progressive, with a clear sensorium until late. Consciousness and time-course separate them.

Mannerism versus stereotypy

A mannerism is an odd but *goal-directed* movement; a stereotypy is a repetitive *non-goal-directed* movement. Purpose is the discriminator.

COMMON TRAP

The word "unreal" hides three different phenomena. A patient who feels the world is unreal but knows it is a feeling has *derealisation* (insight kept); a patient who has a vivid inner-space voice they know is not a true perception has a *pseudohallucination*; a patient convinced as fact that they do not exist has a *nihilistic delusion*. The content overlaps; the discriminators are the locus and the insight, never the word itself. Likewise "hears voices" is not automatically a hallucination: an illusion elaborates a real sound, a functional hallucination is triggered by one, and a pseudohallucination sits in inner space.

GOOD TO REMEMBER

- **Test selection:** start from the referral question (ability, cognitive profile, personality, development, symptom severity), then choose the test family that answers it.
- **ID work-up:** intelligence test plus an adaptive-behaviour measure (both are required for the diagnosis).
- **Illusion vs hallucination vs pseudohallucination:** real stimulus (illusion only); outer vs inner space (hallucination vs pseudohallucination); insight lost only in the true hallucination.
- **Obsession vs overvalued idea vs delusion:** resisted and ego-dystonic with insight (obsession); absolute conviction, unresisted, no insight (delusion); the overvalued idea is in between.
- **Blunting vs incongruity:** reduced range vs mismatched affect. **Delirium vs dementia:** clouded fluctuating vs clear chronic. **Mannerism vs stereotypy:** goal-directed vs purposeless.

Apply and consolidate

21 · Apply: four assessment and phenomenology vignettes

Four short worked vignettes put these notes to use. Each gives a brief presentation, then the reasoning, then the read. Cover the reasoning and try to reach the answer first; the discriminator that carries each case is the point to internalise.

21.1 A test-selection case

VIGNETTE 1

Case: A 7-year-old boy is referred because he is failing at school and is slow to acquire self-care skills. The paediatrician asks whether he has intellectual disability and, if so, how severe.

Reasoning. Intellectual disability is defined by two things together, significantly subaverage intellectual functioning *and* a deficit in adaptive behaviour, both with childhood onset. A single test cannot answer the referral. The intellectual limb needs an individually administered intelligence test normed for Indian children (the Binet-Kamat test or Malin's MISIC; a Wechsler where appropriate). The adaptive limb needs an adaptive-behaviour measure (the Vineland scales or the VSMS, yielding a social quotient). Severity is then graded, and in current systems (DSM-5, ICD-11) the grading rests on adaptive functioning rather than the IQ score alone.

The read. Choose an intelligence test *and* an adaptive-behaviour scale, not an IQ test alone. Grade severity primarily on adaptive functioning. Add a developmental and sensory work-up to exclude a treatable cause.

21.2 An IQ interpretation

VIGNETTE 2

Case: An adult completes the WAIS. The Verbal Comprehension index is 108, the Perceptual Reasoning index is 71, and the Full-Scale IQ is 88. What does the profile mean?

Reasoning. The deviation IQ has a mean of 100 and a standard deviation of 15, so a Full-Scale IQ of 88 falls in the low-average band (80 to 89), which alone might be read as mild global underfunctioning. But the Full-Scale IQ conceals a large split: verbal comprehension is average (108) while perceptual reasoning is borderline (71), a 37-point gap. When the index scores diverge this much, the Full-Scale IQ is not a meaningful summary of a single ability; the split itself is the finding and points to a selective, often perceptual-organisational or nonverbal, deficit that warrants a neuropsychological work-up.

The read. Do not report the Full-Scale IQ of 88 as "low average and homogeneous". Report the significant verbal-performance split and investigate the low perceptual reasoning index; the pattern, not the single number, carries the clinical meaning.

RULE **When the index scores scatter widely, the Full-Scale IQ stops being a meaningful summary.** The split itself is the finding; report and investigate it rather than the single global number.

21.3 A phenomenology spotter

VIGNETTE 3

Case: A man reports that whenever, and only when, the ceiling fan is running, he hears a clear voice speaking to him through the room; he still hears the fan as a fan at the same time. Name the sign.

Reasoning. There is a real external stimulus (the fan) that is *necessary* to provoke the experience, the stimulus is still perceived normally as itself, and the added percept, the voice, occurs together with it and in the same (auditory) modality. That is not an illusion (the voice is not an elaboration of the fan noise), not an ordinary hallucination (a real stimulus is required), and not a reflex hallucination (which would cross to a different modality). It is a functional hallucination.

The read. Functional hallucination: same modality as the triggering stimulus, both perceived together. Contrast the reflex hallucination, where a stimulus in one modality triggers a hallucination in another.

21.4 A first-rank-symptom read

VIGNETTE 4

Case: A young woman says that when she saw a red car pass in the street, she knew instantly and with total certainty that she had been chosen by God to save the country. She is sure the two are connected. What is the sign, and does it clinch a diagnosis?

Reasoning. A real, normally perceived object (the red car) is given an immediate, self-referential delusional meaning that is not understandable from the perception itself. This is a delusional perception, one of Jaspers' primary delusional experiences and a Schneiderian first-rank symptom. The important second half of the question is diagnostic weight: first-rank symptoms are suggestive of schizophrenia but are *not* pathognomonic (they occur in mania and organic psychoses, and a fifth of people with schizophrenia never show them; Carpenter and colleagues 1973), and DSM-5 and ICD-11 have removed their special diagnostic status.

The read. Delusional perception (a primary delusion and a first-rank symptom). It raises the probability of schizophrenia but does not clinch it; the diagnosis rests on the whole picture and course, not one sign.

HOLD THIS

Two meta-lessons carry every vignette: on the test side, the pattern beats the single number; on the phenomenology side, the named form beats the content, and no single sign clinches a diagnosis.

GOOD TO REMEMBER

- **Vignette 1 (test selection):** intellectual disability needs an intelligence test *and* an adaptive-behaviour scale; grade severity by adaptive function.
- **Vignette 2 (IQ interpretation):** a large verbal-performance / index split makes the Full-Scale IQ misleading; report and investigate the split.
- **Vignette 3 (spotter):** a real stimulus needed, perceived alongside the hallucination in the same modality, is a functional hallucination.
- **Vignette 4 (first-rank):** a real percept given sudden delusional meaning is a delusional perception; first-rank symptoms are suggestive of, but not pathognomonic for, schizophrenia.

22 · Consolidate: mnemonic, retrieval and synthesis

Three devices close these notes: a master mnemonic that chains both bands, a set of answer-free retrieval prompts to test yourself against, and the whole-day synthesis map to redraw from memory. Use them in that order.

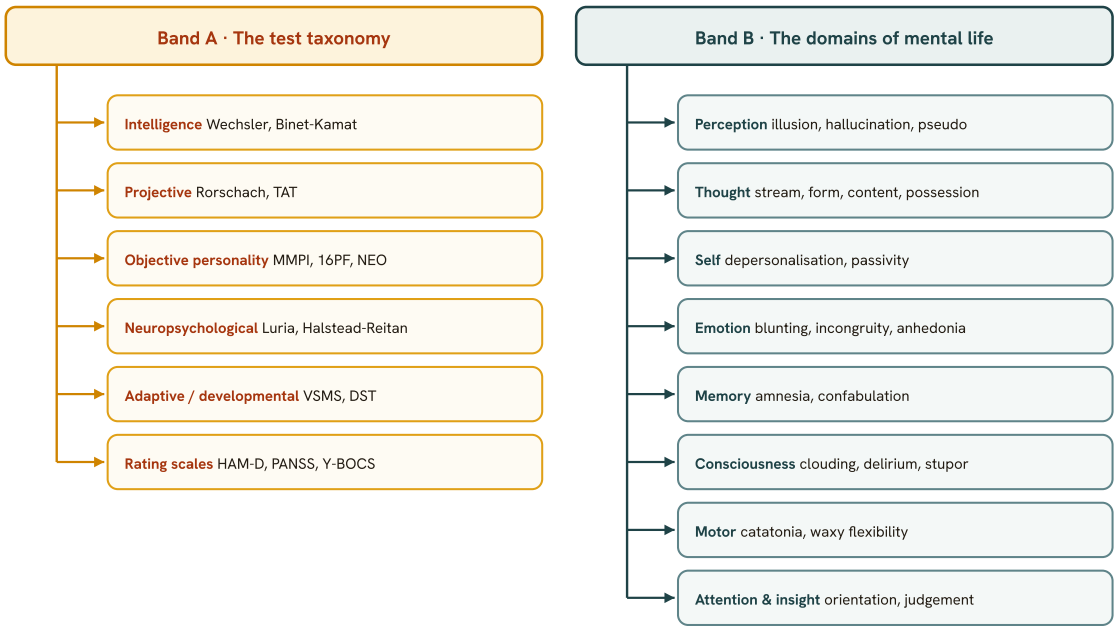


Fig 6.31 The synthesis map. It has two halves that mirror each other: a taxonomy of the tests we use to measure the mind, and a taxonomy of the domains in which the mind can go wrong. Redraw each band from memory, filling in the example instruments on the left and the example signs on the right, then check one against the other. If both columns come back, the material is consolidated.

22.1 The master mnemonic

MNEMONIC

Tests "I-PONAR"; Mind "PT-SEM-CMA"

This **mnemonic** chains the whole set of notes. The **test taxonomy (I-PONAR)**: **I**ntelligence, **P**rojective, **O**bjective personality, **N**europsychological, **A**daptive/developmental, **R**ating scales. The **domains of mental life (PT-SEM-CMA)**: **P**erception, **T**hought (with delusions and the first-rank symptoms), **S**elf, **E**motion, **M**emory, **C**onsciousness, **M**otor, and **A**ttention/orientation/insight. Recall the two strings and every topic in these notes hangs off a letter: the tests you would reach for, and the domains in which the mind can go wrong.

22.2 Retrieval practice

RETRIEVAL PRACTICE, COVER THE ANSWERS

Use these as **active recall** prompts: cover the answers, answer each aloud or on paper, then check. Spaced **retrieval practice** across the two bands is what fixes this material.

1. Name the six families of psychological test and one instrument in each.
2. Distinguish the types of reliability from the types of validity; which one caps the other?
3. What is the mean and standard deviation of the deviation IQ, and where does the intellectual-disability range begin?
4. Describe the two-phase administration of the Rorschach and name the five Exner coding axes.
5. List the MMPI validity scales and say what each detects.
6. Name three frontal or executive neuropsychological tests and what each measures.
7. Which Indian tests adapt the Stanford-Binet and the WISC?
8. Define an illusion, a hallucination and a pseudohallucination on the discriminators of stimulus, locus and insight.
9. Give the four Jaspersian ways thought can be disordered (stream, form, content, possession) with one example of each.
10. Separate a primary from a secondary delusion, and name three primary delusional experiences.
11. List the Schneiderian first-rank symptoms, and state whether they are pathognomonic of schizophrenia.
12. Define depersonalisation and derealisation, and give the feature that keeps them from being delusions.
13. Distinguish blunting from incongruity of affect, and anhedonia from alexithymia.
14. Separate the four types of stupor, and name the two changes in the field of consciousness.
15. Define waxy flexibility, negativism, mannerism and stereotypy, and give the discriminator between mannerism and stereotypy.

22.3 The synthesis map

Redraw these notes in two halves. The final device is the **synthesis map** for these notes, which you should **redraw from memory** on a blank page. It has two mirror halves. On the left, the test-taxonomy band: the six families, each with what it measures and one anchoring instrument. On the right, the domains-of-mental-life band: the eight domains, each with its characteristic signs. Cover one half and reconstruct it from the other, filling in the example instruments on the left and the example signs on the right. If both columns come back cleanly, the material is consolidated; if a branch is blank, that is the topic to revisit. The figure accompanying this section is the map to copy first, then reproduce unaided.

Previously asked

Real long-essay (25-mark) and short-note (10-mark) questions from the psychometry, assessment and descriptive-psychopathology territory, most-recent year shown.

LONG ESSAYS (25 MARKS)

- Define emotions. Discuss the various theories and the psychopathological presentations related to emotion. MUHS 2017
- Describe the perceptual processes and the various disorders of perception. MUHS 2014

SHORT NOTES (10 MARKS)

- Rorschach test. MUHS 2020
- Indications of various psychiatric disorders on the Rorschach test. MUHS 2020
- Minnesota Multiphasic Personality Inventory (MMPI). MUHS 2016
- Rating scales in psychiatry. MUHS 2020
- Clinical features of catatonia. MUHS 2020

This territory is examined in two recurring ways. On the psychometry side the projectives (the Rorschach above all), the MMPI and the rating scales come as short notes, so prepare each test to give its author, what it measures and how it is scored in a few lines. On the phenomenology side the disorders of perception and the psychopathology of emotion recur as full essays, and catatonia as a short note, so be able to define each sign precisely and place it in its domain. The theories of intelligence, emotion and personality are covered in the General and Developmental Psychology and Social, Learning & Personality Psychology notes; the acute assessment and management of the catatonic or violent patient is developed in the emergency psychiatry chapter; and the fuller catalogue of clinician rating scales is taken up again in the Paper III psychotherapy and assessment notes.

Quick review

The whole picture in one table	
THE TEST TAXONOMY	Every test belongs to a family defined by what it measures: intelligence (ability), projective and objective (personality), neuropsychological (brain-behaviour), adaptive and developmental (functioning), and rating scales (symptom severity). Read a referral by deciding which family it points to.
TEST CONSTRUCTION	A good test is standardised (uniform administration, norms), reliable and valid. Reliability (consistency): test-retest, inter-rater, internal consistency (Cronbach's alpha, split-half). Validity (measures what it claims): face, content, criterion (concurrent, predictive), construct (convergent, discriminant). Item analysis and test bias. Validity requires reliability, not the reverse. Distinct from research reliability and validity, covered in the Research Methods, Biostatistics & Epidemiology notes.
INTELLIGENCE TESTS	Ratio IQ (mental age over chronological age) gave way to the deviation IQ (mean 100, SD 15). The Stanford-Binet lineage and the Wechsler scales (WAIS, WISC): verbal and performance subtests to four index scores to a Full-Scale IQ. Classification bands: average 90 to 109, intellectual disability below 70 (mild, moderate, severe, profound). DSM-5 grades ID by adaptive function. Theories are covered in the General and Developmental Psychology notes.
RORSCHACH	Ten inkblot cards (Hermann Rorschach, 1921); a projective test of personality and thought organisation. Free-association then inquiry; scored on the Exner system by location, determinants, form quality, content and popular responses (R-PAS is the successor). Reliability and validity are contested.
PROJECTIVE TESTS	The projective hypothesis: ambiguous stimuli reveal unconscious material. TAT (Murray, story-telling to ambiguous cards; CAT for children), sentence completion (Rotter), Draw-a-Person (Machover). Rich but low-reliability; the counterpart to the objective inventories.
OBJECTIVE PERSONALITY	Structured self-report with fixed scoring. MMPI (Hathaway and McKinley, empirically keyed; validity scales L, F, K and ten clinical scales), 16PF (Cattell), NEO-PI-R (the Big Five), EPQ (Eysenck's PEN). Operationalise the personality theories from the Social, Learning & Personality Psychology notes; validity scales guard against faking.
NEUROPSYCHOLOGICAL TESTING	Fixed batteries (Halstead-Reitan) versus the flexible, hypothesis-driven approach; the Luria-Nebraska battery. Frontal and executive tests: Wisconsin Card Sorting (set-shifting), Stroop (inhibition), Trail Making A and B, verbal fluency. Bender Gestalt for visuoconstruction. Used in dementia, TBI and localisation.
ADAPTIVE AND DEVELOPMENTAL SCALES	Adaptive behaviour (now central to the ID diagnosis): the Vineland scales and the VSMS (social

The whole picture in one table	
	quotient). Developmental screening and assessment: DST (Bharat Raj), Denver, Bayley, Gesell schedules, Seguin form board. Yield developmental and social quotients.
RATING SCALES	Clinician-rated symptom scales by domain: depression (HAM-D, MADRS), mania (YMRS), psychosis (BPRS, PANSS), OCD (Y-BOCS); global (CGI), movement (AIMS), cognition (MMSE, MoCA). Used to quantify severity and track response in trials and in the clinic.
INDIAN TEST ADAPTATIONS	Intelligence: Binet-Kamat (BKT), Malin's MISIC (Indian WISC), Bhatia's performance battery. Adaptive and developmental: VSMS Indian norms (Malin), DST (Bharat Raj). Neuropsychology: the NIMHANS neuropsychological battery, PGI Battery of Brain Dysfunction and PGI Memory Scale. Adaptation matters for norms, language and literacy.
DESCRIPTIVE PSYCHOPATHOLOGY	The theory-free description of abnormal experience (Jaspers, Fish, Sims). Form (the kind of experience) before content (what it is about). The domains of mental life: perception, thought, self, emotion, memory, consciousness, motor, and attention, orientation and insight. A precise sign is the unit of the mental state examination.
DISORDERS OF PERCEPTION	Sensory distortions (a real percept altered); illusions (a real stimulus misperceived); hallucinations (a percept without a stimulus, in outer space, full reality, no insight) by modality and the special types (functional, reflex, extracampine, autoscopy, hypnagogic); pseudohallucination (inner subjective space, lacks full substantiality, insight retained). Mechanism theories are covered in the General and Developmental Psychology notes.
DISORDERS OF THOUGHT	Stream (flight of ideas, thought block, circumstantiality), form (formal thought disorder: loosening, derailment, knight's-move, neologisms), content (overvalued ideas, obsessions, delusions), and possession (thought insertion, withdrawal, broadcast, the first-rank alienations).
DELUSIONS	A fixed false belief, absolute conviction, incorrigible, out of cultural keeping. Jaspers' primary (autochthonous: delusional mood, delusional perception, sudden idea, delusional memory) versus secondary. Types by content: persecutory, grandiose, referential, nihilistic (Cotard), erotomanic, jealousy, misidentification (Capgras). Delusion versus overvalued idea versus obsession.
FIRST-RANK SYMPTOMS	Schneider's pragmatic markers: thought echo and third-person voices with running commentary; thought insertion, withdrawal, broadcast; passivity of act, impulse, affect and somatic passivity; delusional perception. Not pathognomonic (seen in mania and organic states; absent in some schizophrenia) and stripped of special status in DSM-5 and ICD-11.
DISORDERS OF SELF AND EMOTION	Self: loss of the ego boundary, depersonalisation (the self feels unreal) and derealisation (the world does),

The whole picture in one table	
	the "as if" quality preserving insight; the dimensions of ego-consciousness; passivity. Emotion: distinguish affect, mood and emotion; blunting and flattening, incongruity of affect, lability, anhedonia and alexithymia.
MEMORY AND CONSCIOUSNESS	Memory: anterograde and retrograde amnesia, Korsakoff, transient global amnesia, and the paramnesias (confabulation, deja vu, jamais vu). Consciousness: the level (clouding, delirium, stupor, coma) and the field (twilight and oneiroid states). Cross-refers to the delirium and organic psychiatry chapters.
MOTOR, ATTENTION AND INSIGHT	Motor: catatonia (waxy flexibility, negativism, posturing, stupor, automatic obedience) and abnormal movements (mannerism, stereotypy, echopraxia). Then the cognitive close of the mental state: attention and concentration, orientation, insight (graded, not all-or-none) and judgement.
DISCRIMINATE AND APPLY	Band A: match the clinical or referral question to the right test (query ID to a Wechsler plus a Vineland; cognitive decline to a neuropsychological battery; depression severity to HAM-D or MADRS). Band B: tell illusion from hallucination from pseudohallucination, and obsession from overvalued idea from delusion. Then read four vignettes: a test choice, an IQ interpretation, a phenomenology spotter and a first-rank read.

References

These notes are grounded in the standard texts (the source hierarchy below); each test is attributed to its author and each sign to its describing text, and landmark, contested or numeric claims carry a PubMed-verified journal citation. Every PMID here was checked against PubMed this build, and any citation whose identifier did not resolve to the cited paper was corrected or dropped.

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PART VII

VII

Research Methods, Biostatistics & Epidemiology

Reading a study and reasoning about its numbers: designs, statistics and the epidemiology of disorder.

01 Research methodology

02 Biostatistics

03 Epidemiology

04 Discriminate

05 Apply and consolidate

PAPER I

Research Methods, Biostatistics & Epidemiology

Five sections · 21 topics · one complete notes document

This material gathers the whole research and statistics toolkit of the first paper into one place, because the examiner tests it as one skill: the ability to read a study and reason about numbers. The first band is **research methodology**, the architecture of clinical evidence: the hierarchy that ranks a case report below a cohort below a randomised trial below a systematic review, the three observational designs and their measures of association, the randomised controlled trial with its machinery of randomisation, allocation concealment, blinding and intention-to-treat analysis, the taxonomy of validity and bias and confounding, the sampling methods, the qualitative approaches, the systematic review and meta-analysis with its forest plot, and the reporting guidelines and research ethics that govern the whole enterprise. The second band is **biostatistics**, the grammar of the numbers: the scales of measurement that decide which test is legal, the description of data and the normal curve, the parametric and non-parametric significance tests, correlation and regression, the diagnostic test statistics built on the 2x2 table, statistical inference with its p-values and confidence intervals and errors, and survival and ROC analysis. The third band is **epidemiology**: incidence and prevalence, relative risk and the odds ratio, the National Mental Health Survey numbers that anchor the Indian picture, and the principles of screening. The examinable skill is judgement on both fronts: choosing the right design for a question, choosing the right test for the data, and interpreting the result correctly.

HOW TO USE THESE NOTES

Read the three bands as one argument. In **methodology**, every named design ends with a **Good to remember** box giving what it is, when to use it, and the one number or feature to know, so the reference facts sit apart from the reasoning. In **biostatistics**, the same box holds each test's one-line rule: what data it takes and what it answers. The **Discriminate** section is the payoff, two selector tables, one to choose a study design from the question and one to choose a statistical test from the data, and the **Apply** section works four short appraisal cases end to end. Figures declare one axis and code it in colour and shape: **petrol** marks structure and the neutral case, **coral** marks the trap or the point of discrimination, and **marigold** highlights the number to hold. Two boundaries are worth stating up front: the twin, family and adoption designs as genetic methods live in the Psychiatric Genetics notes, and the epidemiology of specific disorders lives in the clinical chapters of Paper II, while this material owns the general research toolkit and the national survey numbers; and the reliability and validity of a study here are a different idea from the psychometric reliability and validity of a test in the Psychometry, Assessment and Descriptive Psychopathology notes. This is doctor-facing revision, so the full technical vocabulary is used.

Research methodology

1 · Orientation: evidence-based medicine and the hierarchy of evidence

These notes cover one examinable skill wearing two hats: reading a study and reasoning about its numbers. That is all research methods and statistics really are for the psychiatrist. A paper arrives; you must place its **design**, judge whether its **data** were handled correctly, and decide whether its estimate of a **disease frequency** or a treatment effect can be trusted enough to change what you do on Monday. Methods and statistics are not two subjects but the front and back of the same coin, and the examiner tests them together: a viva that hands you an abstract wants to hear you name the design, state what it can and cannot answer, spot the trap, and read the confidence interval.

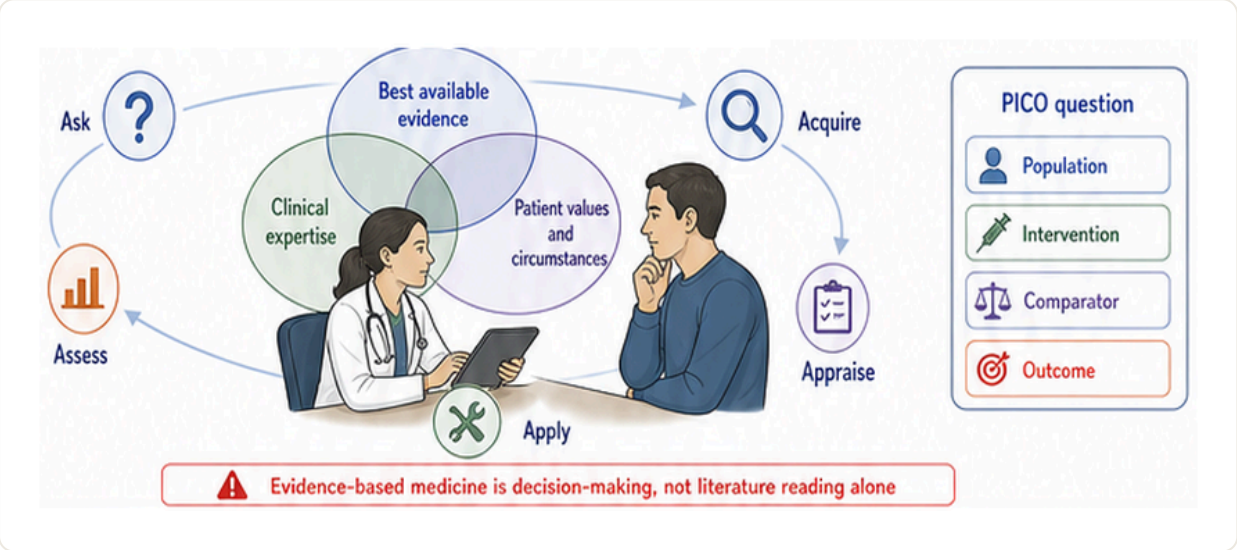


Fig 7.1 Evidence-based medicine: three sources, five actions.

Why this opens the notes. Before any single test or design can be defended, you need the map that ranks them, because the whole discipline is organised around one idea: some kinds of evidence are more trustworthy than others, and the trustworthiness follows from the design, not from the conclusion. That map is the **study-design hierarchy**, the evidence pyramid of evidence-based medicine. Learn the pyramid first and every later topic, from the randomised controlled trial to the odds ratio to the funnel plot, hangs on a rung you already recognise (Cipriani, Leucht & Geddes 2020).

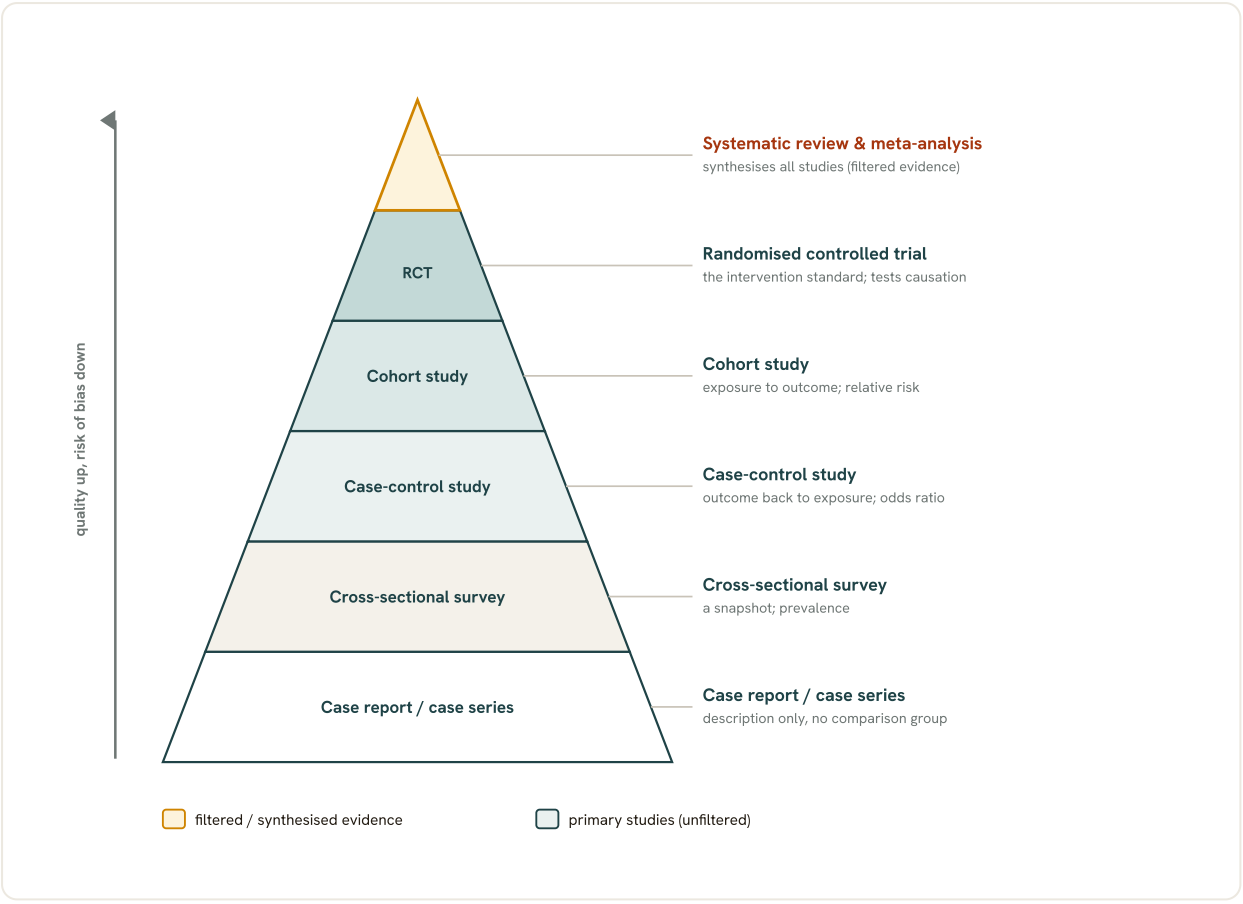


Fig 7.2 The hierarchy of evidence. Study designs rank by how well they control bias: the case report at the base offers only description, the observational designs add comparison groups, the randomised controlled trial adds the control of randomisation, and the systematic review with meta-analysis at the apex synthesises the whole body of filtered evidence. Reading a study begins with placing it on this pyramid, because the design sets the ceiling on the strength of the conclusion.

1.1 Evidence-based medicine: the definition and why it is more than "reading trials"

Definition. Evidence-based medicine is the conscientious integration of best research evidence with clinical expertise and patient values (Sackett et al. 1996). Three legs, not one: the *best current research evidence* from methodologically sound studies, the *clinician's own expertise* built from cumulative experience and skill, and the *patient's preferences, concerns and values*. Drop any leg and the stool falls: pure evidence with no clinical judgement is cookbook medicine, pure expertise with no evidence is eminence-based medicine, and neither is defensible. The term **ebm** in an exam answer should always cue all three components, because a common one-mark question is simply "define evidence-based medicine and name its components".

RULE **Three legs or none.** If your answer names research evidence but omits clinical expertise and patient values, it is not a definition of ebm.

1.2 The five steps of practising ebm (the 5 A's)

The cycle. Practising evidence-based medicine is a repeatable loop. The classic account gives four steps of doing plus a fifth of self-audit, usually taught as the **five steps** or 5 A's. These are the **5 steps** the examiner wants listed in order:

1. Ask

Convert the clinical problem into a focused, answerable question (the PICO question, 1.3).

2. Acquire
Search efficiently for the best available evidence, choosing the right resource (systematic reviews before single trials).

3. Appraise
Critically appraise the evidence for validity (closeness to the truth), size of effect, and applicability.

4. Apply
Integrate the appraised evidence with clinical expertise and the patient's values, and act.

5. Assess
Evaluate your own performance in steps 1 to 4 and the outcome in this patient, then refine.

Steps 1.2 through the rest of these notes are really an expansion of the middle three A's: how to frame the question, how to rank and read the designs you acquire, and how to appraise the numbers.

WORKED EXAMPLE

A patient with treatment-resistant depression asks about adding lithium. **Ask:** in adults with unipolar depression not responding to an antidepressant (P), does adjunctive lithium (I) versus continued antidepressant alone (C) improve response (O)? **Acquire:** a systematic review of augmentation trials sits above any single trial. **Appraise:** check randomisation, blinding, effect size and confidence interval. **Apply:** weigh the benefit against monitoring burden and the patient's willingness to have blood levels checked. **Assess:** review response and tolerability at follow-up. That is one full turn of the five steps.

1.3 The focused question: PICO

Framing. A vague question ("does lithium help?") cannot be searched or answered; a focused one can. The standard scaffold for a therapy or aetiology research question is PICO: **P**opulation (which patients), **I**ntervention (or exposure), **C**omparison (against what, often placebo or usual care), and **O**utcome (measured how). The word **pico** is the examiner's cue for "how do you build an answerable clinical question", and a well-built PICO also tells you which design and which search terms you need. For a harm or prognosis question the I becomes an exposure and the C its absence, but the four slots hold.

TRAP **The missing comparator.** A "study" with no C slot ("patients on drug X improved") is a case series, not a comparative study, and cannot establish that X did the improving.

1.4 The hypothesis: why we test the null

Setting up the test. Once the PICO question is framed, the statistics needs it as a testable hypothesis. Two hypotheses are stated as a pair. The null hypothesis (H0) is the hypothesis of *no difference* between the groups, or *no association* between exposure and outcome; the alternative hypothesis (H1) is that a difference or association does exist. The logic of frequentist testing is deliberately conservative: we never "prove" the alternative, we assume the null is true, compute how surprising the observed data would be under it, and reject the null only if that probability (the p-value) is small enough (Bland 2015).

Why the null, and not the alternative. The null is a single, precise statement ("the two means are equal") whose sampling behaviour we can calculate exactly; the alternative is a whole family of possibilities ("they differ, by some unknown amount") that we cannot. So we test the tractable one. Rejecting H0 lets us *infer* H1; failing to reject H0 is not proof of H0, only absence of evidence against it. This asymmetry, assume no difference and demand the data disprove it, is the spine of null hypothesis significance testing (Altman 1991).

HOLD THIS

We test the null hypothesis of "no difference" because it is the one precise, calculable statement; a small p-value lets us reject it and infer the alternative, but failing to reject it never proves the null.

1.5 The study-design hierarchy: the evidence pyramid

The map. Studies are ranked into a hierarchy of evidence, drawn as a pyramid, because design determines how well a study controls bias and confounding, and therefore how close its estimate sits to the truth. From the broad, weak base up to the narrow, strong apex the study-design hierarchy runs: the case report and case series, then the cross-sectional survey, then the case-control study, then the cohort study, then the randomised controlled trial, and at the top the systematic review and meta-analysis. The base is wide because weak evidence is abundant and easy to generate; the apex is narrow because strong evidence is scarce and expensive. Only the designs near the top are called "best evidence" for a question of treatment efficacy, where the randomised controlled trial reigns because randomisation is the only known way to balance both known and unknown confounders (Cipriani, Leucht & Geddes 2020).

Filtered versus unfiltered. A second cut runs across the pyramid. The single studies (case report through randomised controlled trial) are *unfiltered* or primary evidence: you must appraise each one yourself. The top band, systematic reviews and meta-analyses, is *filtered* or secondary evidence: someone has already gathered, appraised and (in a meta-analysis) statistically pooled the primary studies for you. This is why an efficient search in step 2 starts at the top and works down only if nothing filtered exists.

RULE **Match the design to the question.** The pyramid ranks designs for *treatment efficacy*; for a rare adverse effect a case-control study, not a randomised controlled trial, may be the best feasible design.

1.6 Levels of evidence: Oxford CEBM and GRADE

From pyramid to grade. The pyramid is a picture; formal schemes turn it into ranked levels of evidence. The Oxford Centre for Evidence-Based Medicine (Oxford CEBM) scheme assigns levels by design and question type, with systematic reviews of randomised trials at the top level and expert opinion at the bottom. GRADE takes a different route: rather than ranking by design alone, it starts each body of evidence high (for trials) or low (for observational studies) and then rates it up or down across four certainty grades, high, moderate, low and very low, according to risk of bias, inconsistency, indirectness, imprecision and publication bias. The examinable contrast is that Oxford CEBM ranks *studies* by design, whereas GRADE rates the *certainty of the*

whole body of evidence for a specific outcome, which is why the same trial can support a high or a low GRADE depending on the other studies and the outcome asked about.

INDIA

Indian clinical practice guidelines, including those of the Indian Psychiatric Society, adopt GRADE-style certainty ratings and the same evidence hierarchy, so the language of levels of evidence is not academic decoration: it is how a national guideline tells you the strength behind each recommendation you are expected to follow in a viva on management.

1.7 Systematic review and meta-analysis: the apex, and why it is not automatic

The top band. A systematic review answers a narrow, pre-specified question by an explicit, reproducible method: define the question, search comprehensively, apply stated inclusion criteria, appraise every included study, and synthesise. A *meta-analysis* is the optional statistical step inside a systematic review that pools the primary studies into one summary effect size with greater power than any single trial (Cipriani, Leucht & Geddes 2020). Not every systematic review contains a meta-analysis, and pooling is only justified when the studies are similar enough to combine.

The apex can still mislead. A meta-analysis inherits the flaws of its inputs. Its most serious threat is publication bias: if positive trials are published and negative ones buried, pooling the survivors overstates the effect. This is why the apex is a rung on a ladder, not a guarantee, and appraisal never stops just because a paper says "systematic review" in the title.

TRAP **Apex worship.** "It is a meta-analysis, so it is true" ignores publication bias and heterogeneity; a meta-analysis of biased trials produces a precise, confident, wrong answer.

1.8 The master mnemonic: design, then data, then disease-frequency

The spine of everything that follows. These notes move through three bands in order, and one chained mnemonic holds the whole arc: read the **design** first, then check the **data** handling, then interpret the **disease-frequency** (or effect) it estimates. Every topic is a D in that chain. The pyramid you have just learned is the design band; the statistics topics are the data band; the epidemiology topics are the disease-frequency band.

MNEMONIC

THREE D's: Design, Data, Disease-frequency

The three bands of these notes, in reading order. **Design**: place the study on the evidence pyramid and know what its rung can answer. **Data**: was the null tested correctly, the right statistical test chosen, the p-value and confidence interval read honestly. **Disease-frequency**: what does it say about incidence, prevalence, risk or effect, and can that be generalised. Name the design, trust the data, then quote the frequency: any exam abstract can be attacked in that order.

1.9 What each design answers and where it sits

The catalogue in one view. Before the detailed topics, fix each rung with the question it answers and the one measure it yields. This table is the reference you will return to whenever an abstract lands.

DESIGN (BASE TO APEX)	WHAT IT ANSWERS	SIGNATURE MEASURE	DIRECTION / TIME
Case report / series	Does this phenomenon exist at all; hypothesis generation	**Description only, no rate**	None (no comparator)
Cross-sectional	How common is it now; is there an association at one time point	**Prevalence**	Snapshot (one moment)
Case-control	What exposures differ between those with and without the disease (good for rare disease)	**Odds ratio**	Backward (outcome to exposure)
Cohort	Do the exposed develop the outcome more than the unexposed (good for rare exposure)	**Relative risk, incidence**	Forward (exposure to outcome)
Randomised controlled trial	Does the intervention cause the outcome (efficacy)	**Relative risk, NNT**	Forward, allocation randomised
Systematic review / meta-analysis	What does all the evidence together say	**Pooled effect size**	Synthesis of the above

The evidence pyramid as a table: each rung with the one question it answers and the one measure it yields. The odds ratio, relative risk and NNT are unpacked in their own topics; here, hold which design gives which.

GOOD TO REMEMBER

- **Case report / series:** a description of one or a few patients with no comparison group; use to flag a novel presentation or generate a hypothesis; gives no rate at all.
- **Cross-sectional study:** measures exposure and outcome at a single time point in a defined population; use to estimate how common something is; the one number is prevalence = cases / total population at that time.
- **Case-control study:** starts from the outcome and looks back at past exposures, comparing cases with controls; best for rare diseases; the one measure is the odds ratio = odds of exposure in cases / odds of exposure in controls.
- **Cohort study:** follows exposed versus unexposed forward in time to see who develops the outcome; best for rare exposures and gives incidence; relative risk = incidence in exposed / incidence in unexposed.
- **Randomised controlled trial:** allocates the intervention by a concealed random method to balance confounders; the top design for efficacy; yields relative risk and number needed to treat, NNT = 1 / absolute risk reduction.
- **Systematic review and meta-analysis:** an explicit, reproducible synthesis of primary studies, optionally pooling them statistically; the apex and filtered evidence; the meta-analysis gives one pooled effect size with tighter confidence intervals than any single study.
- **Oxford CEBM levels:** a scheme that ranks individual studies into levels by design and question type; use to grade a single paper; systematic reviews of trials sit at the top level.
- **GRADE:** rates the certainty of a whole body of evidence per outcome into four grades; use in guideline-making; starts high for trials, low for observational studies, then moves up or down.

PEARL

Two axes cross the pyramid and both are examinable. The *vertical* axis is trustworthiness by design (case report at the base, meta-analysis at the apex). The *horizontal* axis is filtered versus unfiltered: everything from case report to randomised controlled trial is unfiltered primary evidence you must appraise yourself, while systematic reviews and meta-analyses are filtered secondary evidence pre-appraised for you. Say both axes and you have shown you understand the pyramid, not just memorised its order.

For genetic study designs such as twin, family and adoption studies, which sit alongside the cohort and case-control designs but answer questions of heritability, see the Psychiatric Genetics notes. For the epidemiology of specific disorders and the national prevalence figures, see the clinical chapters of Paper II. The reliability and validity discussed here belong to *study* quality; the distinct psychometric reliability and validity of a *test* are covered in the Psychometry, Assessment and Descriptive Psychopathology notes.

2 · Observational study designs

This is the map every research question is read against. In an **observational** study the investigator watches nature take its course and measures exposures and outcomes, but does not allocate the exposure. That single fact separates the whole family from the interventional trial (where the investigator assigns the exposure) and is the first fork in any study-design question. The examiner wants you to name a design from a one-line vignette, state its **direction of enquiry** (does it start from exposure or from outcome?), and give the correct measure of

association it yields. Get those three right and almost every stem falls open (Bland 2015; Altman 1991).

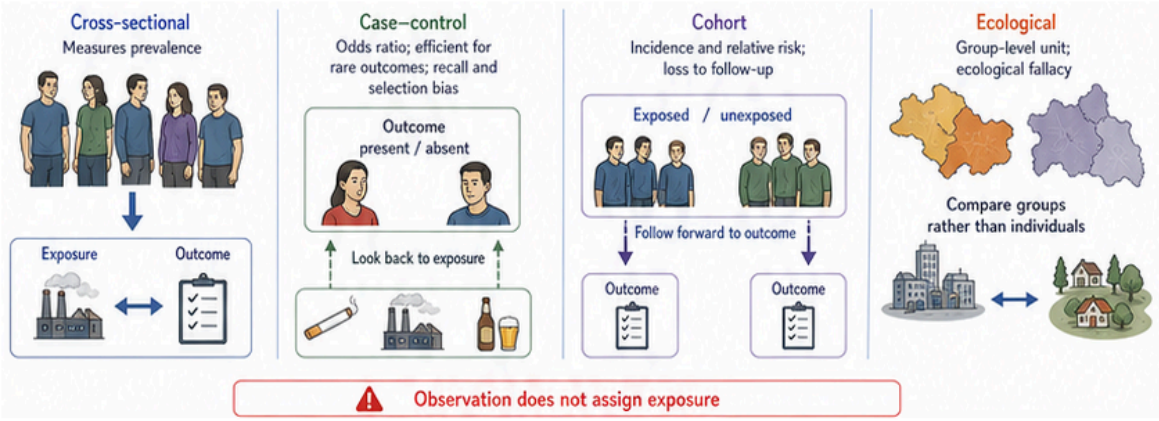


Fig 7.3 Observational designs: direction determines the measure.

The three analytic **observational** designs (cross-sectional, case-control, cohort) differ chiefly in their **time axis**: the cross-sectional design takes a single snapshot, the case-control design looks backward from outcome to exposure, and the cohort design follows forward from exposure to outcome. The ecological study sits apart because its unit of analysis is the group, not the individual. Hold the time axis and the rest is bookkeeping.

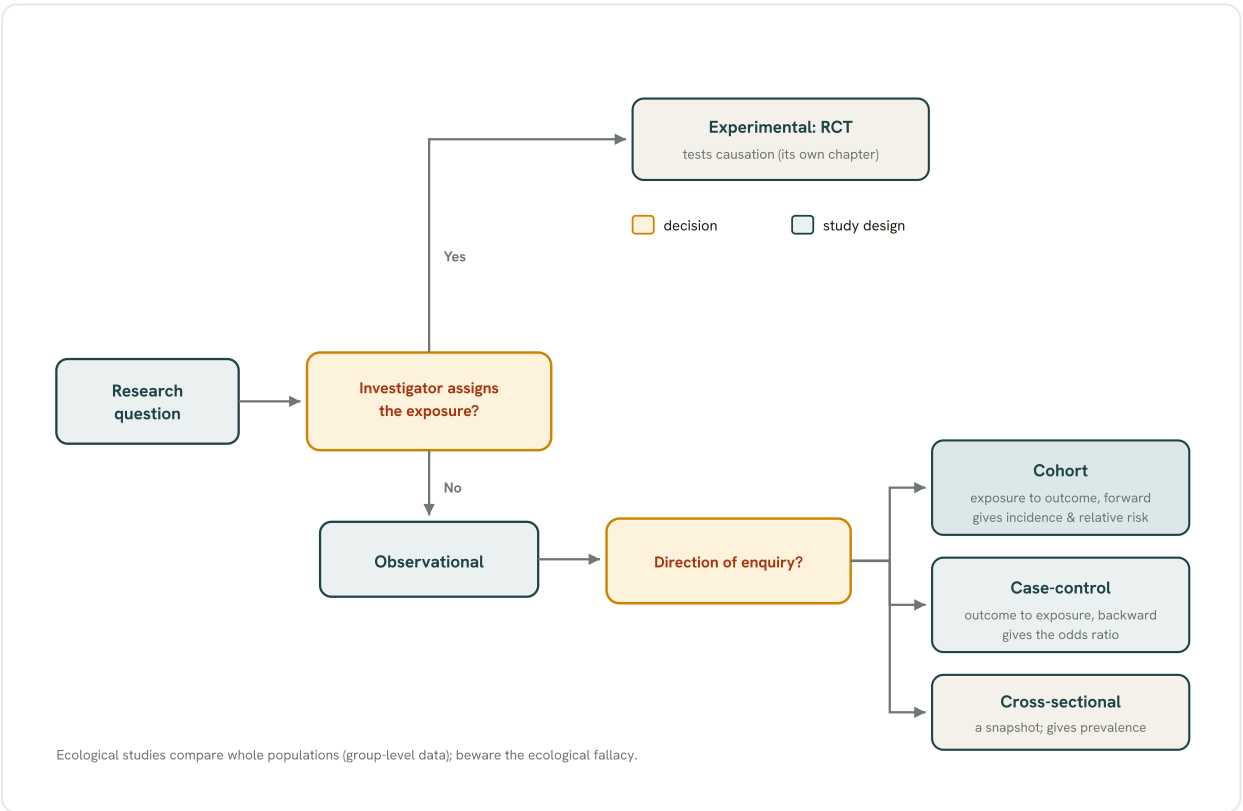


Fig 7.4 Choosing a study design. The first question is whether the investigator assigns the exposure: if so the design is experimental (the randomised controlled trial, developed in its own chapter). If not, the study is observational, and the direction of enquiry then decides the design: following exposure forward to outcome is a cohort (yielding incidence and the relative risk), tracing outcome back to exposure is a case-control (yielding the odds ratio), and measuring both at once is cross-sectional (yielding prevalence).

2.1 Observation versus intervention: the first fork

Who assigns the exposure? The primary division of all analytic study designs is **intervention vs observation**. In an interventional (experimental) study, most rigorously the randomised controlled trial, the investigator allocates the exposure or treatment; randomisation balances known and unknown confounders and gives the design its causal strength (Bland 2015). In an **observational** study the investigator only measures what is already happening, so confounding must be handled at analysis (matching, stratification, regression) rather than by design. Everything in this topic lives on the observational side of that fork; the trial designs are treated with the experimental methods. Descriptive observational work (case reports, case series, correlational surveys) describes without a comparison group; the analytic designs below all carry a comparison group and can test associations.

RULE **Name the fork first.** If the investigator assigned the exposure it is a trial; if they only observed it, it is one of the observational designs, and you then read the direction of enquiry.

2.2 The cross-sectional study: the snapshot

Exposure and outcome measured together, at one point in time. A **cross-sectional** study measures exposure and outcome simultaneously in a defined population at a single point, a snapshot (Bland 2015; Altman 1991). Because everyone is examined once, it is the natural design for a prevalence survey: it counts how many people currently have the condition. It is quick, comparatively cheap, needs no follow-up, and can study several exposures and several outcomes at once, which is why community psychiatric morbidity surveys use it. Its defining weakness is that it *cannot establish temporality*: measuring cause and effect at the same instant, you usually cannot tell which came first, so it is weak for causal inference and prone to reverse causation. It also over-represents long-lasting (prevalent) cases and under-represents brief or rapidly fatal ones.

Direction of enquiry

None: exposure and outcome are read simultaneously.

Measure yielded

Prevalence; and the prevalence ratio as a crude measure of association.

Best for

Prevalence surveys, health-service planning, generating hypotheses.

INDIA

The National Mental Health Survey of India (2015 to 2016) is the flagship cross-sectional example: a snapshot across 12 states giving a current weighted prevalence of any mental disorder of about **10.6** percent (lifetime near **13.7** percent) and a treatment gap for common mental disorders exceeding **80** percent. A snapshot design is exactly right for asking "how many people have the disorder now and how many are in treatment", but it cannot tell you what caused the disorder.

2.3 Prevalence and incidence: what each design can count

Existing cases versus new cases. The measure a design can produce depends on its time axis, so the two frequency measures anchor the whole topic. **Prevalence** is the proportion of a population that *has* the condition at a given time (existing cases); it is what a cross-sectional snapshot yields. **Incidence** is the rate of *new* cases arising over a period in a population initially free of the disease; it requires follow-up over time and so is the property of the cohort design. The link is that prevalence rises with both incidence and duration (roughly, prevalence is proportional to incidence multiplied by average duration in a steady state), which is why chronic disorders look common on a snapshot even when few new cases arise.

TRAP **Prevalence is not incidence.** A cross-sectional survey gives prevalence (existing cases); only a cohort followed over time gives incidence (new cases). Do not report a snapshot as an incidence.

2.4 The case-control study: from outcome, looking back

Start with the outcome, look back for the exposure. A **case-control** study assembles a group who already have the outcome (cases) and a comparable group who do not (controls), then looks back to compare how often each group was exposed. It is therefore **retrospective** in direction: the enquiry runs from outcome to exposure (Bland 2015; Altman 1991). Because you start from the diseased, you can study a rare outcome efficiently with a modest sample, examine several exposures at once, and get an answer quickly and cheaply. Its measure of association is the odds ratio (the odds of exposure among cases divided by the odds among controls). The design's weaknesses are its Achilles heel in exams: it is vulnerable to recall bias (cases search their memories harder for exposures than controls do) and to selection bias (through the way controls are chosen), and it cannot directly measure incidence or, ordinarily, relative risk.

Direction of enquiry

Outcome to exposure (backward): starts from cases and controls.

Measure yielded

The odds ratio (OR); OR approximates the relative risk only when the outcome is rare.

Best for

Rare outcomes, diseases with long latency, quick and cheap enquiry, multiple exposures.

Main weakness

Recall bias and selection bias; cannot give incidence.

TRAP **Case-control gives an odds ratio, not a relative risk.** Because there is no denominator population followed over time, a case-control study cannot yield incidence or a true relative risk; the OR only approximates the RR when the disease is rare.

2.5 The nested case-control study

A case-control study built inside a cohort. The **nested case-control** design draws its cases and controls from within an already-assembled cohort: as outcomes accrue in the cohort, each case is matched to one or more members of the same cohort who were at risk at that time but had not (yet) developed the outcome. Because exposure was recorded at cohort entry, before any outcome,

the nested design largely defeats recall bias, and because controls come from the same source population as the cases it reduces selection bias. It is efficient when a costly exposure measurement (an assay on stored blood, an expensive biomarker) need only be run on the sampled cases and controls rather than the whole cohort. It keeps the temporal clarity of the cohort while retaining the economy of the case-control approach.

2.6 The cohort study: from exposure, following forward

Start with the exposure, follow forward to the outcome. A **cohort** study starts by defining a group free of the outcome, classifies them by exposure status, and follows them forward in time to see who develops the outcome (Bland 2015; Altman 1991). Its direction of enquiry runs from exposure to outcome, and when the following is done in real time it is **prospective**. Because it observes new cases arising in a defined population over time, the cohort design is the one that measures **incidence** directly and yields the relative risk (incidence in the exposed divided by incidence in the unexposed). It is the design of choice for a rare exposure (you deliberately oversample the exposed at entry), it can examine multiple outcomes of a single exposure, and its temporal sequence (exposure demonstrably precedes outcome) makes it the strongest observational design for causal inference. Its costs are the mirror image: large samples, long follow-up, expense, and loss to follow-up, and it is inefficient for a rare outcome.

Direction of enquiry

Exposure to outcome (forward): starts from exposed and unexposed.

Measure yielded

Incidence and the relative risk (RR); the incidence rate ratio.

Best for

Rare exposures, multiple outcomes, establishing temporality.

Main weakness

Slow, costly, loss to follow-up; inefficient for rare outcomes.

2.7 Prospective versus retrospective cohorts

Same design, different position of the observer in time. A **cohort** can be run two ways. In a **prospective** cohort the investigator defines the cohort now, measures exposure now, and waits for outcomes to accrue: exposure data are collected before any outcome, which maximises data quality but demands time and money. In a retrospective (historical) cohort the whole exposure-to-outcome sequence has already happened by the time the study begins; the investigator reconstructs it from existing records (occupational registers, case notes, linked health databases), classifying past exposure and then counting outcomes that have already occurred. Both are true cohort studies (they follow exposure forward to outcome and yield incidence and relative risk); the retrospective form is faster and cheaper but is limited by the completeness and quality of the pre-existing records. Do not confuse the retrospective *cohort* (still exposure to outcome) with the retrospective *direction* of a case-control study (outcome to exposure).

WORKED EXAMPLE

Read a 2x2 table by design. In a **cohort** of 200 exposed and 200 unexposed, followed forward, 40 exposed and 10 unexposed develop the disorder. Incidence in exposed = 40/200 = **0.20**; incidence in unexposed = 10/200 = **0.05**; relative risk = 0.20 / 0.05 = **4.0** (the exposed are four times as likely to develop the outcome). Now take the same table as a **case-control** study (50 cases, 350 controls): odds of exposure in cases = 40/10 = 4; odds of exposure in controls = 160/190; odds ratio = (40 x 190) / (10 x 160) = 7600 / 1600 = **4.75**. Same underlying data, read in two directions: the cohort reads *across* the exposure rows (incidence in the exposed is a / (a + b)) to give an RR, the case-control reads *down* the disease columns (fixing the outcome, then comparing exposure odds) to give an OR, and the OR overshoots the RR because the outcome here is not rare.

2.8 The ecological study and the ecological fallacy

The unit of analysis is the group, not the person. An **ecological** study correlates an exposure and an outcome measured at the level of populations (countries, states, districts, time periods) rather than individuals: for example, plotting national fish consumption against national depression rates, or state lithium-in-water levels against state suicide rates. It is cheap and fast because it reuses routinely collected aggregate data, and it is a useful hypothesis-generating and hypothesis-testing tool at the population level. Its signature hazard is the ecological fallacy: an association that holds between group averages need not hold for the individuals within those groups, so a group-level correlation cannot be assumed to describe individual-level risk. It is the price of losing the individual as the unit of analysis, and it is the single most examined criticism of the ecological design.

TRAP **The ecological fallacy.** Inferring an individual-level relationship from a group-level (aggregate) correlation is invalid; a correlation between country averages tells you nothing certain about any individual.

2.9 The design decision logic: intervention, direction, time axis

Three questions choose the design. Faced with a vignette, decide in order. First, *intervention vs observation*: did the investigator assign the exposure (trial) or merely observe it (one of these designs)? Second, the *direction of enquiry*: does the study start from the outcome and look back (case-control) or start from the exposure and look forward (cohort), or read both at once (cross-sectional)? Third, the *time axis*: a single snapshot (cross-sectional, gives prevalence), backward from outcome (case-control, gives an odds ratio), or forward from exposure (cohort, gives incidence and relative risk). Layered onto that is the frequency logic that decides between the two comparative designs: match the rarity of the exposure or the outcome to the design that captures it efficiently.

DESIGN	DIRECTION OF ENQUIRY	MEASURE OF ASSOCIATION	BEST FOR	MAIN WEAKNESS
Cross-sectional	Simultaneous (snapshot)	**Prevalence (prevalence ratio)**	Prevalence surveys; service planning; several exposures and outcomes at once	No temporality; reverse causation; favours long-duration cases
Case-control	Outcome to exposure (backward, retrospective)	**Odds ratio (OR)**	Rare outcomes; long-latency disease; quick and cheap; multiple exposures	Recall bias; selection bias; no incidence, no true RR
Nested case-control	Outcome to exposure, within a cohort	**Odds ratio (OR)**	Costly exposure assays; when exposure was recorded before outcome	Still smaller than the full cohort; needs the parent cohort
Cohort	Exposure to outcome (forward, prospective)	**Relative risk (RR); incidence**	Rare exposures; multiple outcomes; establishing temporality	Slow, costly, loss to follow-up; poor for rare outcomes
Ecological	Group-level correlation	**Correlation of population rates**	Cheap hypothesis generation from aggregate data	Ecological fallacy: group data cannot be read to the individual

The observational family read across design, direction, measure, best use and main weakness; the hit column is the measure of association each design yields.

2.10 The two selectors: choosing a design, choosing a test

Match the question to the design; match the data to the test. Two interleaved selectors carry a research vignette from question to result. The first turns a clinical question into a design; the second turns the resulting data into the correct statistical test. The design chooser turns on the rarity of what is being studied and on whether temporality matters; the test chooser turns on the type of data, the number of groups, and whether the groups are paired or unpaired.

QUESTION / SITUATION	DESIGN TO PICK
How common is the condition now?	**Cross-sectional (prevalence)**
Rare outcome, or a long-latency disease?	**Case-control**
Rare exposure, or many outcomes of one exposure?	**Cohort**
Need to prove exposure preceded outcome (temporality)?	**Prospective cohort**
Costly exposure assay, cases arising inside a cohort?	**Nested case-control**
Only aggregate, population-level data available?	**Ecological (mind the fallacy)**

Study-design chooser: read the clinical question, pick the design (question to design).

DATA TYPE	GROUPS / PAIRING	CORRECT TEST
Continuous, normal	2 unpaired groups	**Unpaired (independent) t-test**
Continuous, normal	2 paired groups	**Paired t-test**
Continuous, normal	3+ groups	**One-way ANOVA**
Continuous, non-normal	2 unpaired groups	**Mann-Whitney U**
Continuous, non-normal	2 paired groups	**Wilcoxon signed-rank**
Continuous, non-normal	3+ groups	**Kruskal-Wallis**
Categorical (counts)	2+ unpaired groups	**Chi-squared test**
Categorical, paired	2 paired groups	**McNemar test**

Statistical-test chooser: data type by number of groups by pairing, giving the correct parametric or non-parametric test.

HOLD THIS

Case-control starts from the outcome and gives an odds ratio; cohort starts from the exposure and gives incidence and a relative risk; cross-sectional is a snapshot and gives prevalence.

COMMON TRAP

Two mirror-image errors examiners set. First, reporting a **relative risk** from a case-control study, which cannot yield one (it gives an odds ratio; the OR approximates RR only when the outcome is rare). Second, choosing a case-control design for a rare *exposure* (it is efficient for a rare *outcome*): a rare exposure calls for a cohort that oversamples the exposed. Keep the pairing straight: rare outcome to case-control, rare exposure to cohort.

PEARL

The odds ratio and the relative risk converge when the outcome is rare (the "rare disease assumption"): with a low outcome frequency the OR from a case-control study is a good approximation of the RR you would have got from a cohort. As the outcome becomes common the OR increasingly exaggerates the RR, which is exactly why a case-control OR should never be quoted as a relative risk when the outcome is frequent.

MNEMONIC

"Cohort = Cause first; Case-control = Consequence first."

The cohort begins with the putative cause (the exposure) and follows forward; the case-control begins with the consequence (the outcome) and looks back. Both start with C, so anchor on the second word: cause-first is forward-looking cohort (relative risk), consequence-first is backward-looking case-control (odds ratio).

GOOD TO REMEMBER

- **Cross-sectional:** measures exposure and outcome at once, a snapshot; use it for a prevalence survey; gives prevalence and the prevalence ratio, and cannot establish temporality.
- **Case-control:** starts from the outcome and looks back for exposure (retrospective); use it for a rare outcome or long-latency disease; gives the odds ratio, OR = (odds of exposure in cases) / (odds of exposure in controls).
- **Nested case-control:** a case-control study drawn from within a cohort; use it when a costly exposure assay makes measuring the whole cohort wasteful; gives an odds ratio while defeating recall bias.
- **Cohort:** starts from exposure and follows forward to outcome (prospective); use it for a rare exposure or multiple outcomes; gives incidence and the relative risk, RR = (incidence in exposed) / (incidence in unexposed).
- **Ecological:** correlates exposure and outcome at the group level; use it for cheap hypothesis generation from aggregate data; the number to fear is the ecological fallacy, that group correlations do not transfer to individuals.

3 · The randomised controlled trial and drug-trial phases

The randomised controlled trial (RCT) is the only truly **experimental design** in clinical research and the acknowledged gold standard for testing whether a treatment actually works (Companion to Psychiatric Studies 2010). Everything else in this chapter observes; the RCT intervenes, allocates by chance, and so earns the right to speak about cause. The examiner rarely asks "what is an RCT"; the marks sit in the machinery that protects it: randomisation, allocation concealment, blinding, and an analysis that keeps the randomised groups intact.

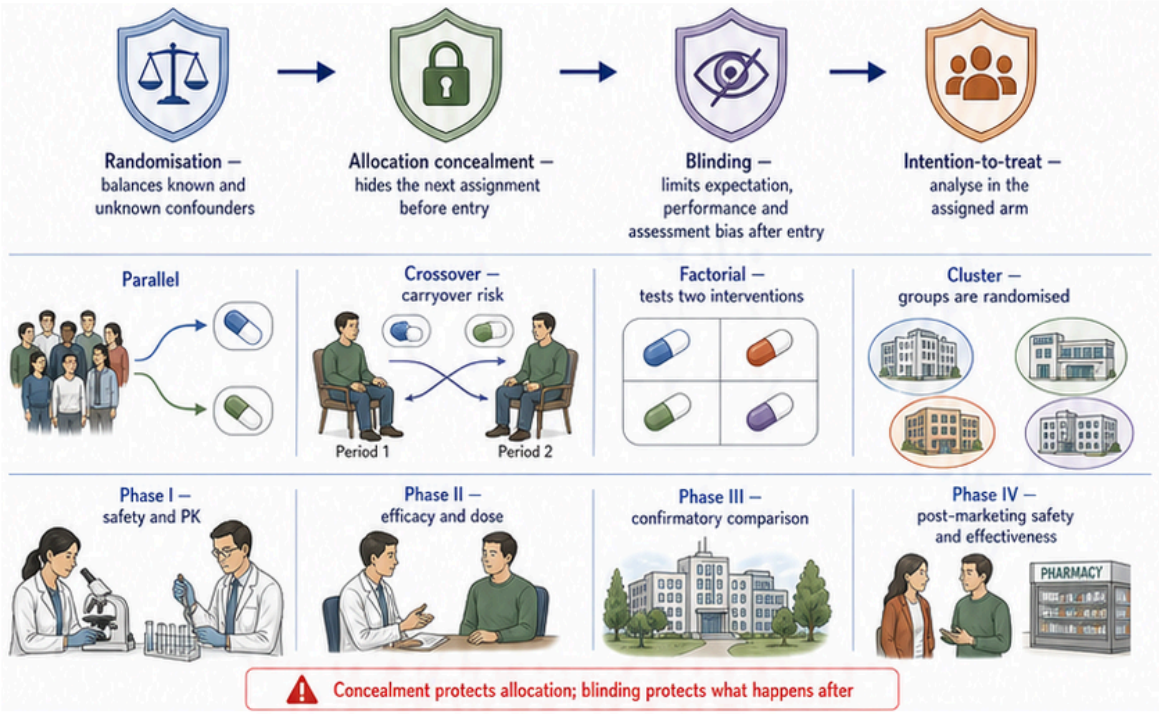


Fig 7.5 Randomised trials: safeguards do different jobs.

Read this topic as a chain in which each link defends the last. Randomisation creates comparable groups; allocation concealment stops the recruiter from breaking the randomisation at entry;

blinding stops patients, clinicians and assessors from biasing what happens afterwards; intention-to-treat keeps the analysis faithful to the randomisation. Break any link and the design degrades toward a mere observational comparison.

3.1 The randomised controlled trial as the experimental design

Only a controlled trial with random allocation is truly experimental. In a **randomised controlled** trial the investigator assigns each consenting participant to an intervention or a comparator by a chance mechanism, follows both arms forward, and compares a pre-specified outcome. Because the investigator controls the exposure and allocates it at random, the RCT (equivalently the **randomized controlled** trial in American spelling) is the design least vulnerable to selection bias and confounding, which is why it anchors the top of the evidence hierarchy for questions of therapy. Non-randomised comparisons tend to over-estimate benefit because the newer treatment is quietly given to less severe or better-prognosis patients, the problem of confounding by indication. Even within randomised trials, inadequate or unclear allocation concealment inflates the estimated treatment effect, by around **30% to 41%** on average (Schulz et al 1995).

3.2 Randomisation: why it works, and its varieties

Randomisation balances known and, crucially, unknown confounders. Randomisation (American: randomization) has two purposes. First and foremost it distributes both the measured prognostic factors (age, sex, severity) and, more importantly, the *unmeasured and unknown* ones evenly between arms, so that any difference in outcome can be attributed to the treatment. Second, it removes the recruiter's ability to steer sicker or healthier patients into a preferred arm. No other design can balance confounders you have not even thought to measure, and that is the single reason the RCT out-ranks the cohort study for causal claims about therapy (Bland 2015).

Simple randomisation

Each patient allocated independently by chance (the equivalent of a fair coin or a random-number list); can leave unequal group sizes in small trials, but self-corrects as the trial grows large.

Block randomisation

Patients randomised in small blocks (of four, six, and so on) so that the numbers in each arm stay equal throughout recruitment; the cost is that the last allocation in a block can become guessable.

Stratified randomisation

A separate randomisation schedule is run within each level of a key prognostic variable (for example centre, or baseline severity) so that variable is balanced by design rather than left to chance; usually combined with blocks.

RULE **Random allocation is the only tool that balances unknown confounders.** That is why the RCT, not the cohort study, is the design for a causal therapy question.

3.3 Allocation concealment: guarding the moment of assignment

Concealment hides the *upcoming* assignment from whoever recruits. Allocation concealment means that the person enrolling a patient cannot know, at the moment of consent, which arm that patient is about to enter. If the schedule is predictable (allocation by date of birth, alternate

days, an unsealed list), a recruiter can consciously or unconsciously include or exclude patients to load one arm, and the randomisation is subverted before it happens. The robust solution is a remote or independent system: the recruiter phones or logs in, enters the patient's baseline data, and only then is the allocation released. Trials in which allocation was easy to subvert were far more likely to report a significant effect (trials with subvertible allocation were consistently more likely to report a significant effect; Chalmers et al 1983).

TRAP **Allocation concealment and blinding are not the same thing.** Concealment protects the assignment *before* and *at* entry; blinding protects perception *after* entry. A trial can be double-blind yet have had broken concealment, and vice versa.

3.4 Blinding: what single, double and triple each conceal

Blinding stops knowledge of the assigned arm from biasing what comes next. Where allocation concealment guards entry, blinding (masking) guards everything after it by keeping the arm hidden from one or more parties. A **placebo** is the instrument that makes patient-level blinding possible, an inert comparator indistinguishable from the active drug. The purpose of single, double and **double-blind** or triple blinding is to reduce observer, performance and ascertainment bias.

LEVEL	WHO IS KEPT UNAWARE OF THE ARM	BIAS IT CHIEFLY PREVENTS
Open (unblinded)	Nobody; all parties know the arm	None; maximally biased
Single-blind	**The patient only**	Patient expectation / placebo response
Double-blind	**Patient and treating clinician**	Patient expectation plus clinician performance bias
Triple-blind	**Patient, clinician and the outcome assessor / analyst**	Adds ascertainment (assessment) bias

Each blinding level conceals the arm from one more party; the extra party in triple-blind is the outcome assessor or data analyst (Companion to Psychiatric Studies 2010).

Blinding is often imperfect. Distinctive side-effects (anticholinergic dryness, extrapyramidal signs) can unmask the active drug; a useful check is to ask patients and raters to guess their arm at the end, where successful blinding gives no-better-than-chance guessing (Even et al 2000).

3.5 Intention-to-treat versus per-protocol analysis

Analyse everyone in the arm to which they were randomised. Intention-to-treat (ITT) analysis includes every randomised participant in their originally allocated arm, regardless of whether they completed, complied with, or even received the treatment. Per-protocol (completer) analysis restricts to those who finished per protocol. ITT is preferred because the moment you exclude dropouts or non-compliers you re-introduce exactly the selection you randomised away: dropout is rarely random (people leave because a drug failed or was not tolerated), so a completer analysis flatters the treatment. ITT preserves the randomisation and therefore keeps the groups

comparable and the comparison unbiased (Altman 1991). It gives the more conservative, more clinically realistic estimate of effectiveness; per-protocol answers the narrower "did it work in those who took it" question and is more prone to bias.

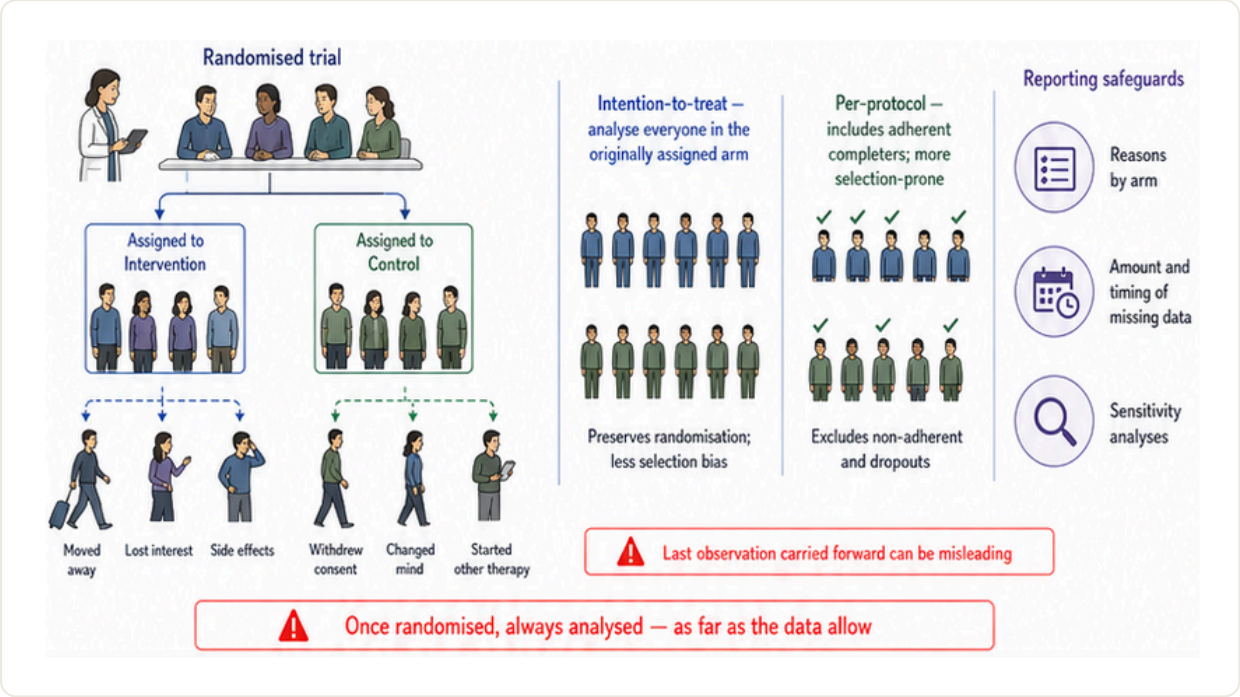


Fig 7.6 Attrition, adherence and missing outcomes.

RULE **ITT analyses everyone as randomised.** "Once randomised, always analysed" preserves the balance that randomisation bought and gives the honest, conservative effect estimate.

For missing outcomes, last-observation-carried-forward (LOCF) has been used to complete ITT datasets but is statistically dubious, since trial dropout in psychiatry is often substantial and treatment-related, so the missing values are rarely missing at random (Companion to Psychiatric Studies 2010).

3.6 Trial architectures: parallel-group, crossover, factorial, cluster randomised

The architecture is chosen to fit the disease and the question. The default is the parallel-group trial, in which independent arms run side by side. Three important variants exist. A crossover trial gives every participant each treatment in turn in random order, so each patient serves as their own control. A factorial design tests two or more interventions simultaneously in one trial (a two-by-two factorial gives A, B, both, or neither), efficiently answering more than one question and probing interaction. A cluster randomised (American: cluster randomized) trial randomises whole groups, such as clinics or general-practice teams, rather than individuals.

ARCHITECTURE	STRUCTURE	WHEN TO USE IT	THE CATCH
Parallel-group	Separate arms compared concurrently	**The default for most therapeutic questions**	Needs the full sample size in each arm

ARCHITECTURE	STRUCTURE	WHEN TO USE IT	THE CATCH
Crossover	**Each patient receives both treatments in random sequence, own control**	Rare or stable chronic disease where recruiting large parallel groups is impractical	Carryover and order effects; needs a washout; not for curable or unstable conditions
Factorial	**Two-plus interventions crossed in one trial (2x2: A, B, both, neither)**	Two questions, or a suspected interaction, tested economically at once	Assumes no strong interaction between the factors; complex to interpret if there is one
Cluster randomised	**Groups (clinics, practices, wards) randomised, not individuals**	Service-level or educational interventions that cannot be given to one person without contaminating neighbours	The cluster is the unit of analysis; needs many clusters for power

Crossover buys power in rare stable diseases at the price of carryover; factorial buys a second answer if the factors do not interact; cluster is forced whenever the intervention cannot be confined to an individual (Companion to Psychiatric Studies 2010).

3.7 Superiority, non-inferiority and equivalence framing

The objective determines the hypothesis and the sample size. A **superiority** trial asks whether the new treatment beats the comparator (or placebo). A **non-inferiority** trial asks whether the new treatment is not worse than an established one by more than a pre-specified acceptable margin, used when a new agent offers a side benefit (cheaper, safer, easier) and a placebo arm would be unethical. An **equivalence** trial asks whether two treatments differ by no more than a margin in either direction, typical for bioequivalence. The direction of the question changes the null hypothesis, so a non-inferiority or equivalence claim cannot simply be read off a failed superiority test.

COMMON TRAP

"No significant difference" in a superiority trial does not prove the treatments are equivalent; absence of evidence is not evidence of absence. Equivalence and non-inferiority must be designed and powered as such from the outset, with a pre-stated margin. A small, underpowered superiority trial that finds nothing is uninformative, not reassuring.

3.8 The drug trial phases

A new drug is licensed by climbing four phases. Before an RCT can even ask about efficacy, a compound must pass through the staged programme of a drug trial. Each phase has a distinct question and a characteristically larger sample. **Phase i** is first-in-human: small groups of usually healthy volunteers receive the drug to establish safety, tolerability and pharmacokinetics (in oncology and some psychiatry contexts, patients rather than healthy volunteers are used). **Phase ii** moves to patients with the target disorder to look for preliminary efficacy and to find the dose. **Phase iii** is the large, comparative, confirmatory RCT that supplies the pivotal evidence for licensing. Phase IV is post-marketing surveillance after approval, detecting rare or long-term adverse effects in real-world use (Goodman & Gilman 2018).

20 to 100	100 to 300	300 to 3000	thousands
PHASE I (HEALTHY VOLUNTEERS)	PHASE II (PATIENTS)	PHASE III (PATIENTS)	PHASE IV (POST-MARKETING)

PHASE	CORE QUESTION	WHO / TYPICAL N	DESIGN
Phase I	**Is it safe in humans, and how is it handled (PK)?**	Small healthy volunteer groups, roughly **20 to 100**	First-in-human, dose-escalation, often open
Phase II	**Does it show efficacy, and at what dose?**	Patients with the disorder, roughly **100 to 300**	Dose-finding; often placebo-controlled, randomised
Phase III	**Does it work better than the comparator, confirmed?**	Larger patient samples, roughly **300 to 3000**	Large double-blind confirmatory RCT for licensing
Phase IV	**What happens in real-world, long-term use?**	Post-marketing, thousands of users	Surveillance / pharmacovigilance after approval

The question, the sample and the setting all scale up phase by phase: safety in a handful, efficacy and dose in hundreds, confirmation in thousands, then lifelong surveillance (typical Ns per standard pharmacology texts; Goodman & Gilman 2018).

WORKED EXAMPLE

A novel antidepressant: phase I gives single ascending oral doses to about 40 healthy volunteers, measuring half-life and tolerability with no efficacy claim. Phase II randomises roughly 200 patients with major depression across three doses versus placebo to identify the effective dose. Phase III runs two double-blind placebo-controlled RCTs of around 500 patients each, the pivotal evidence submitted for licensing. After approval, phase IV registries pick up a rare hepatic signal invisible in the pre-licensing sample. The same drug thus needs every phase; a positive phase III cannot substitute for phase IV vigilance.

3.9 How the pieces defend one another

The safeguards form one continuous chain. Randomisation manufactures comparable groups; allocation concealment stops that randomisation being unpicked at recruitment; blinding stops it being eroded during treatment and assessment; intention-to-treat stops it being discarded at analysis. Assess any published RCT by walking this chain, and you will locate its weakest link. A trial that is randomised but with poor concealment, or double-blind but analysed per-protocol, has a leak precisely where the exam wants you to point.

HOLD THIS

Allocation concealment guards the assignment at entry; blinding guards perception after entry; intention-to-treat keeps everyone analysed in the arm they were randomised to; and the drug phases climb safety (20 to 100 healthy volunteers) to efficacy/dose (100 to 300 patients) to confirmatory licensing (300 to 3000) to post-marketing surveillance.

GOOD TO REMEMBER

- **Randomised controlled trial:** the only experimental therapeutic design; allocates treatment by chance and compares arms forward; the one design that balances unknown confounders, which is why it is the therapy gold standard.
- **Randomisation:** distributes known and unknown confounders evenly; simple (self-corrects when large), block (keeps arms equal), stratified (balances a key prognostic factor by design).
- **Allocation concealment:** hides the upcoming assignment from the recruiter at the moment of entry; best achieved by remote / independent randomisation; distinct from blinding, which acts after entry.
- **Blinding:** conceals the arm to cut bias; single (patient), double (patient plus clinician), triple (plus outcome assessor); a placebo makes patient blinding possible.
- **Intention-to-treat vs per-protocol:** ITT analyses all as randomised and preserves comparability (conservative); per-protocol counts only completers and is prone to bias; "once randomised, always analysed".
- **Parallel-group:** concurrent independent arms; the default; needs full N per arm.
- **Crossover:** each patient is own control receiving both treatments in sequence; use in rare, stable, chronic disease; watch carryover and order effects, use a washout.
- **Factorial:** two-plus interventions crossed (2x2 = A, B, both, neither); answers two questions and tests interaction in one trial; valid if the factors do not strongly interact.
- **Cluster randomised:** randomises groups (clinics, practices) not individuals; use for service or educational interventions that cannot be confined to one person; needs many clusters because the cluster is the analysis unit.
- **Superiority / non-inferiority / equivalence:** beats comparator / not worse than by a set margin / differs by no more than a margin either way; a non-significant superiority result does not prove equivalence.
- **Drug trial phases:** phase I safety and PK in 20 to 100 healthy volunteers; phase II efficacy and dose-finding in 100 to 300 patients; phase III large confirmatory comparative RCT of 300 to 3000 for licensing; phase IV post-marketing surveillance in thousands.

4 · Validity, bias and confounding

This is the quality-control chapter of research. Every study makes a claim; validity, bias and confounding are the three questions the examiner uses to decide whether the claim is believable. **Validity** asks whether the finding is true (for this sample, and then for the wider world); **bias** is systematic error that pushes the answer consistently in one direction; and **confounding** is a third variable that mimics a real association. The stem usually gives a scenario and asks you to name the flaw, classify it, and say how it should have been controlled. Get the taxonomy clean and almost every methods question falls open (Kaplan & Sadock 2024; Bland 2015; Altman 1991).

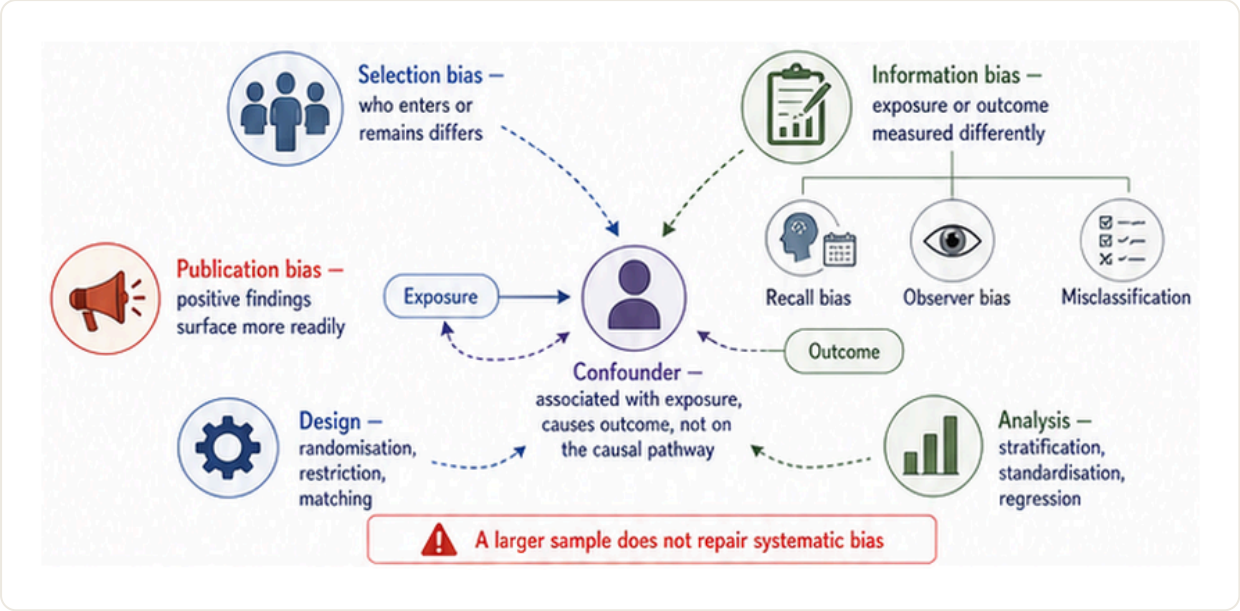


Fig 7.7 Bias and confounding: how results move away from truth.

Two housekeeping distinctions anchor the topic before the detail. First, keep **systematic error** (bias, which no increase in sample size removes) apart from **random error** (chance, which shrinks as the sample grows and is quantified by confidence intervals and the p-value). Second, the study reliability and validity discussed here (are the study's results reproducible and true) are a DIFFERENT idea from the psychometric-test reliability and validity of a scale or instrument (whether a questionnaire measures consistently and measures what it claims); those are taught in the Psychometry, Assessment and Descriptive Psychopathology notes. Keep the two vocabularies separate: here the object is a whole study, there it is a single test; this separation is restated where reliability is defined below.

4.1 Internal validity: are the results true for this sample

Does the study answer its own question correctly, free of bias and confounding? Internal validity is the degree to which the observed association between exposure and outcome is real for the participants actually studied, rather than an artefact of bias, confounding or chance (Kaplan & Sadock 2024). It is the first and non-negotiable property: a study with poor internal validity is simply wrong, and how far it generalises is then irrelevant. Threats to internal validity are exactly the topics of this chapter, selection bias, information bias and confounding, plus chance. The randomised controlled trial earns its rank because randomisation and blinding protect internal validity better than any observational design can. Efficacy trials in tightly selected samples are built to maximise internal validity (Kaplan & Sadock 2024).

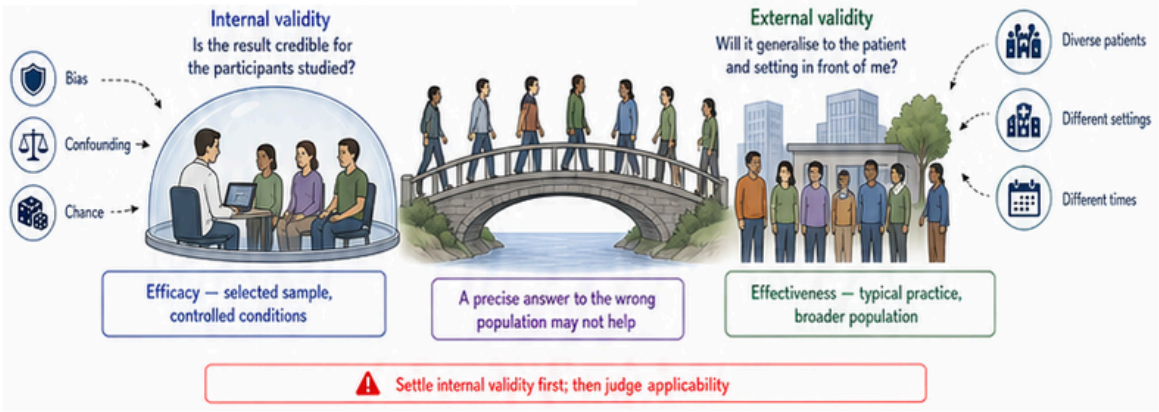


Fig 7.8 Internal and external validity: true here, useful there.

RULE **Internal validity comes first.** If the result is not true for the sample studied, it does not matter whether it generalises: settle internal validity before external validity.

4.2 External validity: do the results generalise

Can the finding be applied beyond the study sample? External validity, also called **generalisability** (spelled generalisability or generalizability), is the extent to which the results hold for patients outside the study, in other settings, populations and times (New Oxford Textbook of Psychiatry). A trial can have flawless internal validity yet poor external validity if its participants were so narrowly selected (single-diagnosis, no comorbidity, no substance use) that the result cannot be read across to the messy patients of ordinary practice. This is the efficacy versus effectiveness trade-off: efficacy studies maximise internal validity in narrow samples, whereas effectiveness (pragmatic) studies use broad, typical, comorbid populations so that external validity carries more weight (Kaplan & Sadock 2024). The two validities pull against each other, and reading which one a design has bought is a favourite question.

WORKED EXAMPLE

An antidepressant RCT enrols only patients aged 18 to 45 with major depression and no comorbidity, randomises and double-blinds cleanly, and reports a clear drug effect. Its internal validity is high: the effect is real for those studied. Its external validity is low: most real depressed patients are older, or have anxiety, alcohol use or physical illness, so the result may not generalise to them. High internal, low external validity is the signature of a tightly controlled efficacy trial.

4.3 Reliability: reproducibility of the measurement

Does the study measure the same thing consistently on repetition? Study reliability, or **repeatability**, is the reproducibility of a measurement: if the same subjects were measured again under the same conditions, would the same values result. Reliability concerns precision (random scatter), whereas validity concerns accuracy (systematic closeness to the truth); the classic image is the target, where a reliable-but-invalid instrument lands its shots tightly clustered but off the bullseye, and a valid-but-unreliable one scatters around the centre. A measurement can be reliable without being valid, but it cannot be valid without first being reliable, so reliability is necessary

but not sufficient for validity. As flagged in the intro, this study-level reliability is distinct from the psychometric-test reliability (internal consistency, test-retest, inter-rater) covered in the Psychometry, Assessment and Descriptive Psychopathology notes.

4.4 Bias: systematic error, and its two great families

Bias is systematic error, built into the study, that no larger sample can fix. Bias is any systematic (non-random) error in the design, conduct or analysis of a study that produces a result consistently distorted away from the truth (Kaplan & Sadock 2024). Because it is systematic, adding participants only makes a biased study more precisely wrong; bias is defeated by better design, not by size. Following the standard epidemiological division, bias falls into two great families plus a literature-level form: selection bias (who gets into the study and who is compared), information bias (how exposure and outcome are measured once in), and publication bias (which studies reach print). Naming the family first, then the specific mechanism, is the reliable way to answer a bias vignette (Tasman Psychiatry).

4.5 Selection bias

A systematic error in how participants enter or are compared. Selection bias arises when the way subjects are selected, or the way exposed and unexposed (or cases and controls) are chosen, is related to both the exposure and the outcome, so the compared groups differ systematically from the start (Tasman Psychiatry). Textbook varieties include the **healthy worker effect** (employed populations are healthier than the general population, so occupational cohorts understate harm), **self-selection (volunteer) bias** (people who respond to advertisements or agree to take part differ from those who do not, and the exposed with symptoms may be keener to enrol), **Berkson's bias** (hospital-based cases and controls carry a spurious association because admission itself depends on having one or more conditions), and **loss to follow-up (attrition) bias** (differential dropout in a cohort or trial, a serious threat when dropout is related to both exposure and outcome). The defence is at the design stage: define the source population, sample and recruit exposed and unexposed identically, and choose controls from the same population that produced the cases.

4.6 Information bias, including recall and observer bias

A systematic error in how exposure or outcome is measured. Information bias (also called observation or measurement bias) occurs when data on exposure or outcome are obtained in a non-comparable manner between the groups, so that one group's information is systematically more or less accurate than the other's (Tasman Psychiatry). Its named forms are high-yield. Recall bias is differential accuracy of memory: people with the outcome (cases, or mothers of an affected child) search their past for exposures more thoroughly than unaffected controls, inflating the apparent association; it is the classic weakness of the retrospective case-control study. **Observer (or interviewer) bias** is systematic error introduced by the assessor: an interviewer who knows a subject's disease status probes exposure harder in cases, or an unblinded rater scores the outcome more favourably in the treated arm; masking (keeping the assessor blind to exposure or allocation) is the remedy (Tasman Psychiatry). **Misclassification** is the mechanism by which information bias operates: non-differential misclassification (errors unrelated to group) usually

dilutes an association toward the null, whereas differential misclassification (errors that differ by group, as in recall bias) can bias in either direction and is the more dangerous. Publication bias is a special, literature-level information problem addressed at 4.7.

TRAP **Recall bias needs two groups remembering differently.** It is not just "poor memory": it is differential recall between cases and controls. Symmetric forgetting in both groups is non-differential misclassification, not recall bias.

4.7 Publication bias

Positive studies are published more, and sooner, than negative ones. Publication bias is the tendency for studies with statistically significant, positive or striking results to be submitted, accepted and published more readily than studies with null or negative findings, so the published literature systematically overstates an effect. It is the reason a meta-analysis restricted to published trials can be misleading, and it is detected within the systematic-review and meta-analysis topic by an asymmetric funnel plot (and formal tests such as Egger's), and mitigated by trial registries and grey-literature searching. It is treated more fully as a threat to the systematic review; here, hold that it is a bias of the literature, not of a single study's internal conduct.

4.8 Confounding: the third variable

A third variable linked to both exposure and outcome, and not on the causal path. Confounding occurs when a third factor is associated with the exposure and is independently a cause of the outcome, so that it distorts (creates, inflates, masks or even reverses) the apparent exposure to outcome association (Tasman Psychiatry). Three conditions define a **confounder**: it must be associated with the exposure, it must be an independent risk factor for (cause of) the outcome, and it must NOT lie on the causal pathway between exposure and outcome (a variable on that pathway is a mediator, not a confounder). The examiner's classic is the unemployment to suicidal behaviour question in which **alcoholism** is related both to unemployment and to suicidal behaviour, and therefore confounds the association unless it is adjusted for (Tasman Psychiatry). Other stock examples are age and sex confounding almost any exposure to disease link, and the coffee to lung-cancer association confounded by smoking (smokers drink more coffee and smoking causes lung cancer). Spot a confounder by testing the three conditions, then decide whether it was handled at design or at analysis.

WORKED EXAMPLE

A study finds unemployed people have more suicidal behaviour, crude relative risk **2.0**. But alcohol dependence is commoner among the unemployed AND independently raises suicide risk, so it satisfies both confounder arms and is not on the causal path. Stratify by alcohol status: within non-drinkers RR is **1.2** and within dependent drinkers RR is **1.3**. The crude 2.0 was inflated by confounding; the adjusted (stratum-specific) estimate near 1.2 to 1.3 is the truer effect of unemployment itself. Adjusting for alcohol is correct here because alcohol is a confounder, not a step on the pathway from unemployment to suicide.

4.9 Controlling confounding at the design stage

Prevent the imbalance before data are collected. Four design tools handle confounding up front. Randomisation allocates subjects to groups by chance so that, on average, both known AND unknown confounders are balanced between arms; it is the only method that controls confounders you have not measured or even thought of, which is the entire reason the RCT is the reference standard. **Restriction** admits only one level of the confounder (for example, study only non-smokers), which removes its confounding effect but narrows external validity. **Matching** selects comparison subjects to have the same distribution of a confounder as the index group (individual or frequency matching), balancing that specific confounder, though matched data then require a matched analysis. Two further design safeguards protect randomisation itself: allocation concealment hides the upcoming assignment from the recruiter so that selection into arms cannot be manipulated, and blinding (masking) keeps participants, clinicians and assessors unaware of allocation; a **double-blind** design masks both the participant and the assessor, defending against performance and observer (ascertainment) bias. Note that allocation concealment governs entry into the arms whereas blinding governs everything after; they are distinct and both matter.

RULE **Only randomisation controls unknown confounders.** Restriction, matching, stratification, standardisation and regression each control confounders you have measured; solely randomisation balances the ones you have not.

4.10 Controlling confounding at the analysis stage

Correct for the measured confounder after data are collected. When a confounder was recorded but not designed out, three analytic tools adjust for it. Stratification divides the data into strata of the confounder, computes the association within each stratum where the confounder is held constant, and pools the stratum-specific estimates (the Mantel-Haenszel method); comparing the crude and adjusted estimates reveals how much confounding was present. **Standardisation** re-weights rates to a common reference population (direct or indirect), the method behind age-standardised and sex-standardised rates, so groups with different age or sex structures can be compared fairly. Multivariable (regression) adjustment models the outcome on the exposure plus the confounders simultaneously (linear, logistic or Cox regression), yielding an exposure effect adjusted for every covariate in the model; it is the workhorse of modern observational analysis. The hard limit of every analytic method is that you can only adjust for confounders you measured, and residual confounding from unmeasured or mismeasured variables always remains, which is precisely why randomisation is unique.

TRAP **Never adjust for a mediator.** Confounding is NOT a type of bias, and a variable on the causal pathway (a mediator) is not a confounder: adjusting for it wrongly blocks part of the real effect (overadjustment).

CLASS	NAMED FORM	WHAT GOES WRONG	TYPICAL DESIGN	DEFENCE
Selection bias	**Healthy worker effect**	Employed sample healthier than general population, harm understated	Occupational cohort	Suitable external comparison group
Selection bias	**Self-selection (volunteer)**	Participants differ systematically from non-participants	Advertised recruitment, surveys	Define and sample a source population
Selection bias	**Berkson's bias**	Hospital cases and controls carry a spurious association via admission	Hospital case-control	Community (population) controls
Selection bias	**Loss to follow-up (attrition)**	Differential dropout related to exposure and outcome	Cohort, RCT	Minimise and analyse dropout; intention-to-treat
Information bias	**Recall bias**	Cases remember exposures more thoroughly than controls	Retrospective case-control	Records-based exposure; nested design
Information bias	**Observer / interviewer bias**	Unblinded assessor probes or scores groups differently	Any assessed study	Masking (blinding) of assessors
Information bias	**Misclassification**	Errors in exposure/outcome labelling (non-differential dilutes; differential either way)	Any measurement	Validated, objective, blinded measures
Publication bias	**Positive-result bias**	Significant studies published more, literature overstates effect	Meta-analysis of published trials	Trial registries; funnel plot; grey literature
Confounding	**Third-variable distortion**	Factor linked to exposure and outcome, not on causal path, mimics association	Any observational study	Randomisation, restriction, matching; stratification, standardisation, regression

Bias taxonomy: the family, a named form, the mechanism, the design it typically strikes, and the defence; the hit column is the named entity to recognise in a stem.

HOLD THIS

Bias is systematic error split into selection bias and information bias; confounding is a third variable tied to both exposure and outcome but not on the causal path; and randomisation is the only tool that balances UNKNOWN confounders.

COMMON TRAP

Two errors examiners love. First, calling confounding a type of bias: it is a separate category (a real third-variable effect, controllable at analysis), not a systematic measurement or selection error. Second, treating internal and external validity as the same axis: a narrow efficacy trial can have excellent internal validity and poor external validity at once, and confusing the two mis-reads the whole study.

PEARL

To separate confounding from mediation, ask where the third variable sits. If it independently causes the outcome and merely travels with the exposure, it is a confounder, so adjust for it. If the exposure causes it and it in turn causes the outcome, it is a mediator on the causal path, so adjusting for it (overadjustment) erases part of the true effect. The same statistical adjustment is right for the first and wrong for the second.

MNEMONIC

Confounder = "linked to Exposure, causes Outcome, off the Path" (E-O-P).

A confounder must be associated with the Exposure, be an independent cause of the Outcome, and lie off the causal Path. Fail any one of the three and it is not a confounder: variables on the path are mediators, and variables unrelated to the exposure are simply other risk factors.

GOOD TO REMEMBER

- **Internal validity:** are the results true for this sample; threatened by selection bias, information bias, confounding and chance; the one to secure first, before generalisability.
- **External validity (generalisability):** do the results apply beyond the sample; use it to judge whether an efficacy-trial finding transfers to ordinary patients; bought by broad, typical, pragmatic samples.
- **Reliability (repeatability):** reproducibility of a measurement on repetition; the target-clustering property; necessary but not sufficient for validity (reliable can be invalid, but valid needs reliable).
- **Bias:** systematic (not random) error; use design, not sample size, to defeat it; the number to fear is that no increase in n reduces bias.
- **Selection bias:** non-comparable entry or comparison groups; suspect it in volunteer, hospital-based or high-dropout studies; defended by sampling a defined source population identically.
- **Information bias:** non-comparable measurement of exposure or outcome; includes recall bias and observer bias; defended by blinding (masking) and validated measures.
- **Recall bias:** differential memory between cases and controls; the classic flaw of the retrospective case-control study; defended by records-based or nested designs.
- **Confounding:** a third variable associated with exposure and causing the outcome, off the causal path; controlled at design (randomisation, restriction, matching, allocation concealment, blinding) or at analysis (stratification, standardisation, regression); only randomisation handles unknown confounders.

5 · Sampling methods

Whether a study can speak beyond its own participants is decided the moment the sample is drawn. **Sampling** is the process of drawing a subset of units (the sample) from the whole population of interest so that a study can be run on the few while conclusions are made about the many. The examiner wants three things from a one-line vignette: name the sampling method, say whether it is **probability** or **non-probability**, and state whether the resulting sample can support a generalisation to the population (Bland 2015; Altman 1991; Kaplan & Sadock 2024). The single hinge is that only probability sampling, where every unit has a known non-zero chance of selection, permits valid statistical inference from sample to population.

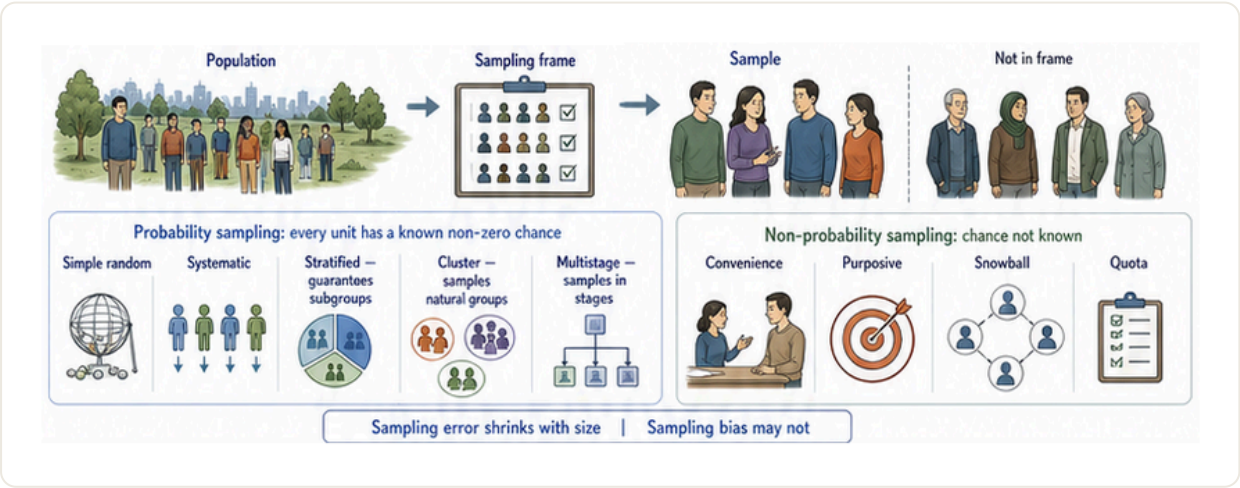


Fig 7.9 Sampling: who gets a chance to enter?.

The family splits cleanly. **Probability sampling** methods (simple random, systematic sampling, stratified, cluster sampling, multistage) use a chance mechanism and allow generalisable

inference; **non-probability sampling** methods (convenience, purposive, snowball, quota) select by accessibility or judgement and cannot support a population estimate. Hold the two-column split and the rest is detail.

5.1 The population, the sampling frame, and the sample

Three nested objects define every sampling problem. The **target population** is the whole group about whom conclusions are wanted (for example, all adults in a district). The sampling frame is the actual list or operational device from which units are drawn (an electoral roll, a household census list, a clinic register): it is the population as it is really available to be sampled. The **sample** is the subset finally selected and measured (Bland 2015). Most real-world error enters at the frame: if the frame omits part of the target population (the homeless are missing from an electoral roll, the untreated are missing from a clinic register) the sample is biased before a single unit is drawn, however elegant the selection method. Naming the frame is the first discipline of good sampling.

Target population
The whole group about whom inference is wanted.

Sampling frame
The actual list or device from which the sample is drawn; the practical stand-in for the population.

Sampling unit
The element selected at each draw (a person, a household, a school, a village).

5.2 Probability sampling: the licence to generalise

Every unit has a known, non-zero chance of selection. In **probability sampling** selection is by a chance mechanism, so the probability that any given unit enters the sample is known and greater than zero (Kaplan & Sadock 2024; Bland 2015). This is what makes a sample *representative in expectation* and lets sampling theory attach a standard error and a confidence interval to an estimate: only under a known selection probability can the mathematics of inference from sample to population be justified. Community psychiatric morbidity surveys therefore use probability sampling (the National Comorbidity Survey and the WHO World Mental Health surveys used multistage household probability sampling precisely to license generalisation to their target populations). If you cannot state each unit's chance of selection, you are not doing probability sampling and you forfeit the right to a population estimate.

RULE **Known chance, valid inference.** Only when every unit has a known non-zero probability of selection can a sample estimate be generalised to the population with a valid standard error and confidence interval.

5.3 Simple random and systematic sampling

The two basic single-stage probability methods. In **simple random** sampling every unit in the frame has an equal and independent chance of selection, drawn by lottery or random-number generator; it is the reference standard against which all other methods are judged and needs a complete numbered frame (Bland 2015; Altman 1991). **Systematic sampling** selects every kth unit from the ordered frame after a random start, where the sampling interval k equals the

population size divided by the desired sample size (draw a random start between 1 and k, then take that unit, then every kth thereafter). Systematic sampling is quicker and needs no full random draw, and it spreads the sample evenly through the list; its one hazard is a hidden periodicity in the frame that coincides with the interval k (for example, if every kth bed is a corner bed), which can bias the sample. Both are probability methods and both give generalisable estimates.

Simple random
Equal, independent chance for every unit; the gold-standard probability method.

Systematic sampling
Every kth unit after a random start, k = population size / sample size; fast but vulnerable to periodicity in the frame.

WORKED EXAMPLE

You have a numbered frame of 1,000 clinic attenders and want a sample of 100. The sampling interval is k = 1000 / 100 = **10**. Pick a random start between 1 and 10, say 7, then take attender 7, 17, 27, 37 and so on to 997: that is **systematic sampling**. Every attender had a 1 in 10 (0.1) chance of selection, so it is a probability sample and the estimate generalises, provided the list carries no repeating pattern that lands on the interval of 10.

5.4 Stratified sampling: guaranteeing the subgroup

Divide first into strata, then sample within each. Stratified sampling first partitions the population into mutually exclusive strata defined by a characteristic that matters (age band, sex, urban versus rural, diagnosis), then draws a random sample *within each stratum* (Bland 2015; Altman 1991). Its whole purpose is to guarantee representation: because each stratum is sampled deliberately, even a small subgroup that a simple random draw might miss by chance is certain to appear, and stratifying on a variable related to the outcome also reduces the standard error of the overall estimate (it removes between-stratum variability). In proportionate stratification each stratum contributes in proportion to its share of the population; in disproportionate stratification a small but important stratum is deliberately over-sampled and the estimates are re-weighted at analysis (this is the oversampling of older adults or minority groups seen in the large epidemiological surveys). Stratified sampling never increases the standard error relative to simple random sampling and usually lowers it.

RULE **Stratify to represent a small subgroup.** When you must be certain a small but important subgroup appears in adequate numbers, stratify on that characteristic and sample within the stratum, oversampling it if needed and re-weighting at analysis.

5.5 Cluster sampling and the design effect

Sample whole groups, not individuals. Cluster sampling divides the population into naturally occurring groups (clusters) such as villages, schools, wards or households, takes a random sample of whole clusters, and then studies every unit within the selected clusters (or a further sample of them). It is chosen for logistics and cost: when the population is geographically dispersed and no

complete individual-level frame exists, it is far cheaper to enumerate and travel to a handful of clusters than to chase a random scatter of individuals across the whole area (Bland 2015). The price is statistical. People within a cluster tend to resemble one another (they share environment, culture, exposures), so each additional person in a cluster adds less new information than an independent draw would. This within-cluster correlation inflates the variance, quantified by the design effect (Deff): the ratio of the variance under the cluster design to the variance a simple random sample of the same size would have given. A design effect greater than 1 means the cluster sample carries less information than its nominal size, so the sample size must be multiplied by the design effect to recover the intended precision. Stratified sampling reduces variance; cluster sampling increases it. That contrast is examined constantly.

Cluster sampling
Randomly sample whole clusters (villages, schools), then study units within them; cheaper for dispersed populations, no individual frame needed.

Design effect (Deff)
Variance under the cluster design divided by the variance a simple random sample would give; Deff > 1 means precision is lost and the sample must be enlarged.

TRAP **Ignoring the design effect.** Analysing a cluster sample as if it were a simple random sample understates the true standard error and gives falsely narrow confidence intervals and falsely small p-values; the sample size must be inflated by the design effect.

5.6 Multistage sampling: the real-world survey design

Sampling in successive nested stages. **Multistage** sampling combines the above into a sequence: sample large primary units first, then sub-sample within them, over two or more stages. A national survey might first randomly select districts (stage 1), then villages within selected districts (stage 2), then households within selected villages (stage 3), then one adult within each selected household (stage 4). It is the practical backbone of almost every large community survey because it needs a frame only for the units selected at the next stage down, never a complete individual-level frame for the whole country. Each clustering stage carries its own design effect, so multistage designs are analysed with survey-weighted methods that account for the stratification, the clustering and the unequal selection probabilities. The National Mental Health Survey type of design and the WHO World Mental Health surveys are multistage household probability samples of exactly this kind (Kaplan & Sadock 2024).

5.7 Non-probability sampling: convenience, purposive, snowball, quota

Selection by access or judgement, not chance. In **non-probability sampling** the chance of any unit being selected is unknown, so no valid generalisation to a population can be made; these methods belong to qualitative research, pilot studies and situations where a frame is impossible (Kaplan & Sadock 2024). **Convenience** sampling takes the units easiest to reach until the target size is met (a volunteer sample, the patients who happen to be in clinic today); it is fast and cheap but its self-selection makes it the least representative method. **Purposive** (judgemental) sampling selects units the researcher judges most informative for the question, the standard approach in

qualitative work where the aim is depth and typicality, not statistical representativeness. **Snowball** sampling starts from a few index participants who then recruit further participants from their own networks, and is the method of choice for hidden or hard-to-reach populations (people who inject drugs, sex workers, the homeless) where no frame exists (Kaplan & Sadock 2024). Quota sampling fills preset quotas for chosen characteristics (so many men, so many women) by non-random selection until each quota is met: it superficially resembles stratified sampling but the crucial difference is that within each quota the units are chosen non-randomly, so it remains a non-probability method. Consecutive sampling, a near neighbour, recruits every accessible unit over a defined period.

TRAP **Convenience sampling cannot support a prevalence estimate.** A prevalence figure is a population statement; a convenience sample has an unknown selection probability, so it can describe only the sample and can never be quoted as the prevalence in the population.

5.8 Sampling error versus sampling bias

Two different failures, only one of which shrinks with size. Sampling error is the random difference between a sample estimate and the true population value that arises simply because a sample, not the whole population, was measured; it is unavoidable, it has no direction, and it is exactly what the standard error and the confidence interval quantify. Crucially, sampling error *decreases as the sample size increases* and disappears if the whole population is measured (Bland 2015). Sampling bias (selection bias) is a systematic error in the way units are selected, so that the sample is unrepresentative in a consistent direction (the classic example is drawing a sample of the mentally ill only from treated populations, which over-represents the more severe and help-seeking). Bias has a direction, it distorts the estimate the same way every time, and, fatally, *a larger sample does not fix it*: it merely produces a more precise wrong answer. Distinguishing the two, and knowing that size cures error but not bias, is one of the most reliably examined points in the whole topic.

Random	Systematic
SAMPLING ERROR: NO DIRECTION, SHRINKS WITH N	SAMPLING BIAS: HAS DIRECTION, NOT FIXED BY N

TRAP **A bigger sample does not cure bias.** Increasing the sample size narrows sampling error but a biased sampling method just gives a more precise wrong estimate; only a better sampling design removes bias.

5.9 The selector: matching the situation to the method

Read the constraint, pick the method. A sampling vignette turns on three things: is a complete frame available, must a particular subgroup be guaranteed, and is generalisation required at all? A complete individual frame invites simple random or systematic sampling; the need to represent a small subgroup calls for stratification; a dispersed population with no individual frame forces cluster or multistage sampling and its design effect; and a hidden population or a purely exploratory aim drops you into the non-probability methods, which forfeit generalisation.

METHOD	PROBABILITY?	HOW IT SELECTS	WHEN TO USE IT
Simple random	**Yes**	Equal, independent chance for every unit (lottery / random numbers)	Complete numbered frame available; the reference standard
Systematic sampling	**Yes**	Every kth unit after a random start, k = N / n	Ordered frame; quicker than a full random draw; no periodicity in the list
Stratified	**Yes**	Split into strata, random-sample within each	Must guarantee a small subgroup; improves precision
Cluster sampling	**Yes**	Randomly sample whole clusters, study units within	Dispersed population, no individual frame; cheaper, but larger design effect
Multistage	**Yes**	Successive nested sampling stages	Large national surveys; needs a frame only stage by stage
Convenience	**No**	Whoever is easiest to reach	Quick pilots only; cannot generalise
Purposive	**No**	Researcher's judgement of who is informative	Qualitative work seeking depth and typicality
Snowball	**No**	Index participants recruit further participants	Hidden or hard-to-reach populations with no frame
Quota	**No**	Fill preset quotas by non-random selection	Fast field surveys; looks stratified but is not random

The sampling family read across method, whether it is probability-based, how it selects, and when to use it; the hit column is the probability-versus-non-probability discriminator that decides generalisability.

HOLD THIS

Probability sampling (known non-zero selection chance) is the only route to a generalisable population estimate; stratify to guarantee a small subgroup, cluster to save cost at the price of a design effect greater than 1, and never quote a prevalence from a convenience sample.

INDIA

The National Mental Health Survey of India (2015 to 2016) is the flagship probability-sampled example: a **multistage** stratified random household survey across 12 states that could therefore report a generalisable current weighted prevalence of any mental disorder of about **10.6** percent and a treatment gap for common mental disorders exceeding **80** percent. Because selection probabilities were known and the design was multistage with clustering, the estimates carry valid confidence intervals: a convenience sample of clinic attenders could never have produced a national prevalence figure.

PEARL

Stratification and clustering pull the standard error in opposite directions. Stratified sampling *reduces* variance because it removes between-stratum variability, so its design effect is typically below 1; cluster sampling *increases* variance because units within a cluster are correlated, so its design effect is above 1. A survey that stratifies and then clusters, as most national surveys do, trades the two off, which is why the net design effect must be computed and the sample size inflated accordingly.

MNEMONIC

Probability sampling: "Some Systems Sort Clusters Multiply."

Simple random, Systematic, Stratified, Cluster, Multistage: the five probability methods. Everything else (convenience, purposive, snowball, quota) is non-probability and cannot generalise.

GOOD TO REMEMBER

- **Simple random:** every unit has an equal, independent chance of selection; use it whenever a complete numbered frame exists; it is the gold-standard probability method against which the design effect of others is judged (Deff = 1).
- **Systematic sampling:** take every kth unit after a random start; use it for a quick draw from an ordered list; the one number is the interval k = population size / sample size.
- **Stratified:** split into strata and random-sample within each; use it to guarantee a small subgroup is represented and to improve precision; its design effect is usually below 1 (it lowers the standard error).
- **Cluster sampling:** randomly sample whole clusters and study units within them; use it for a dispersed population with no individual frame to save cost; the number to know is the design effect (Deff greater than 1), by which the sample size must be multiplied.
- **Multistage:** sample in successive nested stages (districts, then villages, then households, then individuals); use it for large national surveys; it needs a frame only for the units at the next stage, and each clustering stage adds its own design effect.
- **Convenience:** take whoever is easiest to reach; use it only for quick pilots; the fact to hold is that its unknown selection probability means it cannot support a prevalence estimate.
- **Purposive:** select by the researcher's judgement of who is most informative; use it in qualitative research for depth and typicality; it makes no claim to statistical generalisation.
- **Snowball:** index participants recruit further participants through their networks; use it for hidden or hard-to-reach populations with no sampling frame; it is non-probability, so no population estimate follows.

6 · Qualitative research methods

Some questions cannot be answered by counting. **Qualitative** research is the systematic study of meaning and experience: it asks how people understand their illness, why an intervention fails in practice, what a service feels like from the inside. It collects and analyses data that cannot be reduced to numbers (interview transcripts, field notes, documents) and reads them for categories and themes rather than for means and p-values (Bowling 2014; Greenhalgh 2014). The exam wants three things from you: the named approaches with a one-line signature each, the concepts that give a qualitative study its **rigour** (the qualitative counterpart of reliability and validity), and a clear sense of when a qualitative design beats a quantitative one. Get those and any stem, whether it names grounded theory or asks "what is saturation", falls open.

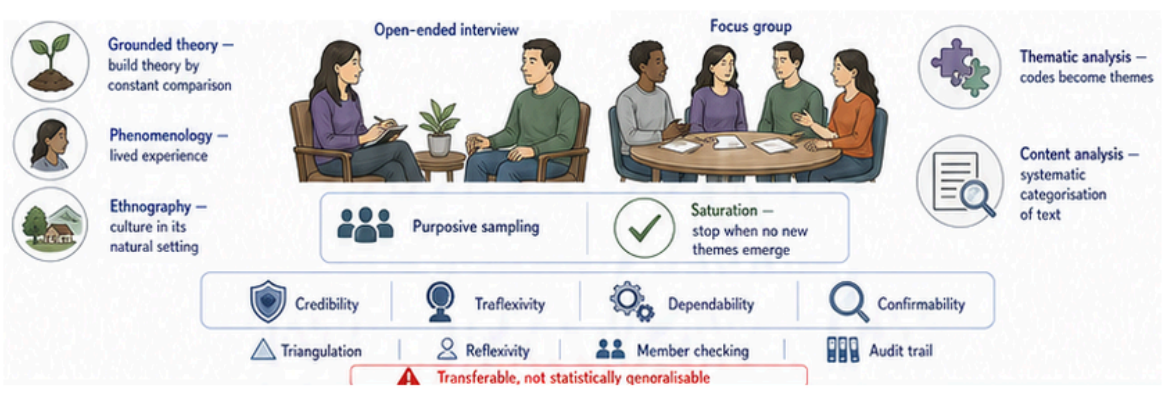


Fig 7.10 Qualitative research: depth, meaning and context.

The mental model is a mirror image of the quantitative one. Where a trial samples randomly to represent a population and tests a pre-set hypothesis, a qualitative study samples **purposively** to capture informative cases and lets categories emerge from the data, with analysis running iteratively alongside collection (Bowling 2014). It generalises to theory and concepts, never to population statistics. Hold that contrast and the rest is detail.

6.1 What qualitative research is, and how it differs from quantitative

Understanding meaning, not measuring frequency. A **qualitative** study seeks to understand a phenomenon through personal encounter, observation and text, rather than to quantify it (Bowling 2014; Greenhalgh 2014). The defining differences from quantitative work are consistent and examinable: sampling is purposive (subjects chosen deliberately for characteristics relevant to the question, not random selection); data collection is open-ended and often interactive (interviews, observation, documents, not standardised scales); analysis is **iterative** and interpretive, generating categories and themes as the data accumulate rather than testing a fixed hypothesis at the end; and the aim is depth of understanding and **transferability** of concepts, not statistical generalisation to a population. The two are complementary, not rivals: a mixed-methods study can nest a qualitative arm inside a randomised trial to explain why participants responded as they did.

RULE **Purpose sets the design.** If the question is "how many / how much / does it work", think quantitative; if it is "why / how / what is it like", think qualitative.

6.2 The five main approaches

Each approach has a distinct object and analytic move. The examiner most often wants the named approach matched to its one-line signature (Bowling 2014; Greenhalgh 2014). Grounded theory builds a theory upward from the data themselves through **constant comparison**, comparing each new piece of data with the emerging categories until a theory grounded in the material is generated (Glaser and Strauss 1967). Thematic analysis is the workhorse method that codes the data and organises those codes into themes, without committing to a deeper theoretical framework (Braun and Clarke 2006). The phenomenological approach studies the **lived experience** of a phenomenon, the essence of what it is like to undergo it, from the first-person perspective. Ethnography studies a culture or group in its natural setting, classically through prolonged participant observation and immersion. Content analysis systematically categorises the content of text or documents, and can be handled qualitatively (interpreting meaning) or quantitatively (counting the frequency of coded categories).

Grounded theory

Theory built from the data by constant comparison; sampling continues until the theory is saturated.

Thematic analysis

Codes distilled into themes; flexible, framework-light, the commonest entry-level method.

Phenomenological

The lived experience and essence of a phenomenon, from the person's own perspective.

Ethnography

A culture or group studied in its natural setting through immersion and participant observation.

Content analysis

Systematic categorisation of textual or documentary content; qualitative or quantitative in flavour.

6.3 Data collection: focus groups and in-depth interviews

Two workhorses, chosen by what you want to hear. The two staple methods of qualitative data collection are the **focus group** and the in-depth interview (Bowling 2014). A focus group brings a small group of participants (typically six to ten) together with a moderator so that the *interaction between members* generates data: people react to and build on each other's views, which surfaces shared meanings, norms and disagreements that a one-to-one setting would miss. Its weakness is that dominant voices can silence others and it is poor for private or sensitive material. In-depth (semi-structured or unstructured) interviews put one participant with one interviewer using an open topic guide, giving privacy and depth on an individual's experience, and are the natural choice for sensitive subjects or for reconstructing a personal account. Both are complemented by participant observation (watching behaviour in its natural context) and by documentary sources. Sampling for all of these is purposive, and often theoretical (sampling driven by the emerging analysis) in grounded theory.

6.4 Saturation and when to stop sampling

Stop when new data stop teaching you anything. Because a qualitative sample is chosen for information richness rather than for a pre-calculated power, its size is not fixed in advance; it is governed by saturation. **Saturation** is the point at which no new codes, categories or themes emerge from further data collection, so additional interviews or observations add nothing to the analysis (Bowling 2014). Reaching it is the qualitative analogue of an adequate sample size: you keep sampling and analysing in parallel and stop once the emerging framework has stabilised. This is why qualitative sample sizes are small and cannot be stated at the outset the way a trial's n can.

RULE **Stop sampling at saturation.** Continue collecting and analysing data until no new codes or themes emerge; that point, not a pre-set number, sets the qualitative sample size.

6.5 Rigour: the trustworthiness criteria and the techniques that build them

The qualitative counterpart of reliability and validity. A good qualitative study is judged not by statistical validity but by its **trustworthiness**, the framework of Lincoln and Guba (1985) with four criteria: credibility (are the findings a believable account of the participants' reality, the qualitative parallel of internal validity), transferability (can the findings be applied to other settings, the parallel of external validity, supported by rich "thick description" so a reader can judge fit), dependability (would the process be consistent and traceable if repeated, the parallel of reliability), and confirmability (are the findings grounded in the data rather than the researcher's bias, the parallel of objectivity). Several techniques operationalise these criteria (Bowling 2014; Greenhalgh 2014):

Triangulation

Triangulation: using multiple sources, methods, investigators or theories and checking that they converge on the same finding; convergence strengthens credibility.

Reflexivity

Reflexivity: the practice of reflexivity means the researcher explicitly examines and discloses how their own values, assumptions and presence shape the data and its interpretation.

Member checking

Member checking (respondent validation): taking the findings back to participants to confirm they recognise their experience in the account; supports credibility.

Audit trail

An audit trail: a transparent, documented record of every decision from raw data to conclusion, so an outsider can follow the reasoning; supports dependability and confirmability.

TRAP **Qualitative findings are not statistically generalisable.** They transfer to theory and to similar settings (transferability), but they cannot be projected onto a population the way a representative quantitative estimate can.

6.6 When qualitative beats quantitative

Reach for qualitative when the number is not the answer. Qualitative methods are the right tool, not a weaker substitute, in defined situations (Bowling 2014; Greenhalgh 2014). Use them for **hypothesis generation**, where little is known and the aim is to discover the relevant concepts and variables before any quantitative study can be designed. Use them to understand **barriers** and facilitators, why an evidence-based intervention is not adopted in practice, why patients disengage, what obstructs help-seeking, since these turn on meaning and context that a scale cannot capture. Use them for **service evaluation**, to gather the attitudes, beliefs and experiences of service users, carers and professionals, and to see how a service actually works on the ground. They also excel at exploring sensitive or stigmatised experiences and at explaining the "why" behind a surprising quantitative result.

6.7 The selector: matching approach and method to the question

Read the aim, then pick the approach. Faced with a stem, first confirm the question is qualitative (a why/how/what-is-it-like question), then match the specific aim to the approach and the setting to the collection method. If the aim is to build an explanatory theory, choose grounded theory; if it is simply to identify patterns of meaning, thematic analysis; if it is the essence of an experience, phenomenology; if it is a group's culture in situ, ethnography; if it is the systematic content of documents, content analysis. The collection method then follows from whether you need group interaction or private depth.

AIM OF THE STUDY	APPROACH / METHOD TO PICK
Build a new explanatory theory from the ground up	Grounded theory (constant comparison)
Identify patterns of meaning across the data	Thematic analysis (codes to themes)
Capture the essence of a lived experience	Phenomenological approach
Understand a group's culture in its natural setting	Ethnography (participant observation)
Systematically categorise documents or text	Content analysis
Surface shared norms and group interaction	Focus group
Explore a private or sensitive individual account	In-depth interview

Qualitative selector: read the study aim, pick the approach or data-collection method (aim to method).

WORKED EXAMPLE

A team wants to know why patients started on a depot antipsychotic stop attending the clinic. A trial can measure the drop-out rate, but not the reasons. They run in-depth interviews with disengaged patients and two focus groups with community nurses, code the transcripts, and organise the codes into themes (a thematic analysis). They keep interviewing until no new theme appears (saturation), take the draft themes back to a few patients to check they ring true (member checking), and confirm that the interview, the nurse focus groups and the case notes all point to the same barriers (triangulation). The output is not a percentage but a set of transferable themes ("feeling talked down to", "side effects not discussed") that a service can act on, and that can seed a later quantitative study.

HOLD THIS

Qualitative research studies meaning and experience, samples purposively, and stops at saturation; its four trustworthiness criteria are credibility, transferability, dependability and confirmability, and its findings transfer to theory, not to population statistics.

COMMON TRAP

Two errors examiners set. First, treating qualitative findings as if they were statistically generalisable to a population: they are not, they offer transferability to similar contexts, judged from thick description, not statistical generalisation. Second, criticising a qualitative study for a "small, unrepresentative sample": small purposive samples are correct by design, and adequacy is judged by saturation, not by size or representativeness. Judge a qualitative study by its trustworthiness, not by the yardstick of a trial.

MNEMONIC

Trustworthiness = "Can These Data Convince" (Credibility, Transferability, Dependability, Confirmability).

The four Lincoln and Guba criteria map onto the quantitative quartet: Credibility to internal validity, Transferability to external validity, Dependability to reliability, Confirmability to objectivity. "Can These Data Convince" fixes the order and reminds you the whole point is a believable, traceable account.

GOOD TO REMEMBER

- **Grounded theory:** builds theory upward from data; use it to generate a new explanatory model; the one move to know is constant comparison, sampling to theoretical saturation.
- **Thematic analysis:** the flexible framework-light method; use it to find patterns of meaning; the one move is coding the data then grouping codes into themes.
- **Phenomenological:** studies the lived experience and essence of a phenomenon; use it to capture what an experience is like from the inside.
- **Ethnography:** studies a culture or group in its natural setting; use it for immersion and participant observation over time.
- **Content analysis:** systematically categorises text or documents; use it on documentary data; it can be qualitative (meaning) or quantitative (frequency counts).
- **Focus group:** six to ten participants with a moderator; use it when the interaction between members is the data; weak for private or sensitive material.
- **Saturation:** the stopping rule; the point at which no new codes or themes emerge; it, not a pre-set n, sets qualitative sample size.
- **Triangulation:** convergence of multiple sources, methods or investigators on one finding; the number to state is at least two independent sources agreeing.
- **Trustworthiness (Lincoln and Guba):** credibility, transferability, dependability, confirmability; the qualitative parallels of internal validity, external validity, reliability and objectivity.

7 · Systematic review and meta-analysis

This is the apex of the evidence pyramid. A single trial answers one question in one sample; the **systematic review** gathers every trial that ever asked that question and reads them together, and the **meta-analysis** is the statistics that pool their numbers into one estimate. The examiner treats these as the most senior methods in the paper, and the marks sit in two places: the distinction between the reproducible **systematic review** method and the older narrative review, and the interpretation of the forest plot with its diamond, its heterogeneity and its funnel-plot check for publication bias (Shorter Oxford Textbook of Psychiatry; Companion to Psychiatric Studies 2010).

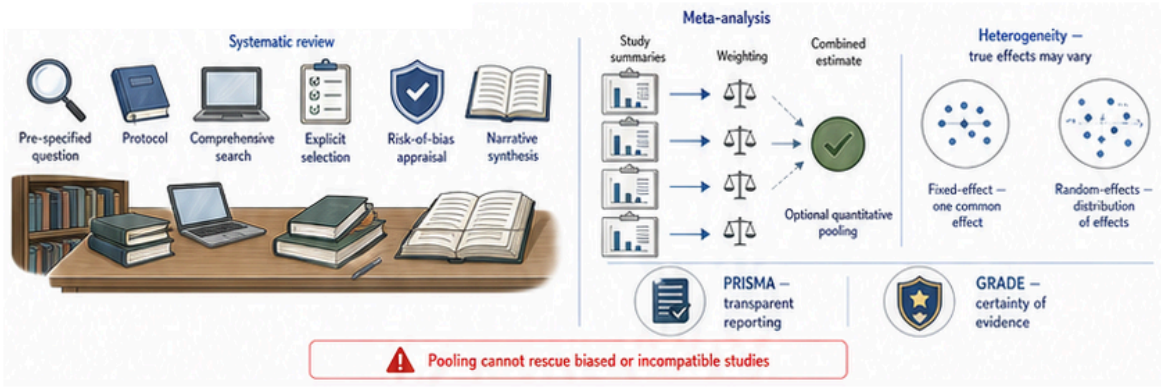


Fig 7.11 Systematic review and meta-analysis.

Read the topic as one pipeline. A protocol fixes the question and the search; a comprehensive search finds the trials; explicit criteria include or exclude them; risk-of-bias appraisal weighs each; and only then, optionally, a meta-analysis pools the results, tests them for heterogeneity, checks the literature for publication bias, and grades the certainty of the whole. The systematic review is the method; the meta-analysis is the arithmetic that may or may not sit inside it (Bland 2015).

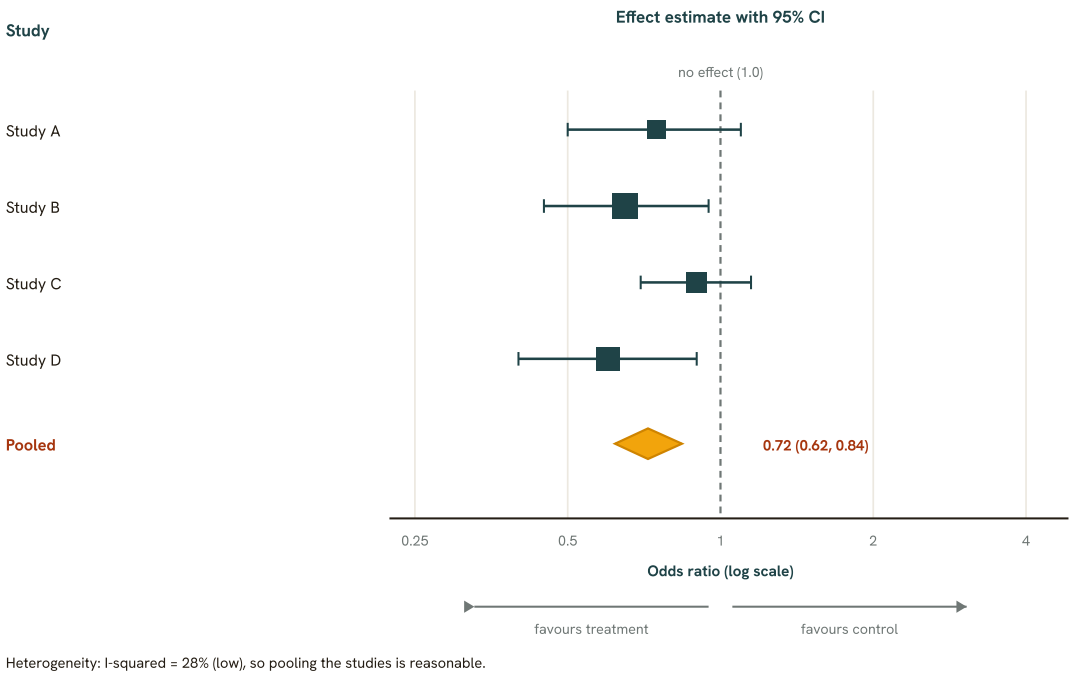


Fig 7.12 Reading a forest plot. Each study is a horizontal line (its 95% confidence interval) with a box marking the point estimate, the box sized by the study's weight in the pool. The vertical dashed line is the value of no effect. A confidence interval that crosses it is non-significant for that study. The diamond at the foot is the pooled estimate, its width the pooled confidence interval. Before trusting the pool, check heterogeneity: a high I-squared means the studies disagree and a single summary may mislead.

7.1 The systematic review: a protocol-driven synthesis, not a narrative review

A systematic review is a reproducible, protocol-driven summary of all the evidence on one question. A systematic review starts from a clearly formulated question, then follows a pre-

registered protocol: a comprehensive and documented search, explicit and pre-stated inclusion and exclusion criteria, formal risk-of-bias (quality) appraisal of each included study, and a transparent synthesis. Because every step is specified in advance and reported, a second team following the same protocol should reach the same set of studies and the same conclusion, which is precisely what makes it reproducible (Shorter Oxford Textbook of Psychiatry). This is the opposite of the traditional **narrative review**, in which an expert selects and weights the literature by personal judgement, so the reader cannot tell what was searched, what was left out, or why. The two-investigator rule, that study selection and quality scoring be done independently by at least two reviewers, exists to keep even the systematic review honest.

RULE **Systematic review = method; meta-analysis = optional statistics.** A systematic review is defined by its protocol (question, search, criteria, appraisal); the pooling is a separate step that it may or may not include.

TRAP **Not every systematic review contains a meta-analysis, and not every pooled analysis is systematic.** If the trials are too clinically diverse to combine, a good systematic review synthesises them narratively and refuses to pool; pooling them anyway is the error.

7.2 The Cochrane Collaboration and the evidence hierarchy

The systematic review of randomised trials sits at the top of the therapy hierarchy. The movement grew from Archibald Cochrane, whose 1972 book argued that treatment provision should rest on randomised controlled trials because they are more reliable than any other evidence (Cochrane 1972). His call for a critical, periodically updated summary of all relevant trials was realised by the Cochrane Collaboration, formed in 1993 and now the largest organisation in the world producing and maintaining systematic reviews (Shorter Oxford Textbook of Psychiatry). In the conventional hierarchy of evidence for questions of therapy, level Ia is a systematic review of randomised controlled trials and level Ib is at least one randomised controlled trial, both above non-randomised controlled studies (II), descriptive studies (III), and expert opinion (IV). The **cochrane** review, with its rigorous protocol and standard software, is the archetype of the method.

INDIA

Cochrane reviews are freely accessible in India through the Cochrane Library and are the standard evidence base cited by Indian clinical practice guidelines. When guidance from a Western meta-analysis is read across to Indian practice, the external-validity question of whether the pooled sample resembles Indian patients still applies, because most pooled trials are from high-income settings.

7.3 Meta-analysis: the statistical pooling, distinguished from the systematic review

Meta-analysis is the quantitative pooling of results across studies into one weighted estimate. A meta-analysis takes the effect estimate from each included study (an odds ratio or relative risk for a binary outcome, a mean difference or standardised effect size for a continuous one) and combines them into a single pooled estimate of greater precision than any one trial

(Shorter Oxford Textbook of Psychiatry). Crucially, it does not weight studies equally: each contributes in proportion to its information, so larger and more precise studies pull the pooled estimate more (the inverse-variance principle). A meta-analysis is therefore a step that lives inside a systematic review, never a substitute for it: pooling numbers gathered without a systematic, unbiased search simply averages a biased sample of the literature. The systematic review supplies the trustworthy set of studies; the meta-analysis does the arithmetic on them.

WORKED EXAMPLE

Three trials of a drug versus placebo report relative risks of relapse of 0.80, 0.70 and 0.75, each with its own confidence interval. A meta-analysis does not average these as (0.80 + 0.70 + 0.75) / 3; it weights each by the inverse of its variance, so the largest, most precise trial dominates, yielding a pooled relative risk near **0.75**, its exact value set by the study weights, with a confidence interval narrower than any single trial. The narrowing of the confidence interval, not a new point estimate, is the gain from pooling.

7.4 Reading the forest plot

The forest plot displays every study, its weight, and the pooled result on one axis. The forest plot is the signature graphic of a meta-analysis, and reading it is a standard viva task (Shorter Oxford Textbook of Psychiatry). Each horizontal line is one study: the central box is its point estimate, and the size of the box marks its weight in the pool (larger box = more precise study, more influence), while the horizontal whiskers are its 95% confidence interval. A vertical **null line** runs down the plot at the value of no effect: **1.0** for a ratio measure (odds ratio, relative risk) and **0** for a difference measure (mean difference). A study whose confidence interval crosses the null line is individually non-significant. At the foot of the plot sits the pooled result as a diamond: its centre is the pooled point estimate and its width is the pooled confidence interval, so if the diamond touches or crosses the null line the overall result is non-significant.

Box (point estimate)

Each study's own effect; the box centre is the estimate, the box size is that study's weight in the pool.

Whiskers

The 95% confidence interval of that single study; if they cross the null line, that study alone is not significant.

Null line

The vertical line of no effect: 1.0 for odds ratio or relative risk, 0 for a mean difference.

Diamond

The pooled estimate at the bottom: centre is the combined effect, width is its confidence interval; crossing the null line means the pooled result is non-significant.

7.5 Fixed-effect versus random-effects models

The choice of model depends on whether the studies share one true effect. The pooling can assume one of two things. A fixed-effect model assumes every study is estimating the same single underlying treatment effect, and all variation between them is sampling error; it weights purely by study size and gives the narrowest, most confident pooled confidence interval. A random-

effects model assumes the true effect genuinely differs from study to study (because of differing doses, patients or settings), so it adds this between-study variance to the weighting; it gives a wider, more conservative confidence interval and lets small studies count for relatively more (Shorter Oxford Textbook of Psychiatry). The decision follows the heterogeneity: when studies are consistent, a fixed-effect model is appropriate and efficient; when significant heterogeneity is present, the random-effects model is the more appropriate and honest choice, and its wider interval reflects the real uncertainty.

RULE **Significant heterogeneity means use a random-effects model.** Fixed-effect assumes one shared true effect; when effects genuinely vary, random-effects widens the interval to tell the truth about that variation.

7.6 Heterogeneity: the chi-square test and the I-squared statistic

Heterogeneity is real variation in the true effect between studies, beyond chance. When some trials show a large effect and others none at all, the studies show heterogeneity, meaning their results are more different than sampling error alone can explain (Shorter Oxford Textbook of Psychiatry). It is assessed two ways. The **chi-square test for heterogeneity** (Cochran's Q, a modification of the chi-square test) formally tests the null hypothesis that all studies share one true effect; because it has low power when trials are few, a lenient threshold such as p less than **0.10** is conventionally used, and a significant result signals heterogeneity. The **I-squared** statistic (written **i-squared** or **i2**) is the more useful companion: it is the percentage of total variation across studies that is due to real heterogeneity rather than chance, running from 0% to 100% and, unlike the chi-square, not dependent on the number of studies. The rough Cochrane bands are worth holding.

0 to 40%	30 to 60%	50 to 90%	75 to 100%
I2: MIGHT NOT BE IMPORTANT	I2: MODERATE	I2: SUBSTANTIAL	I2: CONSIDERABLE

Overlapping I-squared bands from the Cochrane Handbook (Higgins et al 2023); the overlap is deliberate, since the importance of a given value also depends on the direction and strength of the evidence.

TRAP **A tidy pooled diamond over high heterogeneity is misleading.** High i-squared means the studies are answering different questions; the neat pooled estimate then averages apples and oranges and should not be reported as if it were one clean effect.

7.7 Publication bias: the funnel plot and Egger's test

Positive studies are published more, so the pooled literature can overstate the effect. Publication bias is the tendency for statistically significant, positive trials to be submitted and published more readily than null or negative ones, so a meta-analysis restricted to published studies systematically exaggerates the benefit (Shorter Oxford Textbook of Psychiatry). The classic detection tool is the funnel plot: each study's effect estimate is plotted against its precision (or standard error), so small imprecise studies scatter widely at the bottom and large precise ones cluster tightly at the top. With no bias the cloud is a symmetric inverted funnel about the pooled estimate; **funnel plot** asymmetry, a corner of small negative studies missing, suggests that such

studies were run but never published. Because eyeballing asymmetry is subjective, Egger's test provides a formal statistical test of funnel-plot asymmetry (Egger et al 1997). The remedies are structural: trial registries, and searching grey literature and unpublished data.

COMMON TRAP

Funnel-plot asymmetry is not proof of publication bias. Genuine heterogeneity, poorer methodology in smaller trials, or chance can all bend the funnel. Asymmetry is a prompt to investigate, not a verdict; and a funnel plot needs roughly ten or more studies before its shape can be judged at all.

7.8 PRISMA reporting and GRADE certainty

PRISMA standardises the reporting; GRADE rates how much to trust the result. Two frameworks bracket the modern systematic review. The **PRISMA** statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standardises what must be reported about how the review was searched, conducted, analysed and presented, including the flow diagram of records screened, excluded and included (Moher et al 2009). Separately, GRADE (Grading of Recommendations Assessment, Development and Evaluation) rates the certainty of the pooled evidence for each outcome as high, moderate, low or very low. It starts a body of randomised evidence at high certainty and rates it down for five problems, risk of bias, inconsistency (heterogeneity), indirectness, imprecision and publication bias, and can rate observational evidence up for a large effect or dose-response. GRADE is thus the summary judgement on top of the whole pipeline: a meta-analysis can produce a precise diamond and still be graded low certainty if the trials were biased or heterogeneous.

PEARL

Keep the three frameworks in their lanes. PRISMA governs reporting (how the review is written up), the risk-of-bias tool (such as the Cochrane RoB tool) appraises each included trial, and GRADE rates the certainty of the pooled evidence per outcome. A review can be PRISMA-compliant in its reporting yet GRADE-low in its certainty; good reporting of weak evidence is still weak evidence.

7.9 How the pipeline holds together

Each stage protects the next, and the meta-analysis is only as good as the review beneath it. The protocol fixes an unbiased question and search; the comprehensive search and explicit criteria assemble a fair set of studies; risk-of-bias appraisal weighs their quality; the meta-analysis pools them, but only after heterogeneity is checked so that pooling is legitimate; the funnel plot and Egger's test interrogate the literature for missing negative trials; and GRADE delivers the final verdict on certainty. Assess any published meta-analysis by walking this chain: an impressive pooled diamond built on a narrow search, unappraised trials, or ignored heterogeneity is exactly where the exam wants you to point.

HOLD THIS

The systematic review is the reproducible protocol-driven method (question, search, criteria, appraisal); the meta-analysis is the optional inverse-variance pooling inside it, read off a forest plot whose box is each study's weight, whisker is its CI, null line is 1.0 (or 0), and bottom diamond is the pooled estimate; high i-squared means use a random-effects model and distrust a tidy diamond, and a lopsided funnel plot (tested by Egger's) flags publication bias.

GOOD TO REMEMBER

- **Systematic review:** a reproducible synthesis of all evidence on one question; use it whenever a therapy question needs the whole literature, not one trial; defined by its protocol (question, comprehensive search, explicit inclusion, risk-of-bias appraisal), which separates it from a narrative review.
- **Cochrane Collaboration:** the world's largest producer of systematic reviews (formed 1993, from Archibald Cochrane's 1972 argument); the archetype of the method; its review of randomised trials is level Ia, the top of the therapy evidence hierarchy.
- **Meta-analysis:** the statistical pooling of study results into one weighted estimate; use it inside a systematic review when studies are similar enough to combine; weights each study by the inverse of its variance, so the gain is a narrower pooled confidence interval, not a new average.
- **Forest plot:** the display of a meta-analysis; read it to see each study and the pooled result; box = point estimate and weight, whisker = 95% CI, null line = 1.0 for a ratio (0 for a difference), bottom diamond = pooled estimate and its CI.
- **Fixed-effect vs random-effects model:** fixed assumes one shared true effect (narrower CI); random assumes effects vary between studies (wider, more conservative CI); use random-effects when heterogeneity is significant.
- **Heterogeneity (i-squared, chi-square):** real between-study variation beyond chance; the chi-square (Cochran's Q) test flags it at p less than 0.10, and i-squared gives the percentage of variation due to heterogeneity (bands: 0 to 40% low, 30 to 60% moderate, 50 to 90% substantial, 75 to 100% considerable).
- **Publication bias (funnel plot, Egger's test):** positive studies published preferentially, so the pool overstates effect; plot effect against precision, look for an asymmetric funnel (missing small negative studies), and test asymmetry formally with Egger's test; needs roughly ten or more studies.
- **GRADE:** rates the certainty of the pooled evidence per outcome as high, moderate, low or very low; starts randomised evidence high and rates down for risk of bias, inconsistency, indirectness, imprecision and publication bias; the final judgement on top of the whole review.

8 · Reporting guidelines and research ethics

Two examiner favourites sit back to back here: how a finished study should be *reported* so a reader can appraise it, and how a study is allowed to be *done* to human beings in the first place. The first half is a matching game, match the **reporting guideline** to the study design, and it underpins every structured critical appraisal. The second half is the ethical spine, from Nuremberg to the four principles to the consent process to the committee that signs off. Vivas love the crisp discriminators: which checklist for a trial versus a review, which document introduced "respect for persons", why consent is a process and not a signature.

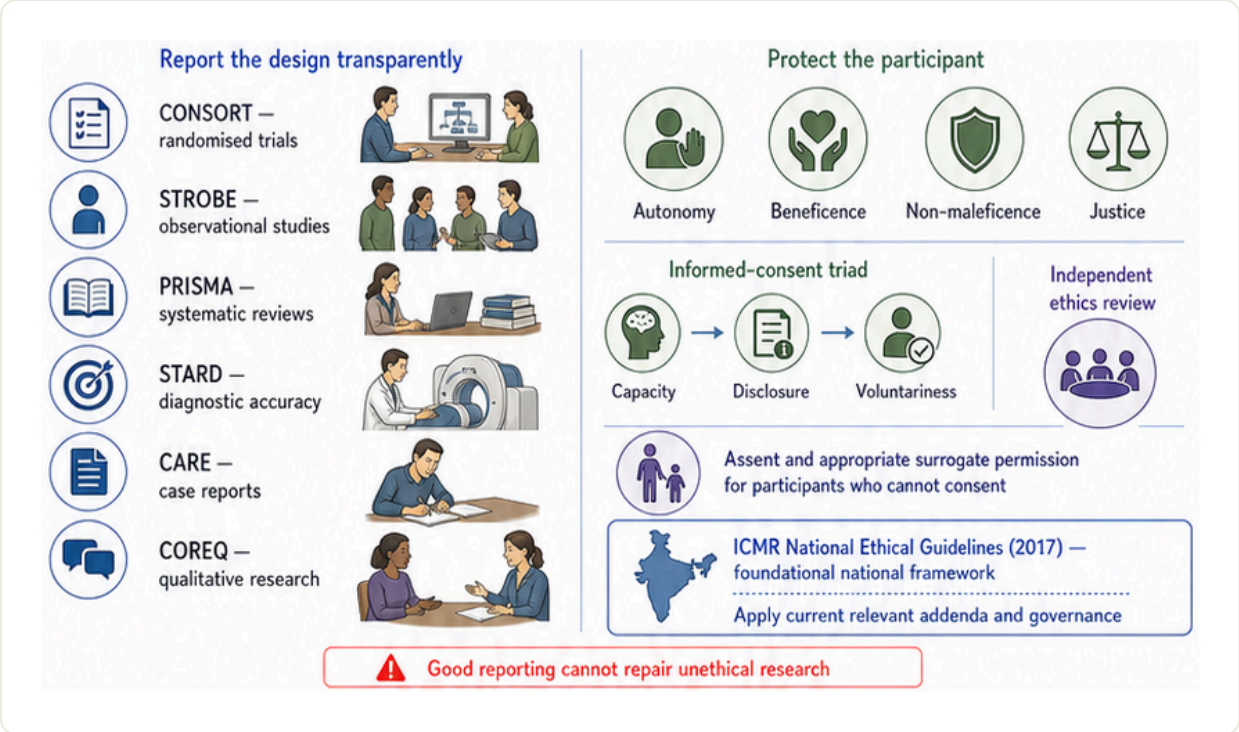


Fig 7.13 Reporting and ethics: transparency does not replace protection.

Frame it as two questions. "Is this paper reported well enough to trust?" is answered by the **reporting guideline** matched to the design. "Was this study ethical to run?" is answered by the historical codes, the four principles, valid **informed consent**, and clearance by an **ethics committee**. Keep them separate and the topic collapses into two short tables.

8.1 Critical appraisal: reading a paper against a checklist

What it is. Critical appraisal is the structured process of judging whether a study's results are valid, what they mean, and whether they apply to your patients (Greenhalgh 2019). It weighs internal validity (was the study done well) against external validity (does it generalise). Reporting guidelines exist so that authors give you every item you need to make that judgement, so a well-reported paper is not automatically a good study, but a badly reported one cannot be appraised at all. This is why a critical appraisal always begins by asking which reporting guideline the design demanded, then checking the paper against it.

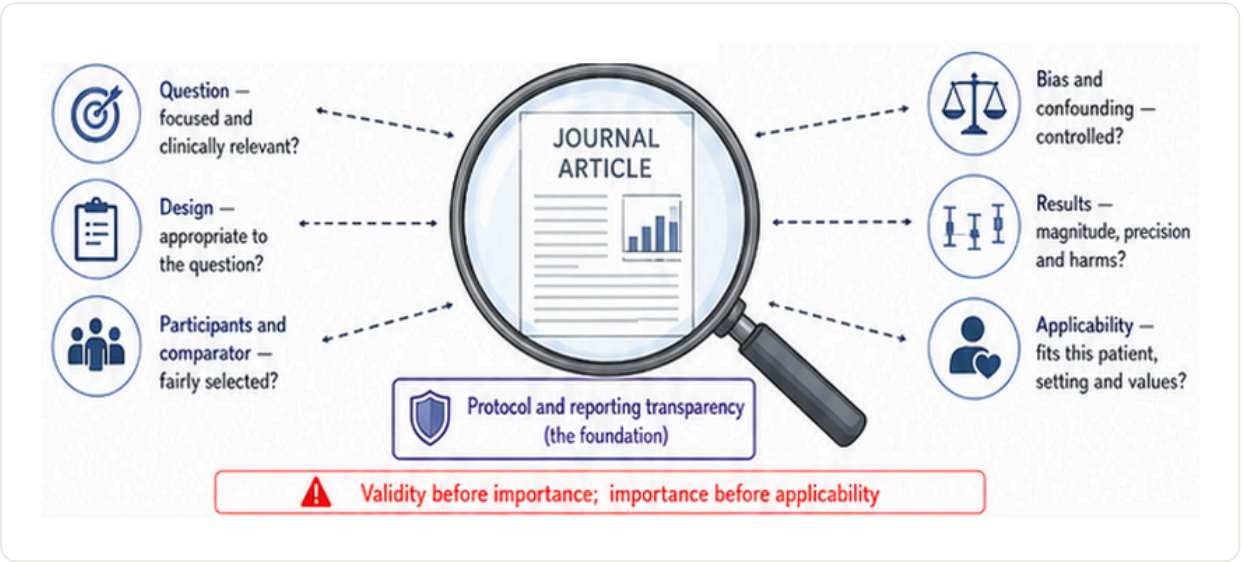


Fig 7.14 Critical appraisal: six questions a paper must survive.

RULE **Appraise before you apply.** Judge validity, size of effect, and applicability in that order; a statistically significant result from a biased study still does not change practice.

8.2 Reporting guidelines matched to design

The matching game. Each major design has its own EQUATOR-network checklist. The three you must never confuse: CONSORT for randomised trials, PRISMA for systematic reviews and meta-analyses, and STROBE for observational studies (Schulz et al. 2010; Moher et al. 2009; von Elm et al. 2007). Two more are named constantly alongside them: GRADE is not a reporting checklist but a system for rating the *certainty* of a body of evidence and the strength of a recommendation (Guyatt et al. 2008), and MOOSE is the reporting guideline for meta-analyses of *observational* studies where PRISMA (built for reviews of trials) is a poor fit (Stroup et al. 2000).

GUIDELINE	DESIGN IT REPORTS	ONE-LINE DISCRIMINATOR
consort (CONSORT)	Randomised controlled trials	**Has the flow diagram: enrolled → randomised → analysed**
prisma (PRISMA)	Systematic reviews and meta-analyses (of trials)	**Has the four-phase flow: identified, screened, eligible, included**
strobe (STROBE)	Observational: cohort, case-control, cross-sectional	**Default for any study with no randomisation by the investigator**
moose (MOOSE)	Meta-analyses of observational studies	**Observational meta-analysis, where PRISMA does not fit**
grade (GRADE)	Certainty of a body of evidence + strength of recommendation	**Rates evidence high/moderate/low/very-low, not a reporting checklist**

Match the guideline to the design; CONSORT, PRISMA, STROBE are the three that get swapped in vivas.

RULE **CONSORT for trials, PRISMA for reviews, STROBE for observational.** Name the design first, then the checklist follows automatically.

TRAP **PRISMA is for the review, not the trials in it.** A meta-analysis of RCTs is reported with PRISMA; each included RCT was reported with CONSORT. GRADE then rates the certainty of the pooled evidence. Do not answer "CONSORT" for a meta-analysis.

GOOD TO REMEMBER

- **CONSORT:** reporting guideline for randomised trials; use when appraising an RCT; the signature item is the participant flow diagram (enrolled, randomised, lost, analysed).
- **PRISMA:** reporting guideline for systematic reviews and meta-analyses; use for a pooled synthesis of studies; the signature item is the four-phase study-selection flow diagram.
- **STROBE:** reporting guideline for observational studies; use for cohort, case-control, or cross-sectional designs; the rule is "no investigator-controlled randomisation, use STROBE".
- **MOOSE:** reporting guideline for meta-analyses of observational studies; use when the pooled studies are observational, not trials; distinguishes itself from PRISMA by the observational input.
- **GRADE:** system to rate certainty of evidence and strength of recommendation; use when grading a body of evidence for a guideline; the four certainty levels are high, moderate, low, very low.

8.3 Research ethics: the historical spine

Why the codes exist. Research ethics is a reaction to abuse. Every modern safeguard traces to a documented harm, and examiners want the three landmark documents in order with what each one introduced (Emanuel et al. 2000; Kaplan & Sadock 2024).

Nuremberg Code (1947)

Written after the Nazi doctors' trial; the first international code; its cardinal rule is that voluntary consent of the human subject is absolutely essential.

Declaration of Helsinki (1964, WMA, revised repeatedly)

The physician-authored standard for medical research; introduced the research ethics committee, the written protocol, and the primacy of the participant's interests over those of science and society.

Belmont Report (1979, USA)

Followed the Tuskegee syphilis study; named three foundational principles, respect for persons, beneficence, and justice, and mapped them to consent, risk-benefit assessment, and fair subject selection.

MNEMONIC

Never Have Bad Research

Nuremberg → Helsinki → Belmont, the chronological spine. Nuremberg gave consent, Helsinki gave the ethics committee and protocol, Belmont gave the principles that became the four-principle framework.

8.4 The four principles

The Beauchamp and Childress framework. Biomedical ethics is standardly taught as four principles that must be balanced against each other (Beauchamp & Childress 2019; Kaplan &

Sadock 2024). Belmont named three; the fourth, non-maleficence, is usually split out from beneficence in the clinical version.

Autonomy
Respect for the person's right to make their own informed, voluntary decision; the ground of informed consent and confidentiality.

Beneficence
Act in the participant's or patient's best interest; maximise benefit.

Non-maleficence
"First, do no harm"; minimise and justify risk; favourable risk-benefit ratio.

Justice
Fair distribution of the burdens and benefits of research; do not exploit vulnerable groups nor exclude those who could benefit.

PEARL

The Belmont-to-four-principles map is a classic one-mark question: respect for persons becomes autonomy, beneficence stays beneficence (and yields non-maleficence), and justice stays justice. Belmont's three "applications" (informed consent, risk-benefit assessment, selection of subjects) map onto the same principles.

8.5 Informed consent: capacity, disclosure, voluntariness

The three elements. Valid informed consent requires three things together (Kaplan & Sadock 2024; Appelbaum 2007). **Capacity** (the clinical term; "competence" is the legal, court-determined term) is the ability to communicate a choice, understand the relevant information, appreciate its application to oneself, and reason with it. **Disclosure** means giving the information a reasonable patient (patient-based standard) or reasonable physician (professional standard) would need: nature, purpose, risks, benefits, and alternatives including no treatment. **Voluntariness** means the decision is free of coercion, manipulation, or undue influence.

TRAP **Consent is a process, not a signature.** A signed form with no genuine understanding is not valid consent; consent is ongoing and can be withdrawn at any time. The form documents the process, it does not constitute it.

GOOD TO REMEMBER

- **Capacity:** the clinical ability to decide; four abilities, communicate a choice, understand, appreciate, reason; "capacity" is clinical, "competence" is the legal adjudication.
- **Disclosure:** the information given; must cover nature, risks, benefits, and alternatives including the option of no treatment; standard is reasonable-patient or reasonable-physician.
- **Voluntariness:** a free choice; invalidated by coercion, manipulation, or undue influence.

8.6 Vulnerable groups, surrogate consent, and assent

When the participant cannot consent alone. Some groups cannot give fully autonomous consent and need extra protection: children, those with impaired capacity (intellectual disability, dementia, acute psychosis), prisoners, and the economically or educationally disadvantaged

where consent may not be truly voluntary. Two mechanisms cover them. **Surrogate consent** is proxy consent by a legally authorised representative (a legally acceptable representative or LAR) who decides in the person's best interest when the participant lacks capacity. **Assent** is the affirmative agreement of a minor or a person lacking full capacity who cannot legally consent; the child's assent is sought *in addition to* the parent's or guardian's consent, and a clear refusal (dissent) is generally respected in non-therapeutic research.

RULE **Consent from the guardian, assent from the minor.** A minor cannot legally consent; obtain the guardian's consent and the child's assent, and honour the child's dissent where the research offers no direct benefit.

GOOD TO REMEMBER

- **Surrogate (proxy) consent:** consent given by a legally authorised representative for a participant who lacks capacity; use for adults unable to decide; the standard is the participant's best interest.
- **Assent:** a minor's affirmative agreement alongside guardian consent; use for children and others lacking legal capacity; a documented refusal (dissent) is respected in non-beneficial research.

8.7 Governance: the ethics committee and institutional review board

The gatekeeper. No human research proceeds without prior clearance by an independent committee, called an ethics committee (EC, the common term in the UK, India, and Europe) or an institutional review board (IRB, the US term). Its job is to protect the rights, safety, and wellbeing of participants: it reviews the protocol, the risk-benefit balance, the consent process and documents, compensation, and provisions for vulnerable groups, and it continues to monitor the study through progress reports and adverse-event reporting. A conflicted or poorly reported study is stopped here before a single participant is enrolled.

GOOD TO REMEMBER

- **Ethics committee / institutional review board:** the independent body that reviews and monitors human research; use before enrolment and throughout; its remit is participant rights, safety, and wellbeing (protocol, risk-benefit, consent, vulnerable-group safeguards).

8.8 The Indian frame: ICMR National Ethical Guidelines 2017

The national standard. In India, biomedical and health research on human participants is governed by the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017, which replaced the 2006 edition. They mandate prior review by a registered ethics committee, informed consent, additional safeguards for vulnerable participants, and are the reference standard for Indian institutional ethics committees. New Drugs and Clinical Trials Rules 2019 (under CDSCO) add the statutory regulatory layer for drug trials.

INDIA

Cite the ICMR National Ethical Guidelines 2017 for any Indian human-research question; they are the exam's expected answer for ethics-committee review and consent standards in India, superseding the 2006 guidelines. For a drug trial, add the New Drugs and Clinical Trials Rules 2019 (CDSCO). Registration of the ethics committee is mandatory.

8.9 Putting it together in an appraisal

The examiner's synthesis. A complete critical appraisal reads on two axes at once. On the reporting axis: name the design, pick the reporting guideline (CONSORT / PRISMA / STROBE), check the paper against it, and if it is a body of evidence for a recommendation, apply GRADE. On the ethics axis: confirm ethics committee approval, valid informed consent, and appropriate handling of any vulnerable participants. A paper that is beautifully reported but ethically unsound, or ethically clean but unappraisable, fails.

COMMON TRAP

Confusing GRADE with a reporting checklist. GRADE rates the *certainty* of evidence (high, moderate, low, very low) and the strength of a recommendation; it is not the checklist you use to report a single study. Report a single RCT with CONSORT; grade the pooled evidence with GRADE.

HOLD THIS

CONSORT reports randomised trials, PRISMA reports systematic reviews and meta-analyses, STROBE reports observational studies; GRADE rates certainty of evidence, MOOSE reports observational meta-analyses; and informed consent is capacity plus disclosure plus voluntariness, a continuing process and never merely a signature.

Biostatistics

9 · Data types and scales of measurement

Before any statistic is computed, one question decides which analysis is legal: what kind of number is this? The **scales of measurement** are the classification that governs which summary statistic and which statistical test may lawfully be applied to a variable. Every stem that hands you a variable ("tumour stage", "temperature in Celsius", "number of admissions", "diagnosis") is really asking you to name its scale, because the scale, not the researcher's preference, fixes whether you may quote a mean or only a median, and whether a parametric or a non-parametric test is permitted (Bland 2015; Altman 1991; Kaplan & Sadock 2024). Get the scale right and the correct description and test follow almost automatically.

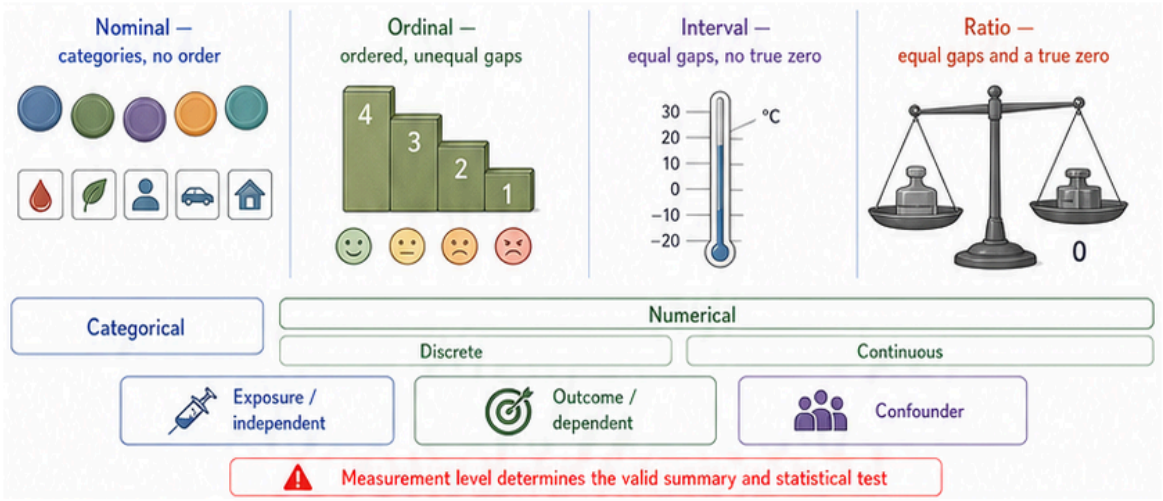


Fig 7.15 Levels of measurement: what can the numbers mean?.

The classification runs on two axes. First, Stevens' four **scales of measurement** in ascending order of information: **nominal**, **ordinal**, **interval**, **ratio** (Stevens 1946). Second, the broader **categorical** versus numerical split, with numerical data further divided into **discrete** and **continuous**. Nominal and ordinal are the two categorical scales; interval and ratio are the two numerical scales. Hold that mapping and the whole topic is scaffolded.

9.1 Why the scale is the first decision, not an abstraction

The scale determines the permitted arithmetic. Distinguishing the **data types** may look like a needless abstraction, but it is essential in fixing the correct method of both data description and analysis (Companion to Psychiatric Studies; Bland 2015). What operations are meaningful climbs with the scale: on a nominal scale you may only count and compare for equality; on an ordinal scale you may additionally rank; on an interval scale you may add and subtract differences because the gaps are equal; on a ratio scale you may also multiply and form ratios because a true zero exists. A mean requires that differences be equal, so it is meaningful only from interval level upward; below that, the median or the mode is the honest centre. This single dependency, arithmetic permitted rises with scale, is the engine behind every choice of statistic and test that follows.

RULE **The measurement scale decides the legal test.** Identify the scale first: it fixes the permissible summary statistic and the permissible test before you look at anything else in the analysis.

9.2 Nominal: named categories with no order

Labels that differ in kind, not in amount. **Nominal** (categorical) data have values that are qualitatively different from one another but carry no inherent order (Companion to Psychiatric Studies). The textbook example is diagnosis: schizophrenia, bipolar disorder and depression are distinct labels, but none is "more" than another, and no arithmetic on the labels is meaningful. Blood group, marital status, sex and the presence or absence of a symptom are all nominal. When a nominal variable has exactly two categories (alive or dead, case or non-case) it is called **dichotomous** or binary. The only legitimate summary is a count or a **proportion**; the only centre

is the mode; and comparisons between groups use the chi-square test (or Fisher's exact test when expected cell counts are small).

9.3 Ordinal: ordered categories with unequal gaps

Rank is real, but the spacing is not. **Ordinal** data have a logical order in their values, but the differences between adjacent values are not necessarily equal and there is no true zero point (Companion to Psychiatric Studies). A single Likert item (strongly disagree, disagree, neutral, agree, strongly agree), tumour stage (I to IV), social class I to V, and a ward observation level all rank the units without promising that the step from stage I to stage II equals the step from stage III to stage IV. Because the gaps are not guaranteed equal, the mean is not strictly meaningful; the correct centre is the **median** with the interquartile range for spread, and group comparisons use **non-parametric** (distribution-free) tests such as the Mann-Whitney U test or the Wilcoxon signed-rank test.

TRAP **Treating an ordinal Likert score as interval without care.** Averaging a single Likert item assumes the psychological distance from "agree" to "strongly agree" equals that from "neutral" to "agree", which is not established; report the median, or justify interval treatment only for a summed multi-item scale.

9.4 Interval: equal gaps, no true zero

Differences are meaningful; ratios are not. **Interval** data have equal differences between values, so the distance between 1 and 2 is the same as the distance between 33 and 34, but the zero is arbitrary rather than absolute (Companion to Psychiatric Studies). The canonical example is temperature in Celsius: 20 degrees is 10 degrees warmer than 10 degrees, yet 20 degrees is not "twice as hot" as 10 degrees, and 0 degrees Celsius does not mean an absence of temperature. Because the zero is not true, sums and differences are valid but ratios are not. Interval data support the **mean** and standard deviation and, given the distributional assumptions, **parametric** tests. Calendar year and IQ score are usually treated as interval.

9.5 Ratio: equal gaps and a true zero

The full arithmetic, ratios included. **Ratio** data share the equal-interval property of interval data and add a true, non-arbitrary zero that marks a complete absence of the quantity (Companion to Psychiatric Studies). Weight, height, age, and number of admissions are ratio: zero admissions genuinely means none, and four admissions are meaningfully twice two. This true zero is what licenses ratios, so "twice as heavy" is a valid statement whereas "twice as hot in Celsius" is not. In practice the interval versus ratio distinction rarely changes the analysis: both are numerical, both are summarised by the mean and standard deviation, and both are analysed with the same parametric tests. That is why many texts pool them as "interval or ratio".

9.6 The categorical versus numerical split, and discrete versus continuous

The higher-level partition that maps onto the four scales. The four scales collapse into two families. **Categorical** data (nominal and ordinal) place units into classes; numerical data (interval and ratio) attach a genuine number. Within numerical data a second cut matters: **discrete** data can take only separate, usually whole-number, values (number of admissions, number of previous

episodes, family size, a count of anything), whereas **continuous** data can in principle take any value on a continuum, limited only by measurement precision (weight, height, serum lithium concentration, reaction time). A count is discrete even though it is ratio-scaled; a measured quantity is continuous. The practical payoff is that discrete-count and continuous data, being numerical, are described by the mean and analysed by parametric methods, while categorical data are described by proportions and analysed by chi-square and its relatives (Companion to Psychiatric Studies).

Categorical
Data sorted into classes; comprises the nominal and ordinal scales; summarised by counts and proportions.

Numerical
Data carrying a true number; comprises the interval and ratio scales; summarised by the mean (or median if skewed).

Discrete
Numerical data limited to separate values, typically whole-number counts (number of admissions).

Continuous
Numerical data able to take any value on a continuum to the limit of measurement precision (weight, concentration).

9.7 Variable roles: independent and dependent, exposure and outcome, confounder

The scale says what a variable is; its role says what it does. A single **variable** can occupy different roles in a study, and naming the role is separate from naming the scale. The independent variable is the presumed cause, the one manipulated or classified on (treatment arm, drug dose); the dependent variable is the measured response that is expected to change with it (symptom score, remission). In epidemiology the same idea is renamed: the exposure is the putative causal factor (a risk factor, a treatment) and the **outcome** is the event or state under study (relapse, mortality). A confounder is a third variable independently associated with both the exposure and the outcome, and not on the causal pathway between them, which distorts the crude exposure-outcome association if left unadjusted (age confounding an association between comorbidity and mortality is the standard example). Roles and scales are orthogonal: an outcome can be nominal (relapsed or not), ordinal (much improved to much worse), or ratio (days to relapse), and the outcome's scale, not its role, still dictates the test.

WORKED EXAMPLE

A trial randomises patients to drug A or drug B and, at 12 weeks, records (i) remission, yes or no, and (ii) the Hamilton depression score. Here the treatment arm is the **independent variable** (nominal, two categories); remission is a **nominal** dependent variable, so groups are compared with a chi-square test on proportions; the Hamilton score is treated as an **interval** dependent variable, so groups are compared with an independent-samples t-test on means. One study, two outcomes, two different tests, chosen entirely by the scale of each outcome. Had the outcome instead been an **ordinal** global-improvement rating, the correct test would switch to the non-parametric Mann-Whitney U test.

9.8 How the scale drives the summary statistic and the test

One scale, one centre, one test family. The chain is direct (Companion to Psychiatric Studies; Bland 2015). **Nominal** data are summarised by proportions and compared with the chi-square test; there is no meaningful measure of central tendency beyond the mode, and no measure of spread. **Ordinal** data are summarised by the median and interquartile range and compared with non-parametric tests. **Interval** and **ratio** data, if reasonably normally distributed, are summarised by the mean and standard deviation and compared with parametric tests (t-test, ANOVA). The scale you can always safely drop *down* to a lower one (treat interval data as ordinal by ranking, or as nominal by categorising) at the cost of throwing away information; you may never lawfully move a variable *up* a scale it does not possess. This is the reason ordinal-treated-as-interval is a genuine error while interval-treated-as-ordinal is merely wasteful.

SCALE	EXAMPLE	CENTRE STATISTIC	TEST FAMILY
Nominal	Diagnosis; blood group; alive or dead	Mode; report as a proportion	**Chi-square (Fisher's exact if cells small)**
Ordinal	Likert item; tumour stage I to IV; social class	Median, interquartile range	**Non-parametric (Mann-Whitney, Wilcoxon)**
Interval	Temperature in Celsius; IQ; calendar year	Mean, standard deviation	**Parametric (t-test, ANOVA)**
Ratio	Weight; age; number of admissions	Mean, standard deviation	**Parametric (t-test, ANOVA)**

The four scales of measurement read across a worked example, the honest measure of central tendency, and the family of tests each scale permits; the hit column is the test-family discriminator that the scale forces on you.

9.9 The statistical-test selector: data type by groups by pairing

Once the scale is fixed, three further questions name the test. Beyond the scale, the correct test for a difference depends on how many groups are compared and whether the observations are paired (the same subjects measured twice, or matched) or unpaired (independent groups). The selector below is the version examined most heavily: read the data type down and the group structure across (Companion to Psychiatric Studies; Altman 1991). Note the clean parallelism, every parametric test on the right has a non-parametric partner on the left, and every categorical row uses a chi-square-family test.

COMPARISON	CATEGORICAL (NOMINAL)	ORDINAL / NON-NORMAL	INTERVAL OR RATIO (NORMAL)
Two groups, unpaired	**Chi-square test**	Mann-Whitney U test	Independent-samples t-test
Two groups, paired	**McNemar test**	Wilcoxon signed-rank test	Paired t-test
Three or more, unpaired	**Chi-square test**	Kruskal-Wallis test	One-way ANOVA
Three or more, paired	**Cochran's Q test**	Friedman test	Repeated-measures ANOVA

COMPARISON	CATEGORICAL (NOMINAL)	ORDINAL / NON-NORMAL	INTERVAL OR RATIO (NORMAL)
Association of two variables	**Chi-square / phi**	Spearman rank correlation	Pearson correlation

The statistical-test selector: data type down, number of groups and pairing across; the hit column is the categorical-data route, and each non-parametric test in the ordinal column is the distribution-free partner of the parametric test to its right.

HOLD THIS

The measurement scale is the first and decisive choice: nominal gives proportions and chi-square, ordinal gives the median and non-parametric tests, interval and ratio give the mean and parametric tests, and you may drop a variable down a scale but never push it up one it does not have.

COMMON TRAP

The commonest measurement error in psychiatry research is running a t-test or reporting a mean on data that are only **ordinal**, above all on single **Likert** items and clinician rating scales, as if the equal-interval property held. A count that looks numerical can also mislead: "number of admissions" is **discrete** and often heavily skewed, so its mean can be a poor centre and a non-parametric test or a count model is safer than a naive t-test.

PEARL

Interval and ratio almost never need to be distinguished in practice: both are numerical, both take the mean and standard deviation, and both are analysed by the same parametric tests, which is why textbooks routinely pool them as "interval or ratio" in their test tables (Companion to Psychiatric Studies). The examinable distinction is one rung lower, categorical (nominal, ordinal) versus numerical (interval, ratio), because that boundary is exactly where parametric analysis becomes permissible.

MNEMONIC

NOIR, in rising order of information: Nominal, Ordinal, Interval, Ratio.

Read left to right you climb from named categories (Nominal) to ranked categories (Ordinal) to equal gaps without a true zero (Interval) to equal gaps with a true zero (Ratio). Each step adds one permitted operation: equality, then order, then addition, then ratios. The categorical break sits between Ordinal and Interval, which is the parametric threshold.

GOOD TO REMEMBER

- **Nominal:** named categories with no order (diagnosis, blood group); use it for qualitative labels; the summary is a proportion and the test is the chi-square test (Fisher's exact when expected cell counts are small).
- **Ordinal:** ordered categories with unequal, unguaranteed gaps and no true zero (Likert item, tumour stage); use it for ranked data; the centre is the median with the interquartile range and the tests are non-parametric (Mann-Whitney, Wilcoxon).
- **Interval:** equal gaps but an arbitrary zero (temperature in Celsius, IQ); use it for numerical data with no true zero; the summary is the mean and standard deviation and the tests are parametric (t-test, ANOVA); differences are valid but ratios are not.
- **Ratio:** equal gaps and a true zero marking absence of the quantity (weight, age, number of admissions); use it for numerical data where "twice as much" is meaningful; summary and tests are the same as interval (mean, SD, parametric), with ratios now also valid.
- **Discrete versus continuous:** discrete numerical data take separate whole-number values (counts of admissions); continuous numerical data take any value on a continuum (weight, concentration); both are numerical, but a skewed count may need a non-parametric test despite being ratio-scaled.
- **Confounder:** a variable independently linked to both exposure and outcome and not on the causal pathway; recognise it whenever a crude association may be distorted by a third factor; it is controlled by stratification, matching, restriction or multivariable adjustment.

10 · Describing data: central tendency, dispersion and the normal curve

Every dataset must first be described before it can be tested. Descriptive statistics answer three questions about a set of numbers: where is its centre, how spread out is it, and what shape does it take. **Central tendency** gives the typical value, **dispersion** gives the scatter around that value, and **shape** (symmetry and peakedness) decides which summary is honest and which inferential test is legitimate. The examiner tests this as a chain: read the data type and shape, pick the correct measure of centre and spread, and only then reach for a test (Companion to Psychiatric Studies; Bland 2015; Altman 1991).

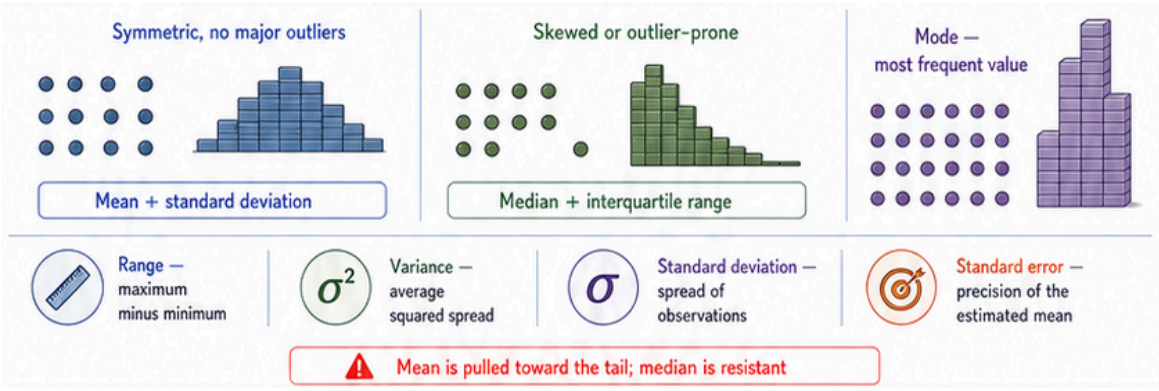


Fig 7.16 Describing data: choose the centre and spread together.

The keystone is the **normal distribution**, the bell-shaped curve on which most parametric statistics rest. Two properties make it examinable: it is fully specified by just its mean and standard deviation, and a fixed, memorisable fraction of the data falls within one, two and three standard deviations of the mean. Master that and a large block of biostatistics becomes

arithmetic (Kaplan & Sadock 2024). The rest of this topic builds the vocabulary of centre, spread and shape, then closes with the probability ideas that feed formal inference.

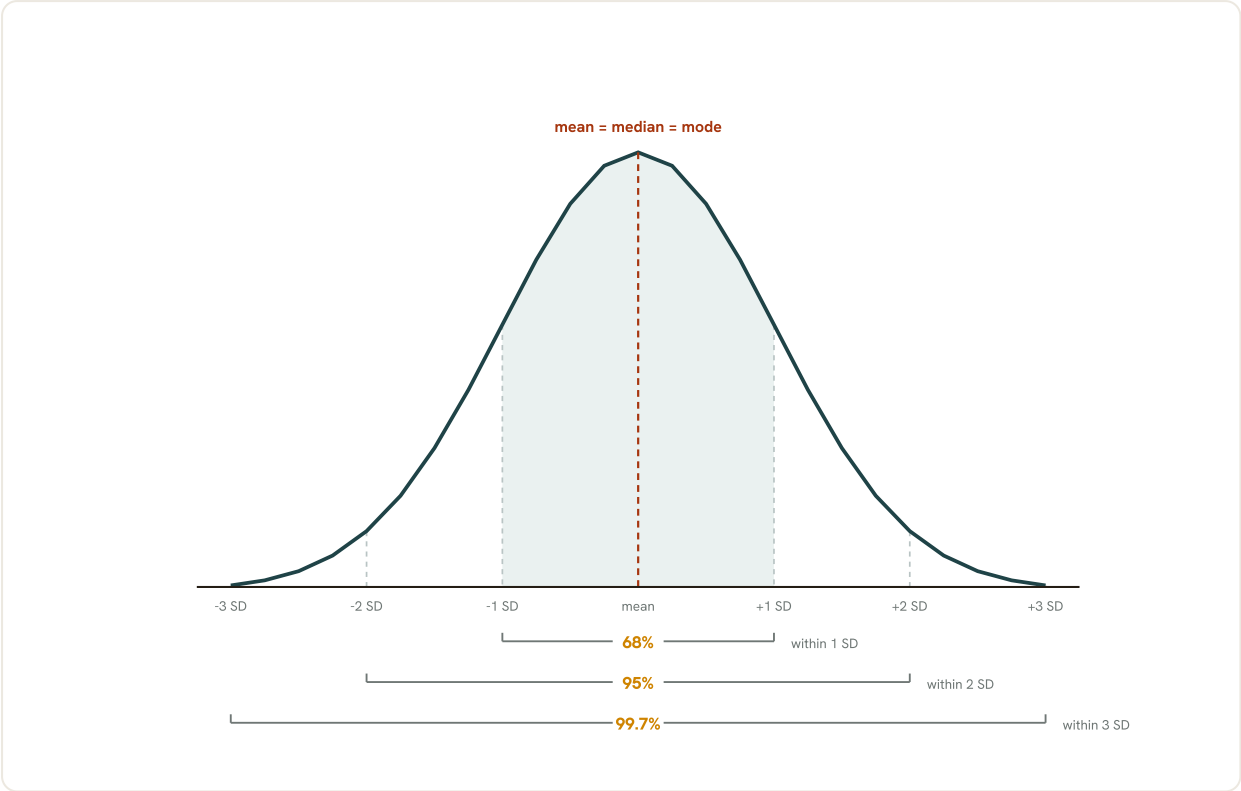


Fig 7.17 The normal curve and the empirical rule. In a normal distribution the mean, median and mode coincide at the peak and the spread is measured in standard deviations. The empirical rule fixes the proportions worth memorising: about 68 percent of observations lie within one SD of the mean, about 95 percent within two, and about 99.7 percent within three. The 95 percent band (more precisely 1.96 SD) is the basis of most confidence intervals and reference ranges.

10.1 Central tendency: the three averages

Central tendency is the single value that best represents a distribution. There are three measures, and the correct one depends on the data type and the shape (Companion to Psychiatric Studies). The mean (the arithmetic average, sum of values divided by n) uses every observation and is the natural summary for symmetric, interval or ratio data. The median (the middle value when the data are ranked, the 50th percentile) splits the data into two equal halves and is the summary of choice for skewed data and for ordinal data. The mode (the most frequently occurring value) is the only measure that can be used for nominal (categorical) data, and it is the one that can be read off a bar chart. A distribution can have one mode (unimodal), two (bimodal), or none.

RULE **Report the median for skewed data.** When a distribution is skewed or the data are ordinal, the median is the honest centre; the mean is right only for symmetric interval or ratio data, and the mode is for nominal data.

10.2 Choosing the centre: mean vs median vs mode

Match the measure to the data. The mean is efficient but not robust: a single extreme value (an outlier) or a long tail pulls it away from the bulk of the data. The median ignores the actual magnitude of extreme values and cares only about rank, which is exactly why it is robust and why

it is preferred for incomes, lengths of stay, symptom counts and any right-skewed clinical variable. The mode is crude for continuous data but indispensable for nominal categories such as diagnosis or blood group, where "average" is otherwise meaningless. The selector table at 10.10 formalises this against data type.

WORKED EXAMPLE

Length of stay for seven patients: 3, 4, 4, 5, 6, 8, 40 days. The mean is (3+4+4+5+6+8+40)/7 = 70/7 = **10** days, which no typical patient experienced. The ranked middle value, the median, is **5** days and describes the group far better. The mode is **4** days (the commonest value). The single long-stay outlier at 40 days has dragged the mean upward, the classic reason to report the median for a right-skewed variable.

10.3 Dispersion: range and interquartile range

Dispersion measures how widely the observations scatter around the centre. The simplest is the range (the difference between the largest and smallest value, or the pair itself). It is quick but fragile, because it depends entirely on the two most extreme observations and grows with sample size. Its robust cousin is the interquartile range, the IQR, which is the distance between the 25th percentile (first quartile, Q1) and the 75th percentile (third quartile, Q3), so it spans the central 50 percent of the data. Because the IQR discards the extreme quarters at each end, it is the natural partner of the median for skewed data, and it is what the box of a box-and-whisker plot draws.

10.4 Dispersion: variance and standard deviation

The variance and standard deviation are the dispersion measures that pair with the mean. The variance is the average of the squared deviations of each value from the mean (Companion to Psychiatric Studies). Squaring removes the sign so that deviations do not cancel, but it leaves the answer in squared units (for example, days squared), which is hard to interpret. Taking the square root of the variance returns to the original units and gives the standard deviation (SD), the single most used measure of spread for symmetric data. A large SD means the data are widely scattered about the mean; a small SD means they cluster tightly. For sample data the variance divides the sum of squared deviations by n minus 1 (Bessel's correction) rather than n, which corrects the tendency of a sample to underestimate the population spread.

HOLD THIS

The mean pairs with the standard deviation (symmetric data); the median pairs with the interquartile range (skewed data). Never a mean with an IQR, never a median with an SD.

10.5 Standard deviation vs standard error of the mean

SD describes the data; the standard error of the mean describes the estimate. This is the single most confused pair in the examination (Companion to Psychiatric Studies). The standard deviation quantifies the spread of the individual observations in your sample and does not shrink as you collect more data (a bigger sample just estimates the true SD more precisely). The standard error of the mean (SEM) is the standard deviation of the sample mean itself, that is, how much

the sample mean would vary from study to study; it equals the SD divided by the square root of n. Because n is in the denominator, the SEM falls as the sample grows, so it is always smaller than the SD. Use the SD to describe how variable the patients are; use the SEM (and the confidence interval built from it) to say how precisely you have pinned down the mean.

TRAP **SEM is not a measure of data spread.** Authors quote the small SEM instead of the SD to make data look tidy; the SEM only reflects precision of the mean and always shrinks with n. To describe the scatter of patients, report the SD.

10.6 The normal distribution and the empirical rule

The normal distribution is the symmetric, bell-shaped curve where mean = median = mode. Also called the gaussian distribution, it is unimodal and perfectly symmetric about its centre, so the three measures of central tendency coincide at the single peak (Companion to Psychiatric Studies; Kaplan & Sadock 2024). It is completely defined by two parameters, the mean (which locates the peak) and the standard deviation (which sets the width). Its key examinable property is the empirical rule (the 68 to 95 to 99.7 rule): for any normal distribution, about **68** percent of observations lie within one SD of the mean, about **95** percent within two SDs, and about **99.7** percent within three SDs. These bands, **68/95/99.7**, are the most reusable numbers in descriptive statistics.

68/95/99.7	1.96
PERCENT WITHIN 1, 2, 3 SD	SD FOR CENTRAL 95 PERCENT

10.7 The standard normal and the z-score

Standardising turns any normal value into a position on one universal curve. The standard normal distribution is the special normal distribution with mean 0 and SD 1. Any raw value x from a normal distribution is converted to it by the z-score, z = (x minus mean) / SD, which expresses how many standard deviations the value sits above (positive z) or below (negative z) the mean. A z-score lets you compare values from different scales and read off the proportion of the distribution beyond any point from a single z-table. The empirical rule is just the z-table at round numbers: z = 1, 2 and 3 cut off the 68, 95 and 99.7 percent bands. More precisely, the central 95 percent of a normal distribution lies within **1.96** SDs of the mean (not exactly 2), and 99 percent within 2.58 SDs; the 1.96 value is the one to memorise because it reappears as the multiplier in the 95 percent confidence interval.

WORKED EXAMPLE

IQ is scaled to a normal distribution with mean **100** and SD **15**. A score of 130 has z = (130 minus 100)/15 = 30/15 = **2**, so it sits exactly two SDs above the mean. By the empirical rule 95 percent of people lie within two SDs (between 70 and 130), leaving 5 percent outside; because the curve is symmetric, about 2.5 percent score above 130. Intellectual disability is conventionally set near two SDs below the mean, an IQ around 70, which is the same 2.5 percent tail at the lower end (DSM-5-TR 2022).

10.8 Shape: skew

Skew is asymmetry, and it tells you where the mean has gone. A skewed distribution has one tail longer than the other, and the direction is named for the tail, not the hump. In a right (positive) skew the long tail points to the high values (as in length of stay, income, or reaction times), and the mean is dragged toward that tail so the order becomes mode less than median less than mean. In a left (negative) skew the long tail points to the low values and the order reverses to mean less than median less than mode. This is the mechanism behind the rule to report the median for skewed data: the mean chases the tail while the median stays near the bulk. A quick sign of right skew is a mean noticeably larger than the median.

> **PEARL**
>
> The mean is pulled toward the longer tail; the median resists it. So in right (positive) skew the mean exceeds the median, and in left (negative) skew the mean falls below the median. Comparing mean and median is a one-line skew detector.

10.9 Shape: kurtosis

Kurtosis describes the peakedness and tail-weight of a distribution. Where skew is about asymmetry, kurtosis is about how heavy the tails are and how sharp the peak is relative to a normal curve. A distribution with positive excess kurtosis (leptokurtic) is more sharply peaked with fatter tails, meaning more extreme outliers than a normal distribution predicts; one with negative excess kurtosis (platykurtic) is flatter with thinner tails. The normal distribution is the reference (mesokurtic, excess kurtosis 0). Kurtosis matters because fat tails break the assumptions of tests that presume normality, and heavy-tailed data are better summarised by the median and IQR.

10.10 Selector: which centre and spread for which data

The measure of centre and its matched spread follow directly from data type and shape. This is the practical payoff of the whole topic and a favourite one-mark question. Read the row, name the pair.

DATA / SHAPE	BEST CENTRE	MATCHED SPREAD	WHY
Symmetric interval/ratio	**Mean**	Standard deviation	Uses all data; SD and mean fully describe a normal curve
Skewed continuous	**Median**	Interquartile range	Median and IQR ignore the outlying tail; robust
Ordinal (ranked)	**Median**	Interquartile range / range	Ranks have order but no equal intervals, so no true mean
Nominal (categorical)	**Mode**	(Counts / proportions)	Only the commonest category is meaningful; no arithmetic

Descriptive selector: data type and shape fix the centre, which fixes the matched spread; the hit column is the answer the stem wants.

10.11 Probability: the bridge to inference

Probability turns a described distribution into a basis for inference. A probability is the long-run relative frequency of an outcome, a number from 0 (impossible) to 1 (certain), and the probabilities of all mutually exclusive outcomes sum to 1 (Companion to Psychiatric Studies). Two ideas carry forward. First, for a continuous variable, area under the curve equals probability, which is exactly what the empirical rule computes: the 95 percent within 1.96 SDs is the area under the central slab of the normal curve. Second, two events are independent when the occurrence of one does not change the probability of the other, the assumption behind treating patients as independent observations. These feed the sampling distribution of the mean, the standard error, confidence intervals and hypothesis tests, where descriptive statistics hand over to formal inference.

MNEMONIC

Mean Moves, Median Middles

In a skewed distribution the MEAN MOVES toward the long tail while the MEDIAN holds the MIDDLE. So report the median (and IQR) whenever the data are skewed, and reserve the mean (and SD) for symmetric data.

GOOD TO REMEMBER

- **Mean:** arithmetic average using all values; for symmetric interval/ratio data; = sum of values / n; pairs with the SD.
- **Median:** the middle (50th percentile) ranked value; for skewed or ordinal data; robust to outliers; pairs with the IQR.
- **Mode:** the most frequent value; the only centre valid for nominal data; read off a bar chart.
- **Range:** largest minus smallest value; crude, driven by the two extremes and grows with n.
- **Interquartile range:** Q3 minus Q1 (75th minus 25th percentile); spans the central 50 percent; robust partner of the median.
- **Variance:** mean of squared deviations from the mean; in squared units; sample version divides by n minus 1.
- **Standard deviation:** square root of the variance, back in original units; the spread that pairs with the mean.
- **Standard error of the mean:** SD of the sample mean = SD / square root of n; a precision measure that shrinks with n, always smaller than the SD.
- **Normal distribution (gaussian):** symmetric bell curve, mean = median = mode; fixed by mean and SD; empirical rule 68/95/99.7 percent within 1, 2, 3 SDs.
- **Standard normal / z-score:** normal with mean 0, SD 1; z = (x minus mean) / SD = number of SDs from the mean; central 95 percent lies within 1.96 SDs.
- **Skew:** asymmetry named for the long tail; right/positive tail drags the mean above the median, left/negative below it.
- **Kurtosis:** peakedness and tail-weight vs normal; leptokurtic = peaked, fat tails; platykurtic = flat, thin tails.

11 · Tests of significance: parametric and non-parametric

A significance test asks a single question: is the difference or association we observed likely to be real, or is it plausibly the play of chance? Every test we cover here re-frames the clinical question

as a **null hypothesis** of no difference, computes a test statistic, and returns a p-value, the probability of a result this extreme (or more) if the null were true (Johnstone et al 2010, Bland 2015). The examiner rarely asks you to compute anything by hand. What they test is whether you can **choose the right test** for the data in front of you, and whether you know why the wrong choice is wrong. That choice turns on three things: the scale of your outcome (nominal, ordinal, interval or ratio), how many groups you are comparing, and whether the observations are paired.

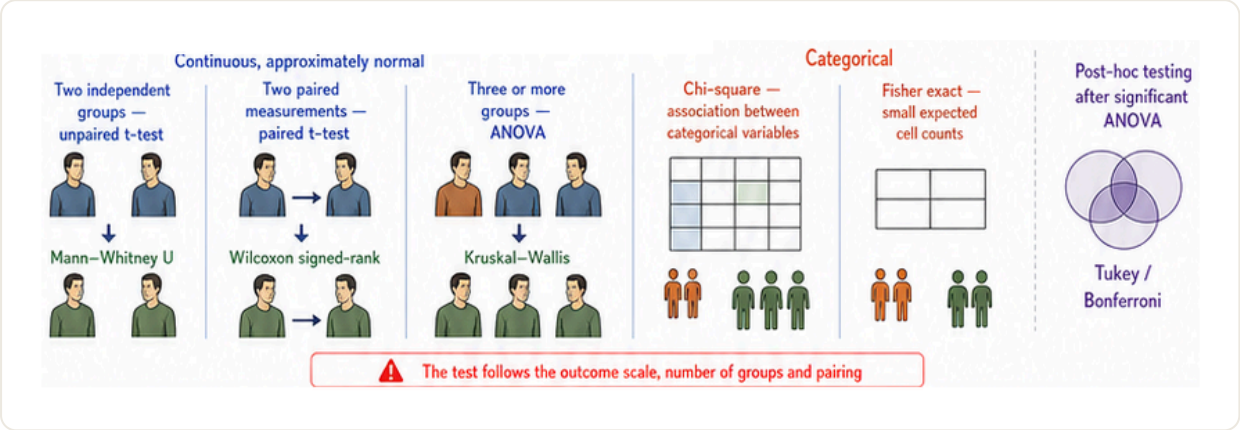


Fig 7.18 Significance tests: match the question, data and pairing.

The great divide is between parametric tests, which assume the data follow a known distribution (usually normal) and estimate population parameters like the mean and variance, and non-parametric tests (also called distribution-free tests), which make no such assumption and work on ranks (Altman 1991, Kaplan & Sadock 2024). Parametric tests are more powerful when their assumptions hold; the non-parametric twins are the safety net for ordinal or non-normal data.

11.1 The three parametric assumptions

What must be true for a parametric test. The correct choice of a parametric test rests on a short list of assumptions (Johnstone et al 2010): the outcome is **interval or ratio** data (continuous, with meaningful equal intervals); each observation is **independent** of the others; the data are approximately **normally distributed**; and the **variance of each group is approximately equal** (homoscedasticity). Meet these and you may use the powerful mean-based tests that use every data value. Fail them badly and you switch to a non-parametric rank-based test, or transform the data (e.g. by taking the log or square root) to restore normality first.

Robustness. A useful caveat: parametric tests are relatively robust to minor departures from normality, contrary to the common misperception that perfect normality is the overriding requirement (Johnstone et al 2010). With a large sample the central limit theorem means sample means tend to normality even when the raw data do not, so a large-sample t-test remains safe even when some assumptions are mildly violated.

RULE **Scale plus groups plus pairing.** Match the test to the data scale, the number of groups, and whether the observations are paired: those three facts pick the test.

11.2 The student t-test: one-sample, two-sample, and paired

The parametric workhorse for one or two groups. The student t-test (use the t-distribution) is one of the most quoted statistics in medicine (Johnstone et al 2010). It comes in three flavours matched to the design:

One-sample t-test

Compares a single sample mean against a known or hypothesised population mean (e.g. mean age of a dementia cohort vs mean age of all elderly inpatients).

Independent two-sample t-test

Compares the means of two independent groups; needs continuous or interval data, approximate normality, and roughly equal variances.

Paired t (paired t-test)

For matched data: the same subjects measured twice (before/after) or individually matched pairs. It analyses the within-pair differences, not the raw group means.

The statistic. In essence, t = observed difference in means / standard error of that difference, with $n1 + n2 - 2$ degrees of freedom for the two-sample test. t grows (and significance becomes more likely) as the difference in means widens or as the standard error shrinks with larger samples (Johnstone et al 2010). Where the equal-variance assumption fails there is a modified two-sample t-test (Welch). Always state t and its degrees of freedom.

11.3 ANOVA and the F-test: three or more groups

Why you cannot just run more t-tests. When there are three or more groups you test the null hypothesis that all group means are equal using the analysis of variance (ANOVA). Counter-intuitively, ANOVA answers a question about means by comparing variances (Johnstone et al 2010). It partitions the total variation into the between-groups variance (how far the group means sit from the grand mean) and the within-groups (residual) variance (scatter inside each group), and takes their ratio as the test statistic F-test (the F ratio):

F = variation between groups / variation within groups = MS(between) / MS(residual). If the groups share one population mean, F is near 1; if the group means truly differ, the between-groups term swells and F rises. A significant F says at least one group differs, but not which one.

TRAP **Do not t-test three groups.** Running a t-test on every pair of three groups inflates the type I error (each test carries its own 5% false-positive risk). Use ANOVA for three or more groups.

Extensions. One-way ANOVA handles a single grouping factor; factorial ANOVA handles several factors at once and reveals interactions; repeated-measures ANOVA is the paired extension for the same subjects measured on several occasions; ANCOVA adjusts the group comparison for a confounding covariate such as age or premorbid IQ (Johnstone et al 2010).

11.4 Post-hoc comparisons: Tukey and Bonferroni

Finding which groups differ, safely. A significant ANOVA licenses post-hoc pairwise comparisons to locate the difference, but every extra comparison is another chance for a false positive, so these tests build in a correction (Johnstone et al 2010). The Tukey Honestly

Significant Difference and the Bonferroni adjustment are the two most-quoted. Bonferroni is the simplest and most conservative: to keep the overall false-positive rate at 0.05 across n tests, each individual test must clear a threshold of p = **0.05** / number of tests. For two comparisons that is roughly 0.025; for many comparisons it becomes very stringent, so critics note it can over-correct and inflate the type II error (Perneger 1998).

11.5 Mann-Whitney U: the non-parametric two independent groups test

The rank-based twin of the independent t-test. When the outcome is ordinal, or interval data that badly break normality, and you are comparing two independent groups, use the mann-whitney U test (Johnstone et al 2010). It ranks all observations across both groups combined and compares the rank sums, so it makes no distributional assumption. It assumes only that the two groups are independent, and because it can detect differences in spread as well as in location, report each group's median alongside a note on skew (e.g. a box plot). Always state U.

11.6 Wilcoxon signed-rank: the non-parametric paired test

The rank-based twin of the paired t. Where measurements are paired (two measurements from the same individual, or matched pairs) and the data are ordinal or non-normal, the wilcoxon signed-rank (matched-pairs) test replaces the paired t-test (Johnstone et al 2010). It ranks the within-pair differences by magnitude, attaches the sign, and tests whether the signed ranks balance around zero. Pair Mann-Whitney with independent groups and Wilcoxon with paired data: swapping them is the classic slip.

11.7 Kruskal-Wallis: the non-parametric ANOVA

The rank-based twin of one-way ANOVA. For three or more independent groups on ordinal or non-normal data, the kruskal-wallis test is the non-parametric equivalent of one-way ANOVA (Johnstone et al 2010). It ranks all observations and tests whether the mean ranks differ across groups; a significant result, like a significant F, says at least one group differs and is followed by post-hoc rank comparisons. Its paired counterpart (repeated measures on the same subjects) is the Friedman test.

11.8 Chi-square: association for categorical data

Comparing proportions, not means. For categorical (nominal) outcomes the chi-square (chi square) test of association is the key test (Johnstone et al 2010). It is distribution-free, and it asks whether the proportion with a characteristic differs across two or more independent groups by comparing observed cell counts with the counts expected under the null. The statistic is chi-square = sum of (O − E)squared / E, where O and E are observed and expected frequencies. Two rules the examiner loves: the cells must contain absolute counts, never percentages (percentages falsely inflate the sample size); and you must state chi-square with its degrees of freedom. The paired analogue for a 2x2 table (same subjects, before/after) is the McNemar test.

11.9 Fisher exact: the small-cell rescue

When the chi-square approximation breaks. The chi-square distribution is an approximation that fails when expected cell counts are small. The classic rule: when any expected frequency falls below **5**, use the fisher exact test (or Yates's continuity correction) instead of the ordinary chi-

square (Johnstone et al 2010). Fisher's exact computes the exact probability of the observed table and is more conservative, so it is less likely to reject the null wrongly when numbers are tiny.

0.05	< 5	n−1
ALPHA THRESHOLD	EXPECTED CELL TO FISHER	DEGREES OF FREEDOM IDEA

11.10 The test-map: pairing each parametric test with its non-parametric twin

The one table to hold. Read across data type, number of groups, and pairing to land on the correct test. This is the selector the examiner is really testing (Johnstone et al 2010, Altman 1991).

GROUPS & PAIRING	CATEGORICAL (NOMINAL)	ORDINAL / NON-NORMAL	INTERVAL OR RATIO (PARAMETRIC)
One sample vs known value	Chi-square goodness-of-fit	Sign test	**One-sample t-test**
Two groups, independent (unpaired)	Chi-square test of association	Mann-Whitney U	**Independent two-sample t-test**
Two groups, paired / matched	McNemar test	Wilcoxon signed-rank	**Paired t-test**
Three or more groups, independent	Chi-square test	Kruskal-Wallis	**ANOVA (one-way), F-test**
Three or more groups, repeated / paired	Cochran's Q	Friedman test	**Repeated-measures ANOVA**
Association between two variables	Chi-square / phi coefficient	Spearman rank correlation	**Pearson correlation**

Every parametric test in the right-hand column has a rank-based non-parametric twin to its left; small-cell categorical data drop to the Fisher exact test.

11.11 Worked reads: a chi-square 2x2 and an ANOVA F

WORKED EXAMPLE

Chi-square, 2x2. Sex distribution is compared between 60 people with schizophrenia and 60 healthy controls (Johnstone et al 2010). Expected counts under no difference are 30 per cell. Summing (O − E)squared / E across the four cells gives chi-square = 1.2 on 1 degree of freedom, p = 0.27. Because 0.27 far exceeds alpha 0.05, the null of no difference in the population proportion cannot be rejected: the sexes are not shown to differ.

ANOVA F. Ages of three diagnostic groups of four patients are compared (Johnstone et al 2010). The between-groups sum of squares is 1711.5 (2 degrees of freedom) and the within-groups (residual) sum of squares is 648.5 (9 degrees of freedom). Dividing each by its degrees of freedom gives mean squares of 855.75 and 72.1, so F = 855.75 / 72.1 = 11.9, p = 0.003. Since 0.003 is below 0.05 we reject the null: at least one group mean differs, and post-hoc tests would then locate which.

COMMON TRAP

Feeding percentages into a chi-square test instead of raw counts falsely inflates the sample size and manufactures spurious significance; chi-square needs absolute frequencies. Equally, treating an ordinal scale (e.g. a 1-to-6 social-class rank) as interval data and running a t-test is a scale error: use Mann-Whitney or Kruskal-Wallis instead.

MNEMONIC

MWWK guards the non-parametric gate: Mann, Wilcoxon, Whitney's cousin, Kruskal.

Two independent groups to **Mann**-Whitney; two paired to **Wilcoxon**; three or more independent to **Kruskal**-Wallis. Their parametric partners are the independent t-test, the paired t-test, and ANOVA in the same order.

HOLD THIS

Match the test to data scale x number of groups x paired?: t-test twin is Mann-Whitney (2 independent) or Wilcoxon (paired), ANOVA twin is Kruskal-Wallis (3+), and categorical goes to chi-square, dropping to Fisher exact when any expected cell is under 5.

GOOD TO REMEMBER

- **Student t-test:** parametric test of means for one or two groups; use when data are interval/ratio, roughly normal, with equal variance; two-sample t has n1 + n2 − 2 degrees of freedom.
- **Paired t-test:** parametric test for matched/before-after data; use when the same subjects are measured twice; it tests the mean of the within-pair differences.
- **ANOVA (analysis of variance):** parametric test for three or more group means; use to avoid multiple t-tests; its statistic is F = MS(between) / MS(residual).
- **F-test:** the ratio of between-groups to within-groups variance inside ANOVA; use to test whether group means are equal; F near 1 supports the null.
- **Post-hoc (Tukey, Bonferroni):** follow a significant ANOVA to find which groups differ; use to control the family-wise error; Bonferroni threshold = 0.05 / number of tests.
- **Mann-Whitney U:** non-parametric test for two independent groups on ordinal/non-normal data; use as the t-test's rank-based twin; report the group medians.
- **Wilcoxon signed-rank:** non-parametric test for paired ordinal/non-normal data; use as the paired-t twin; it ranks the signed within-pair differences.
- **Kruskal-Wallis:** non-parametric test for three or more independent groups; use as the one-way ANOVA twin; the paired counterpart is the Friedman test.
- **Chi-square (chi square) test of association:** non-parametric test comparing proportions across categorical groups; use on absolute counts, never percentages; statistic = sum of (O − E)squared / E, stated with its degrees of freedom.
- **Fisher exact test:** the small-cell rescue for a 2x2 table; use when any expected cell frequency is under 5; it gives the exact, more conservative probability.

For test-selection detail and worked derivations see Altman (1991) and Bland (2015). Reliability and validity of a psychometric instrument itself (as distinct from the reliability of a study) are covered in the Psychometry, Assessment and Descriptive Psychopathology notes; the disorder-specific applications of these tests appear in the clinical chapters of Paper II.

12 · Correlation, regression and factor analysis

Once two or more variables are in play, three questions dominate the stems: do they move together, can one predict another, and do many items collapse into a few? This topic covers the three workhorse techniques of association and prediction: **correlation** quantifies how strongly two variables move together, **regression** models and predicts one variable from others (and adjusts for confounders), and **factor analysis** reduces many correlated items to a few underlying latent dimensions (Companion to Psychiatric Studies; Bland 2015; Altman 1991). The examinable spine is simple: correlation measures, regression predicts and adjusts, factor analysis simplifies, and none of the three, on its own, proves cause.

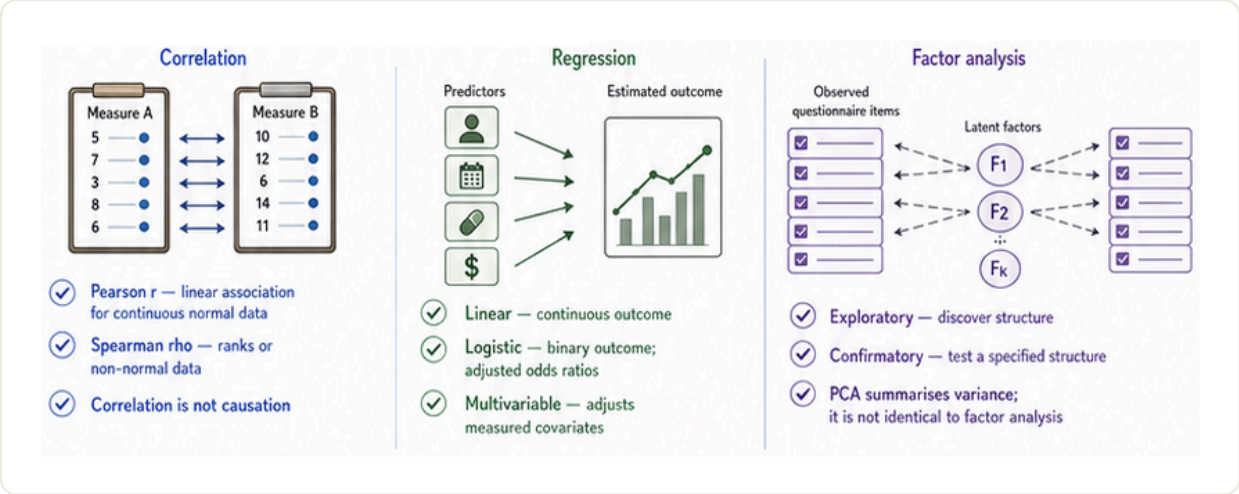


Fig 7.19 Association, prediction and latent structure.

The single most tested idea across the whole cluster is the divorce of statistical association from causation: a strong correlation, a steep regression slope, or a high coefficient of determination each describes the data at hand but licenses no causal claim without a design that supports one (Tasman 2015; Kaplan & Sadock 2024). Hold that caveat and the traps in this area mostly disarm themselves.

12.1 Correlation: measuring linear association between two variables

A single number for how tightly two variables track. A correlation coefficient summarises the strength and direction of the linear relationship between two variables in one number that runs from **-1** through **0** to **+1** (Bland 2015; Altman 1991). A coefficient of **+1** is a perfect positive linear relationship (as one rises the other rises exactly in step), **-1** is a perfect negative linear relationship, and **0** means no linear relationship at all. The sign gives the direction and the magnitude gives the strength; a value near zero does not exclude a strong non-linear (for example U-shaped) relationship, because the coefficient only captures the linear component. Correlation is symmetric: the correlation of x with y equals the correlation of y with x, which is exactly why it can never, by itself, say which variable is cause and which is effect.

12.2 Pearson r: the coefficient for two continuous, normal variables

The parametric correlation, for continuous normally distributed data. The pearson product-moment correlation coefficient, written r, is the correlation used when both variables are

continuous and approximately normally distributed and their relationship is linear (Bland 2015; Altman 1991). It is the default numerical-versus-numerical association measure and the parametric member of the correlation family, the natural partner of the t-test and ANOVA. Being parametric, it is sensitive to outliers and assumes a straight-line relationship; a single extreme point can inflate or collapse it, and a curved relationship can hide behind a near-zero r. Its square, r-squared, carries a direct interpretation covered below.

RULE **Match the correlation to the data.** Two continuous normal variables in a linear relationship take pearson r; ordinal or non-normal (or outlier-ridden) data take the spearman rank correlation.

12.3 Spearman rank correlation: for ordinal or non-normal data

The non-parametric correlation, computed on ranks. The spearman rank correlation coefficient (rho) is the distribution-free counterpart of pearson r: it is applied when the data are ordinal, when a continuous variable is markedly non-normal or skewed, or when outliers make a rank-based measure safer (Bland 2015; Companion to Psychiatric Studies). It is simply the pearson correlation computed on the ranks rather than the raw values, so it captures any monotonic (consistently increasing or decreasing) relationship, not only a strictly linear one, and it shares the same -1 to +1 range and the same sign convention. Because it works on ranks it is robust to outliers and makes no normality assumption, at the modest cost of discarding the exact spacing of the values.

WORKED EXAMPLE

A study reports that clinician-rated illness severity (a five-point ordinal scale) and number of prior admissions (a skewed count) rise together, with a coefficient of **0.62**. Because one variable is ordinal and the other is a skewed count, pearson r is inappropriate and the **spearman** rank correlation is the correct choice; rho of 0.62 says the ranks move together moderately and positively. Note what it does not say: it does not establish that more admissions cause greater severity, nor the reverse, because a third factor (chronicity, poor adherence) could drive both. The coefficient describes the monotonic association and nothing more.

12.4 Correlation is not causation

The caveat that governs the entire topic. A correlation, however strong, cannot by itself be logically read as evidence that one variable causes the other; the non-equivalence of correlation and causation applies with full force (Tasman 2015). Two variables can correlate because one causes the other, because the other causes the one, because a third variable (a **confounder**) causes both, or by chance. The classic pattern is confounding: ice-cream sales correlate with drowning deaths, but summer heat drives both. Reverse causation and selection effects produce the same trap. Establishing causation needs a design that controls these alternatives (a randomised trial, or at minimum multivariable adjustment plus the Bradford Hill considerations), never a correlation coefficient on its own.

TRAP **Reading a strong r, slope, or r-squared as proof of cause.** Association is not causation; a confounder, reverse causation, or chance can generate any of them without a causal link between the two variables.

12.5 Linear regression: predicting a continuous outcome from a line

From describing association to predicting a value. Where correlation gives a symmetric strength-of-association number, linear regression fits an asymmetric predictive model: it estimates the straight line that best predicts a continuous outcome (the dependent variable, y) from one or more predictors (independent variables, x), by minimising the squared vertical distances of the points from the line (least squares) (Bland 2015; Altman 1991). The fitted line has the form y equals intercept plus slope times x. The **slope** (regression coefficient, b) is the heart of the output: it states how many units the outcome changes for each one-unit rise in the predictor, and its sign gives the direction. Unlike correlation, regression is directional, it names a predictor and an outcome, which is why the stem's phrasing ("predict", "for each unit increase") signals regression rather than correlation.

12.6 The coefficient of determination: r-squared as variance explained

The proportion of the outcome's variability the model explains. The coefficient of determination, written **r-squared**, is the square of the correlation coefficient and gives the proportion of the total variability in the outcome that is predictable from, or accounted for by, the predictor(s) (Tasman 2015; Bland 2015). It runs from **0** to **1** (often quoted as a percentage): an r of **0.5** gives an r-squared of **0.25**, meaning **25%** of the variance in the outcome is explained by the predictor and the remaining 75% is unexplained. It is the standard effect-size and goodness-of-fit measure for a linear model. The critical exam point is that a high r-squared measures only how much variance the model captures; it says nothing about whether the relationship is causal.

-1 to +1	0 to 1	0.25
CORRELATION RANGE (R, RHO)	R-SQUARED RANGE	R-SQUARED WHEN R = 0.5

12.7 Logistic regression: predicting a binary outcome, yielding adjusted odds ratios

The regression for yes/no outcomes. When the outcome is binary (relapsed or not, dead or alive, case or non-case) a straight line is inappropriate, and logistic regression is used instead: it models the log-odds of the outcome as a linear function of the predictors (Bland 2015; Kaplan & Sadock 2024). Its coefficients, once exponentiated, yield odds ratios, and because several predictors sit in one model, each odds ratio is *adjusted* for the others in the model. An adjusted odds ratio therefore estimates the effect of one predictor on the odds of the outcome while holding the remaining predictors constant, which is precisely how confounding is handled in observational analyses. An odds ratio of **1** means no association; above 1 means increased odds; below 1 means decreased odds.

12.8 Multivariable regression: adjusting for confounders

Putting several predictors in one model to isolate an effect. The shared power of the regression family is that entering more than one predictor at once gives a **multivariable** model

in which each coefficient is estimated with the others held constant, statistically adjusting the exposure-outcome association for measured confounders (Bland 2015; Altman 1991). This is the analytic answer to confounding introduced in the data-types and validity material: rather than adjusting by design (randomisation, matching, restriction), multivariable regression adjusts in the analysis. Linear regression does this for a continuous outcome, giving adjusted slopes; logistic regression does it for a binary outcome, giving adjusted odds ratios; and the parallel Cox model does it for time-to-event outcomes, giving adjusted hazard ratios. The unadjusted (crude) estimate becomes the adjusted estimate once confounders enter the model.

PEARL

The word that tells you which member of the regression family is meant is the *outcome*. A continuous outcome (symptom score, blood level) means **linear regression** and a slope; a binary outcome (relapse yes/no) means **logistic regression** and an adjusted odds ratio; a time-to-event outcome (time to relapse) means Cox regression and an adjusted hazard ratio. Same logic of adjustment, three outcome types, three models.

12.9 Factor analysis: reducing many correlated items to a few latent factors

Data reduction for scale construction. Factor analysis is a multivariate technique that identifies a small set of underlying, unobserved dimensions (latent factors) that explain the pattern of intercorrelations among a larger set of measured items (Tasman 2015; Kaplan & Sadock 2024). Its starting point is the correlation matrix of all item pairs; from that matrix it extracts factors, each a weighted combination of items that hang together. The paradigm use in psychiatry is scale construction and validation: nine anxiety items might collapse to two factors (say, somatic and cognitive anxiety), giving a more parsimonious measure. The technique underpins the trait structure of personality questionnaires, where extraversion, neuroticism and psychoticism emerge as factors reproducible across cultures (Companion to Psychiatric Studies). Test-construction reliability and validity concepts sit alongside this in the Psychometry, Assessment and Descriptive Psychopathology notes.

12.10 Exploratory versus confirmatory factor analysis

Discovering structure versus testing a hypothesised one. Exploratory factor analysis is used when there is no firm prior model: it lets the data reveal how many factors exist and which items load on which, and is the tool for the first pass at a new scale (Tasman 2015). Confirmatory factor analysis is used later, when a specific factor structure is already hypothesised (from theory or from prior exploratory work): it tests how well a pre-specified model fits new data, reporting goodness-of-fit indices, and is a form of structural equation modelling. The examinable contrast is direction of reasoning: exploratory factor analysis generates the structure, confirmatory factor analysis tests a structure that is already specified.

12.11 Eigenvalues, the Kaiser criterion, loadings and the scree plot

The machinery for deciding how many factors to keep and what they mean. An eigenvalue is the amount of total variance in the item set that a given factor accounts for; larger eigenvalues mark more important factors. The commonest retention rule is the **Kaiser criterion**: retain only

factors with an eigenvalue greater than 1, on the logic that a retained factor should explain more variance than a single original item (Tasman 2015). The scree plot graphs eigenvalues in descending order; the factors above the "elbow" (the point where the curve levels into scree) are retained. A factor loading is the correlation between an item and a factor, and is how factors are interpreted: an item with a high loading defines that factor, and rotation (commonly varimax) is applied to sharpen the pattern so that each item loads highly on one factor and negligibly on the rest. Determining the number of factors is a matter of judgement, not an automatic output.

12.12 Principal component analysis and its relation to factor analysis

The close cousin, and how it differs. Principal component analysis is the related and often-conflated data-reduction method that repackages a set of correlated variables into a smaller set of uncorrelated components ordered by the variance each explains (Tasman 2015). In the factor-analysis workflow, using a communality estimate of 100% (retaining 1.0 on the diagonal of the correlation matrix) makes the extraction principal components. The conceptual difference is what each seeks: principal component analysis is purely descriptive and maximises variance explained, treating components as summaries of the observed variables, whereas true factor analysis (for example principal-factors extraction) posits latent factors that *cause* the observed correlations and separates common variance from item-specific and error variance. In practice they often give similar solutions, and principal component analysis is frequently the default first step.

RULE **Correlation quantifies association; regression predicts and adjusts.** Reach for a correlation coefficient to measure how two variables move together, and for regression to predict an outcome and to adjust for confounders.

TECHNIQUE	WHAT IT DOES	OUTCOME / DATA	KEY OUTPUT NUMBER
Pearson r	Linear association, two variables	Both continuous, normal	**r, from -1 to +1**
Spearman rho	Monotonic association on ranks	Ordinal or non-normal	**rho, from -1 to +1**
Linear regression	Predict a continuous outcome; adjust	Continuous outcome	**Slope (b); r-squared**
Logistic regression	Predict a binary outcome; adjust	Binary outcome	**Adjusted odds ratio**
Factor analysis	Reduce items to latent factors	Many correlated items	**Eigenvalue; factor loading**

The association-and-prediction selector: read the technique down, and let the data type and the question (measure, predict, or reduce) fix the choice; the hit column is the signature output number each technique returns.

HOLD THIS

Correlation measures association (pearson r for continuous normal data, spearman rho for ordinal or non-normal, both running -1 to +1); regression predicts and adjusts (linear regression for a continuous outcome with a slope and r-squared as variance explained, logistic regression for a binary outcome with adjusted odds ratios); factor analysis reduces many correlated items to a few latent factors (eigenvalue greater than or equal to 1 by the Kaiser criterion, interpreted through factor loadings); and none of them, alone, proves causation.

COMMON TRAP

The flagship error is reading a high r-squared (or a strong r, or a steep slope) as proof of causation: the coefficient of determination only states how much of the outcome's variance the model explains, not why, and a confounder or reverse causation can produce a large r-squared with no causal link. A second, quieter trap is applying pearson r to ordinal or skewed data where the spearman rank correlation is required, or reading a near-zero pearson r as "no relationship" when the true relationship is strong but curved.

MNEMONIC

Correlation Counts, Regression Reaches, Factor analysis Folds.

Correlation *counts* the association between two variables (one number, symmetric, no direction of cause). Regression *reaches* forward to predict an outcome and to adjust for confounders (directional, predictor to outcome). Factor analysis *folds* many correlated items into a few latent factors (data reduction for scale building).

GOOD TO REMEMBER

- **Pearson r:** the correlation coefficient for two continuous, approximately normal variables in a linear relationship; use it as the default numerical-versus-numerical association measure; r runs from -1 to +1 and its square is r-squared.
- **Spearman rank correlation (rho):** the non-parametric correlation for ordinal or non-normal data, computed on ranks; use it when data are ordinal, skewed, or outlier-prone; captures any monotonic relationship and also runs from -1 to +1.
- **Linear regression:** predicts a continuous outcome from predictors by a best-fit least-squares line; use it to predict a value or to adjust for confounders; the slope (b) gives the change in outcome per one-unit rise in the predictor, and r-squared gives the proportion of outcome variance explained.
- **Coefficient of determination (r-squared):** the square of the correlation, the fraction of outcome variance the model explains; use it as the goodness-of-fit and effect-size measure; runs 0 to 1, so r of 0.5 gives r-squared of 0.25, that is 25% of variance explained.
- **Logistic regression:** predicts a binary outcome by modelling its log-odds; use it when the outcome is yes/no; its exponentiated coefficients are adjusted odds ratios, an odds ratio of 1 meaning no association.
- **Multivariable regression:** any regression with several predictors entered together; use it to adjust the exposure-outcome estimate for measured confounders in the analysis; each coefficient is estimated with the others held constant, turning a crude estimate into an adjusted one.
- **Factor analysis:** reduces many correlated items to a few latent factors from their correlation matrix; use it for scale construction and validation; retain factors with an eigenvalue greater than or equal to 1 (Kaiser criterion) and interpret each factor through its factor loadings (the item-factor correlations).
- **Exploratory factor analysis versus confirmatory factor analysis:** exploratory factor analysis lets the data reveal the number and structure of factors (new scale, no prior model); confirmatory factor analysis tests a pre-specified factor structure against new data (a form of structural equation modelling) and reports fit.
- **Principal component analysis:** a data-reduction method that repackages correlated variables into uncorrelated components ranked by variance explained; use it as a descriptive first pass or when maximising variance summarised is the goal; it differs from true factor analysis in seeking components that summarise, not latent factors that cause, the observed correlations.

13 · Diagnostic test statistics

Every screening or diagnostic test makes two kinds of promise and two kinds of mistake, and the whole apparatus of test statistics is a way of pinning numbers to those promises and mistakes. It is built on one small object: the **2x2 table** that cross-tabulates the true state of the world (disease present or absent, fixed by a reference or gold standard) against what the test said (positive or negative). The examiner reliably asks you to read that table, to compute an index from it, and above all to know which indices are intrinsic to the test and which shift with the population you apply it to (Kaplan & Sadock 2024, Bland 2015). Get that last distinction wrong and you will over-trust a positive screen in a low-risk clinic, the single most common error in this whole area.

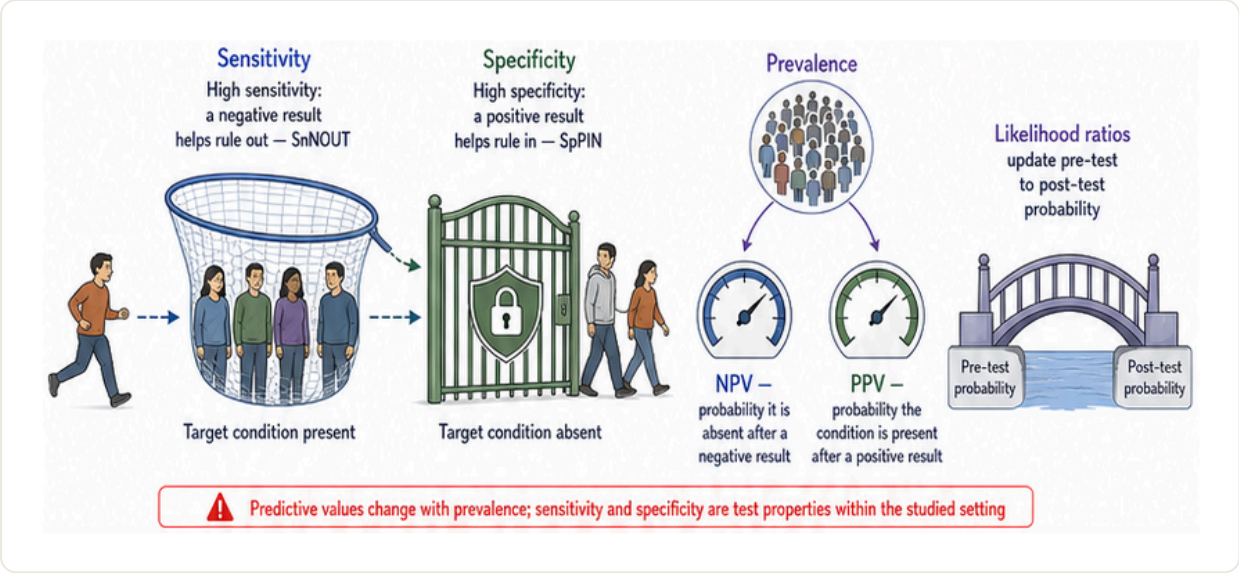


Fig 7.20 Diagnostic tests: from detection to post-test probability.

The four cells carry standard labels (Kaplan & Sadock 2024). The test correctly flags a diseased person as a **true positive** (cell a) and correctly clears a healthy person as a **true negative** (cell d). It errs two ways: a **false positive** (cell b) labels a healthy person diseased, and a **false negative** (cell c) misses a diseased person. Read the table two ways: down the columns (given the true state, how did the test perform?) gives sensitivity and specificity; across the rows (given the test result, what is the true state?) gives the predictive values. That change of direction is the heart of the topic.

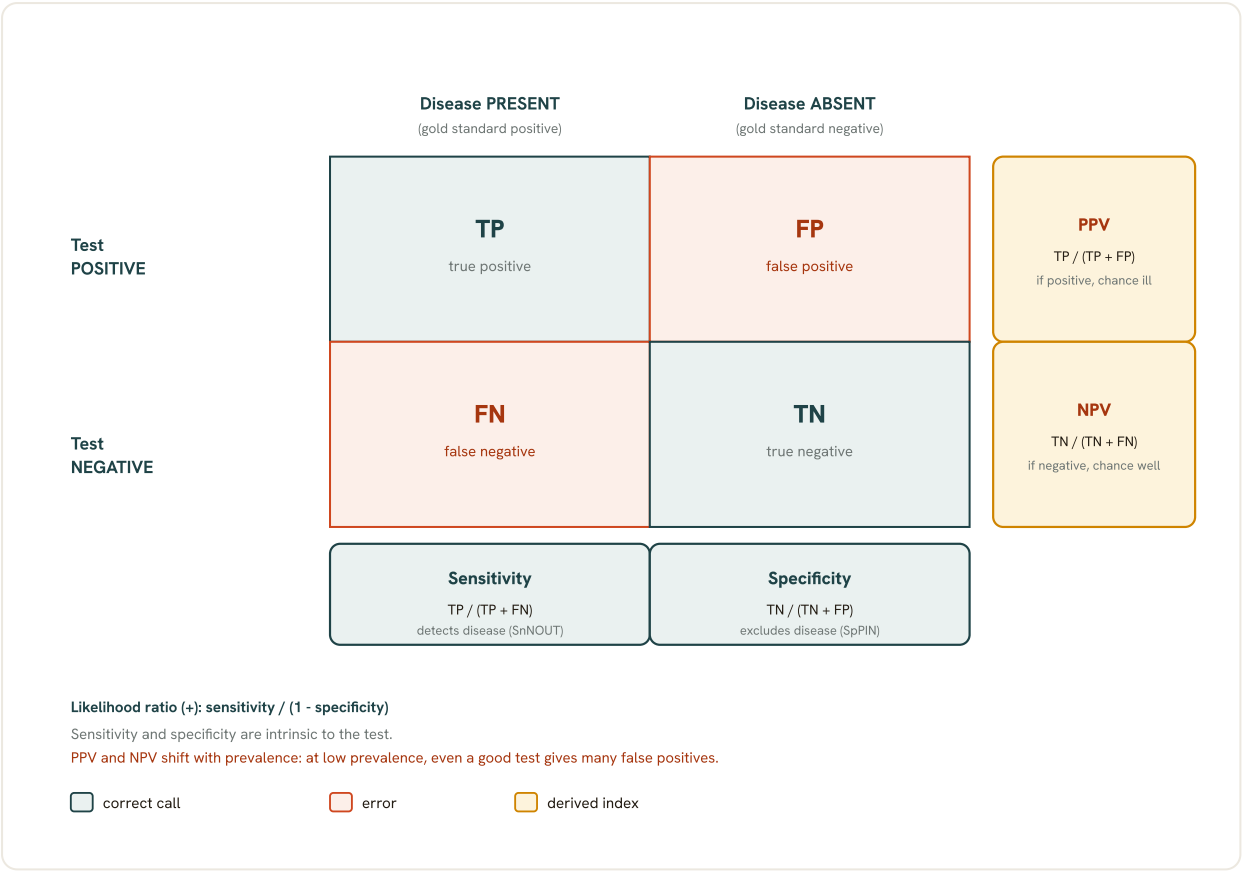


Fig 7.21 The diagnostic 2x2 and its indices. Reading DOWN a column gives the intrinsic properties: sensitivity is the detection rate among the diseased, specificity the correct-negative rate among the well. Reading ACROSS a row gives the predictive values the clinician actually wants: the positive predictive value of a positive test and the negative predictive value of a negative one. The crucial caveat is that sensitivity and specificity stay fixed while the predictive values move with prevalence, which is why a positive screening test in a low-prevalence population is so often a false alarm.

13.1 The 2x2 table: the object everything is read from

Fix the layout before you compute anything. Disease status runs across the top (the gold-standard truth), test result down the side. Populate the four cells with absolute counts, never percentages, and always check that the marginal totals add up before you divide (Bland 2015). Every index below is just one ratio taken from this grid.

TEST RESULT	DISEASE PRESENT	DISEASE ABSENT	ROW TOTAL
Test positive	True positive (a)	False positive (b)	**a + b**
Test negative	False negative (c)	True negative (d)	**c + d**
Column total	a + c (all diseased)	b + d (all non-diseased)	**N**

Columns fix the true state and yield the intrinsic indices (down); rows fix the test result and yield the predictive values (across).

13.2 Sensitivity: detecting the diseased (SnNOUT)

The test's ability to detect disease. Sensitivity (use "sensitivity") is the proportion of truly diseased people the test correctly calls positive: true positives divided by all diseased (Kaplan & Sadock 2024). It is read down the disease-present column, so it is a property of the test in diseased people and does not depend on how common the disease is.

Formula

Sensitivity = a / (a + c) = true positives / all diseased.

Complement

The false-negative rate = c / (a + c) = 1 − sensitivity: the fraction of diseased people the test misses.

Use

A sensitive test misses few cases, so it is what you want for a screening test or for ruling out a dangerous diagnosis.

SnNOUT. A highly **sensitive** test with a **Negative** result rules the disease **OUT**: if a test rarely misses disease, a negative from it makes disease unlikely. Hold the mnemonic SnNOUT (Sackett et al 2000).

RULE **SnNOUT rules out.** A negative result on a highly sensitive test rules the diagnosis out.

13.3 Specificity: clearing the healthy (SpPIN)

The test's ability to exclude disease. Specificity (use "specificity") is the proportion of truly non-diseased people the test correctly calls negative: true negatives divided by all non-diseased (Kaplan & Sadock 2024). It is read down the disease-absent column, so like sensitivity it is intrinsic to the test and independent of prevalence.

Formula

Specificity = d / (b + d) = true negatives / all non-diseased.

Complement

The false-positive rate = b / (b + d) = 1 − specificity: the fraction of healthy people wrongly flagged.

Use

A specific test rarely raises a false alarm, so it is what you want as a confirmatory test after a positive screen.

SpPIN. A highly **specific** test with a **Positive** result rules the disease **IN**: if a test rarely fires falsely, a positive from it makes disease likely. Hold the mnemonic SpPIN (Sackett et al 2000). The two indices trade off against each other along a threshold, which is exactly what an ROC curve plots (covered in the sampling and measurement notes).

13.4 Positive predictive value: trusting a positive result

Of those who test positive, how many are truly diseased. The positive predictive value (use "ppv", "positive predictive") reads across the test-positive row: of everyone the test flagged, what fraction actually has the disease (Kaplan & Sadock 2024). This is the number the clinician and the patient in front of you actually care about, and, crucially, it depends on prevalence.

Formula

PPV = a / (a + b) = true positives / all who test positive.

Reads

Across the top (test-positive) row, so it mixes the test's behaviour with how common the disease is in this population.

Moves with

Prevalence: the rarer the disease, the more the positive column is diluted by false positives, and the lower the PPV.

13.5 Negative predictive value: trusting a negative result

Of those who test negative, how many are truly healthy. The negative predictive value (use "npv", "negative predictive") reads across the test-negative row: of everyone the test cleared, what fraction really is disease-free (Kaplan & Sadock 2024). Like PPV it moves with prevalence, but in the opposite direction: in a low-prevalence setting almost everyone is truly healthy, so a negative result is nearly always right and NPV is high.

Formula

NPV = d / (c + d) = true negatives / all who test negative.

Reads

Across the bottom (test-negative) row.

Moves with

Prevalence, inversely: NPV rises as the disease becomes rarer.

13.6 The worked case: the same test, two prevalences

WORKED EXAMPLE

Setup. Take a test with sensitivity 90% and specificity 90%, and apply it first in a clinic where disease prevalence is 10%. Among 1000 people, 100 are diseased and 900 are not. Sensitivity 90% gives true positives a = 90 and false negatives c = 10. Specificity 90% gives true negatives d = 810 and false positives b = 90.

Verify the intrinsic indices. Sensitivity = a / (a + c) = 90 / 100 = 0.90; specificity = d / (b + d) = 810 / 900 = 0.90. Both reproduce the inputs, as they must.

Predictive values. PPV = a / (a + b) = 90 / (90 + 90) = 90 / 180 = 0.50, so a positive result carries only a 50% chance of true disease even with this good test. NPV = d / (c + d) = 810 / (810 + 10) = 810 / 820 = 0.988, about 99%.

Now drop the prevalence to 1%. Among 10000 people, 100 are diseased and 9900 are not. Sensitivity 90% still gives a = 90 and c = 10; specificity 90% now gives false positives b = 990 and true negatives d = 8910. Sensitivity and specificity are unchanged (90 / 100 and 8910 / 9900 = 0.90). But PPV = 90 / (90 + 990) = 90 / 1080 = 0.083, only about 8%. The very same test, in a low-prevalence population, turns nine out of ten positives into false alarms while its sensitivity and specificity never budge.

50%	8%	90/90
PPV AT 10% PREVALENCE	PPV AT 1% PREVALENCE	SENS/SPEC, UNCHANGED

13.7 Prevalence dependence: what is fixed and what moves

The one distinction the examiner is really testing. Sensitivity and specificity are **intrinsic** properties of the test: they are computed within the diseased and non-diseased columns respectively, so changing the mix of diseased to healthy people leaves them alone (Kaplan &

Sadock 2024, Altman 1991). Predictive values are computed across the test-result rows, which are populated by both true and false cases, so they are hostages to **prevalence** (the pre-test probability). As prevalence falls, PPV falls (a good test still yields many false positives in a low-prevalence screen) and NPV rises; as prevalence climbs toward that of a specialist referral clinic, PPV rises and NPV falls. This is why a screening programme that looks superb in a high-risk clinic can generate a flood of false positives when rolled out to the general population (Wilson & Jungner 1968).

RULE **PPV rises with prevalence; sensitivity and specificity do not.** Predictive values move with the population; intrinsic indices are fixed to the test.

TRAP **A positive is not a confirmation.** A highly sensitive test with a positive result does not confirm disease in a low-prevalence population, where most positives are false; only a specific test's positive rules in.

13.8 The likelihood ratio and Fagan's nomogram

The prevalence-proof way to update probability. The likelihood ratio (use "likelihood ratio") folds sensitivity and specificity into a single number that says how much a given result shifts the odds of disease, and unlike the predictive values it is itself independent of prevalence (Sackett et al 2000, Bland 2015). The positive likelihood ratio, LR+ = sensitivity / (1 − specificity), is how much more likely a positive result is in a diseased than a non-diseased person; the negative, LR− = (1 − sensitivity) / specificity, does the same for a negative result.

Pre-test to post-test. The clinical value of an LR is that it converts a **pre-test** probability (use "pre-test", essentially the prevalence or your clinical suspicion before testing) into a **post-test** probability (use "post-test") after the result is known: post-test odds = pre-test odds x likelihood ratio. Fagan's nomogram (use Fagan for the eponym) draws this as three parallel scales; a ruled line from the pre-test probability through the likelihood ratio reads off the post-test probability without any arithmetic (Fagan 1975). For the worked test above, LR+ = 0.90 / (1 − 0.90) = 0.90 / 0.10 = 9, and LR− = (1 − 0.90) / 0.90 = 0.10 / 0.90 = 0.11. A rough reading: an LR+ above 10 or an LR− below 0.1 shifts probability decisively, while an LR near 1 barely moves it.

13.9 Hold the picture together

Down the columns for the test, across the rows for the patient. Sensitivity and specificity answer "how good is this test?" and are read down the true-state columns; predictive values answer "what does this result mean for this patient?" and are read across the result rows, dragging prevalence in with them; the likelihood ratio is the bridge that carries a pre-test probability to a post-test probability regardless of prevalence (Kaplan & Sadock 2024, Sackett et al 2000). If you can place a formula on each margin of the 2x2 and say in one breath which side prevalence touches, you have the topic.

HOLD THIS

Sensitivity and specificity are intrinsic to the test and do not move with prevalence; PPV and NPV do, so a positive result on even a good test means little in a low-prevalence population (SnNOUT rules out, SpPIN rules in).

MNEMONIC

SnNOUT and SpPIN

A **Sn**sitive test, when **N**egative, rules the disease **OUT** (few misses, so a clear negative is trustworthy). A **Sp**ecific test, when **P**ositive, rules the disease **IN** (few false alarms, so a positive is trustworthy).

PEARL

Predictive values are what the patient hears, but they are borrowed from the population, not the test. Quote sensitivity and specificity to describe a test in the literature; compute PPV and NPV only for the specific prevalence you are working in; quote the likelihood ratio when you want a prevalence-proof measure to carry across settings.

GOOD TO REMEMBER

- **Sensitivity:** the proportion of diseased people the test calls positive; use it when you must not miss cases (screening, ruling out); sensitivity = a / (a + c) = true positives / all diseased; a Negative on a sensitive test rules OUT (SnNOUT); intrinsic, does not move with prevalence.
- **Specificity:** the proportion of healthy people the test calls negative; use it to confirm disease and avoid false alarms; specificity = d / (b + d) = true negatives / all non-diseased; a Positive on a specific test rules IN (SpPIN); intrinsic, does not move with prevalence.
- **Positive predictive value (PPV):** of those testing positive, the fraction truly diseased; use it to interpret a positive result in a given population; PPV = a / (a + b); rises with prevalence.
- **Negative predictive value (NPV):** of those testing negative, the fraction truly healthy; use it to interpret a negative result; NPV = d / (c + d); falls as prevalence rises.
- **Likelihood ratio (LR):** how much a result shifts the odds of disease, independent of prevalence; use it with Fagan's nomogram to move pre-test to post-test probability; LR+ = sensitivity / (1 − specificity), LR− = (1 − sensitivity) / specificity.
- **Prevalence (pre-test probability):** the proportion diseased before testing; recognise it as the lever that moves PPV and NPV while leaving sensitivity and specificity untouched; a low-prevalence screen yields many false positives even with a good test.

The prevalence figures used in a real screening decision come from population studies, so a test that performs well in a specialist clinic must be re-appraised at general-population prevalence before it is offered as a screen (Wilson & Jungner 1968); the prevalence of specific disorders is set out in the clinical chapters of Paper II, and the reliability and validity of a psychometric instrument itself, as distinct from these diagnostic indices, are covered in the Psychometry, Assessment and Descriptive Psychopathology notes.

14 · Statistical inference: p-values, confidence intervals, errors and power

Every significance test hands back two numbers, and the whole of applied statistical inference is the discipline of reading them without over-reading them. The first is the **p-value**, a verdict on chance; the second, ideally beside it, is the **confidence interval**, a statement of where the truth plausibly lies. The examiner is far less interested in whether you can compute either than in whether you know exactly what each does and does not mean, because the classic errors here are errors of interpretation, not arithmetic (Johnstone et al 2010, Bland 2015). Master four ideas and the topic is yours: what a p value actually measures, why the confidence interval is the more honest companion, the two ways an inference can be wrong, and the arithmetic of designing a study large enough to give a true effect a fair chance of being seen.

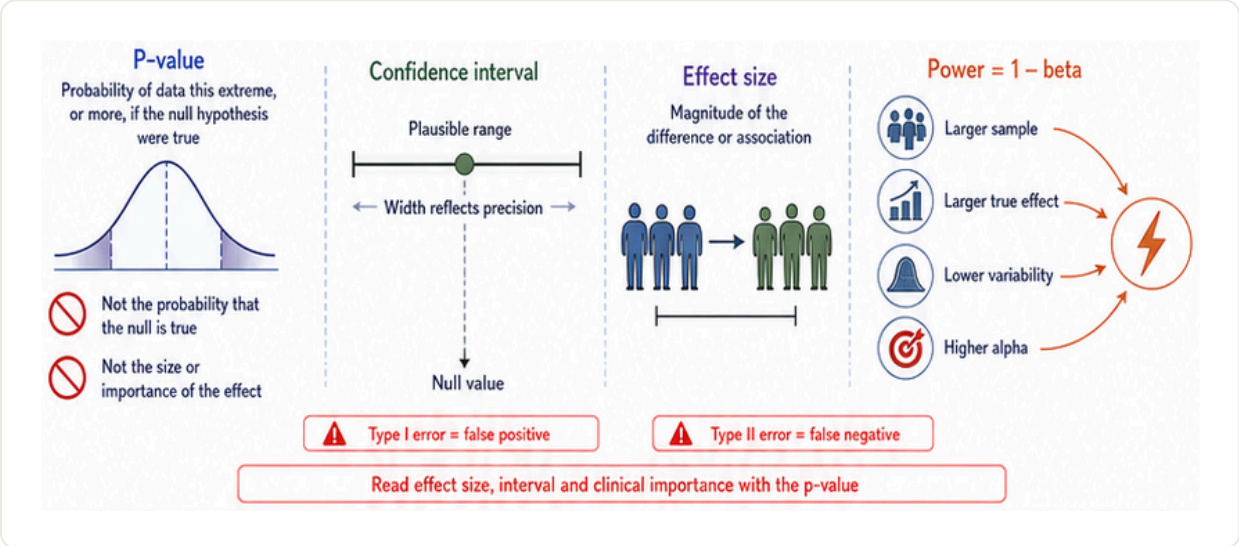


Fig 7.22 Inference: p-value, confidence interval, effect and power.

The **throughline** is the null hypothesis. A test assumes there is no difference (or no association) in the population, then asks how surprising the observed data would be under that assumption. The p value quantifies the surprise; the confidence interval turns the same information into a range of plausible effects. Errors and power then describe what can go wrong and how to guard against it before a single patient is recruited.

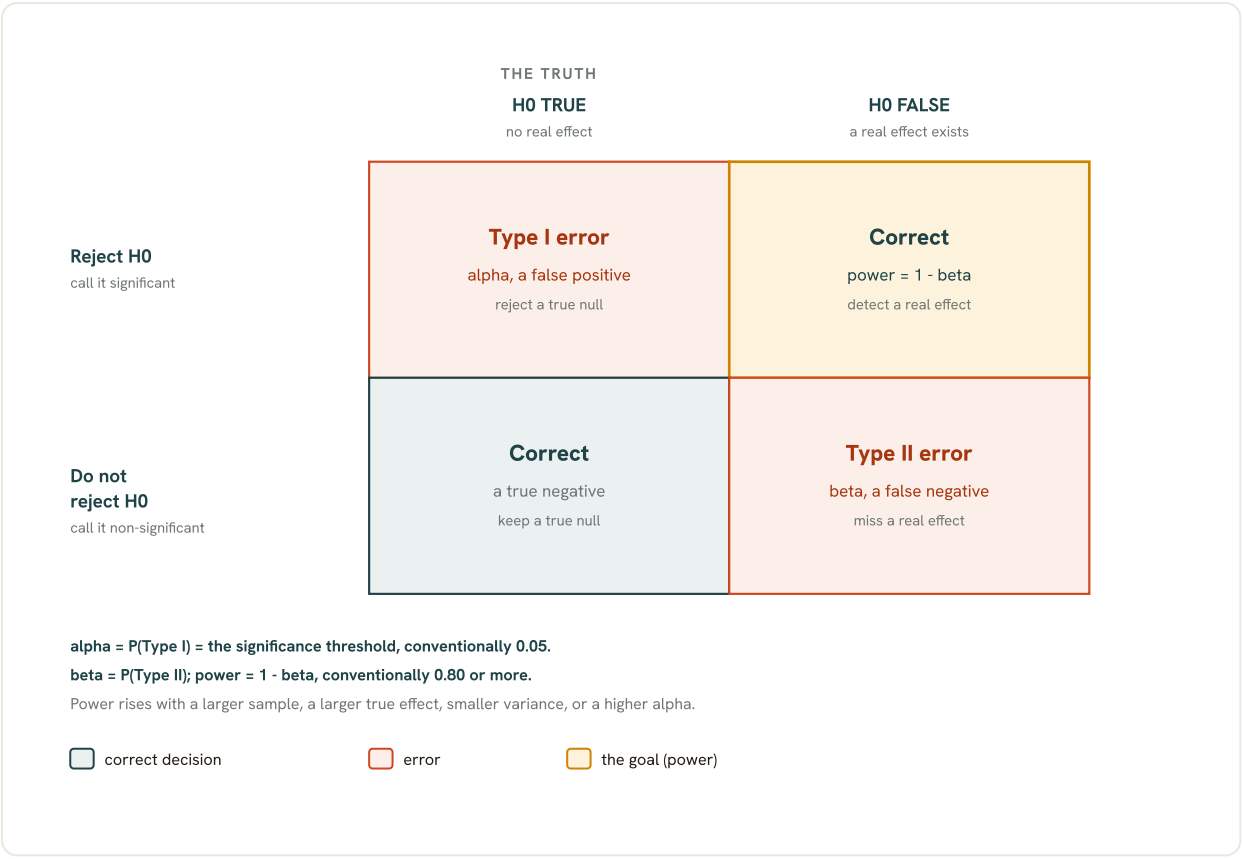


Fig 7.23 Type I and type II error. A test can go wrong two ways. Rejecting a null that is actually true is a type I error, a false positive, and its probability is alpha, the significance level we set. Failing to reject a null that is actually false is a type II error, a false negative, and its probability is beta. Power, the ability to detect a real effect, is one minus beta, and an underpowered study is the commonest reason a true effect is missed.

14.1 The p-value: what it is

A probability about the data, given the null. The p-value (also written p value) is the probability of obtaining the observed result, or one more extreme, if the null hypothesis of no true difference were correct (Johnstone et al 2010, Altman 1991). It is a measure of how compatible the data are with the null: a small p value says the data would be a rare fluke under the null, so we doubt the null. It is emphatically a probability about the data assuming the null is true, not a probability about the null itself.

14.2 The alpha threshold and significance

Where the line is drawn. Before the study, an investigator fixes a significance threshold, alpha, the p value at or below which the null will be rejected. By convention alpha = **0.05** (Johnstone et al 2010, Bland 2015). A result with p at or below 0.05 is called statistically significant: under a true null we would see a result this extreme less than 1 time in 20, which we treat as evidence against the null. The 0.05 line is a convention, not a law of nature, and stricter thresholds (0.01, or a Bonferroni-adjusted value across many tests) are used where false positives are costly. Alpha is chosen by the investigator; the p value is computed from the data.

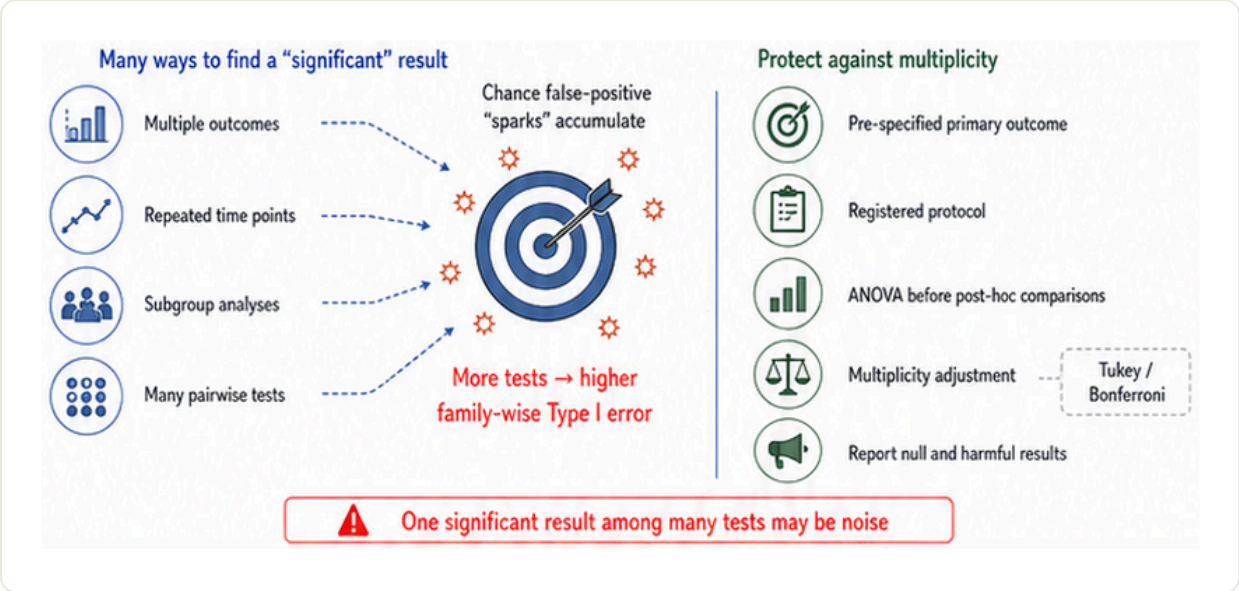


Fig 7.24 Multiplicity and selective reporting.

RULE **Set alpha first, then read p.** Alpha is your pre-declared tolerance for a false positive; the p value is what the data return. Compare the one to the other, never move the goalposts after seeing the data.

14.3 What a p-value is NOT

The three misreadings the examiner hunts for. A p value is not the probability that the null hypothesis is true, and it is not the probability that the result arose by chance in any absolute sense; it is conditional on the null being true (Altman 1991, Sterne & Davey Smith 2001). Nor does a p value measure the size or the importance of an effect: a vanishingly small p value can attach to a trivial difference if the sample is huge, and a non-significant p can hide a large effect measured imprecisely. And a non-significant result (p above 0.05) is not proof that the null is true, absence of evidence is not evidence of absence. Hold these three: p is not the probability the null is true, p is not the effect size, and a large p does not prove no effect.

TRAP **p is not P(null is true).** A p of 0.03 does not mean a 3% chance the null holds; it means data this extreme would occur 3% of the time if the null held. The direction of the conditional is the whole trap.

14.4 The confidence interval: the plausible range

From a yes/no verdict to a range of effects. A confidence interval is the range of plausible values within which the true population value is likely to lie, given the data (Johnstone et al 2010, Altman 1991). A **95 percent CI** is the interval such that, over many repeated samples, 95% of the intervals so constructed would contain the true value; loosely, we can be 95 percent confident the true effect lies inside it. Where the p value gives a bare significant/non-significant verdict, the CI shows both the best estimate (the point estimate at its centre) and its precision (its width). A trial that finds chlorpromazine beats placebo with a relative risk of 2.3 (95% CI 1.2 to 3.5) tells you not only that the effect is real but that the true effect plausibly ranges from modest to large (Johnstone et al 2010).

14.5 Reading significance off a confidence interval

The no-effect value inside the interval. A CI carries the significance test within it, read against the value of no effect. For a **difference** of means (or any subtracted quantity) the no-effect value is **0**: if the 95% CI for the difference crosses 0, the result is non-significant at the 0.05 level. For a **ratio** measure, a relative risk (RR) or odds ratio (OR), the no-effect value is **1** (equal risk, equal odds): if the 95% CI for the ratio crosses 1, the result is non-significant (Johnstone et al 2010, Altman 1991). So an RR of 2.3 with CI 1.2 to 3.5 is significant (the interval sits wholly above 1), whereas an OR of 1.4 with CI 0.9 to 2.1 is not (the interval straddles 1). The CI is more informative than the p value alone because it delivers the significance verdict and the effect size and its precision in a single line.

RULE **Cross 0 for a difference, cross 1 for a ratio.** A 95% CI for a difference that includes 0, or for an RR/OR that includes 1, means the result is not statistically significant.

14.6 Type I and Type II error

The two ways an inference can be wrong. Because inference is a decision under uncertainty, two mistakes are possible against the two states of the truth (Johnstone et al 2010, Bland 2015).

Type I error

A false positive: rejecting a null hypothesis that is actually true, that is, declaring a difference that does not exist. Its probability is alpha, so setting alpha at 0.05 caps the false-positive rate at 5%.

Type II error

A false negative: failing to reject a null hypothesis that is actually false, that is, missing a difference that truly exists. Its probability is termed beta.

The 2x2 of truth against decision. Cross the true state of the world (null true, or null false) with the decision taken (do not reject, or reject) and four cells result: two correct (a true negative, and a true positive), and the two errors above. The type I error sits where a true null is rejected; the type II error where a false null is retained. Tightening alpha to reduce type I error, all else equal, raises beta and so raises type II error: the two trade off against each other.

14.7 Power and its four drivers

The chance of finding a real effect. The power of a test is 1 minus beta, the probability that it will detect a true effect of a given size when one genuinely exists (Tasman et al 2015, Johnstone et al 2010). Colloquially, power is the chance of finding what you are looking for. The convention is to design for power of **80** percent or more, meaning at most a 20% chance of missing a true effect (beta = 0.2). Power is fixed by four interlocking quantities, and moving any one moves power:

Alpha

The significance threshold. A stricter (smaller) alpha lowers power, all else equal.

Sample size

The number of participants. A larger sample sharpens the estimate and raises power; too small a sample is the commonest reason a true effect is missed.

Effect size

The magnitude of the true difference sought. Larger effects are easier to detect, so they need smaller samples.

Variance

The scatter of the data. Less variability sharpens the estimate and raises power.

Fix any four of alpha, power, effect size, variance and sample size and the fifth is determined, which is exactly how a sample-size calculation works.

TRAP **A non-significant result may be an underpowered study.** Failure to reject the null can mean there is no effect, or that the study was too small to see one. The two are not the same, and the p value alone cannot tell them apart.

14.8 Effect size and Cohen's d

Standardising the size of a difference. An effect size expresses the magnitude of a difference in units that are comparable across studies and scales, independent of sample size (New Oxford Textbook 2020). For a difference between two means the standard measure is cohen's d, the difference in means divided by the pooled standard deviation. Cohen's conventional benchmarks are small = **0.2**, medium = **0.5**, and large = **0.8** (New Oxford Textbook 2020). For a correlation, the effect size is r itself (or r-squared, the shared variance). Effect size is the input that most strongly governs the sample a study needs: a large expected effect can be caught with few participants, a small one demands many.

14.9 Sample size, the MCID and the power calculation

Sizing the study before it runs. A sample size calculation is performed at the design stage to find the number of participants needed to give a study adequate power (Johnstone et al 2010, Altman 1991). Its inputs are the other four quantities: the chosen alpha (usually 0.05), the target power (usually 0.8), the smallest effect worth detecting, and an estimate of the variance or event rate (from pilot data or the literature). Feed these in and the power calculation returns the required n; equivalently, given a fixed n, it returns the power to detect a stated effect. The effect fed in should be the minimum clinically important difference, the smallest change that would matter to a patient or alter management, not merely the smallest that could be made statistically significant. Powering a trial for a statistically detectable but clinically trivial difference wastes participants; powering it for the minimum clinically important difference sizes it to answer a question worth asking.

0.05	80%	0.2 / 0.5 / 0.8
ALPHA	POWER	COHEN D SMALL/MED/LARGE

14.10 A worked read: p, CI and the four cells together

WORKED EXAMPLE

Reading a trial result. A relapse-prevention trial reports a relative risk of relapse on active drug versus placebo of RR = 2.3, 95% CI 1.2 to 3.5, p = 0.01 (Johnstone et al 2010). Read it in three moves. First the p value: under a true null of no difference, a result this extreme would occur about 1 time in 100, below alpha 0.05, so we reject the null and call it significant. Second the confidence interval: the 95% CI runs 1.2 to 3.5 and does not cross the ratio no-effect value of 1, which confirms significance, and its width tells us the true effect plausibly ranges from modestly (1.2) to substantially (3.5) raised, an imprecise estimate a larger sample would tighten. Third the error frame: in rejecting the null we risk a type I error, capped at alpha = 0.05; had the CI instead been 0.8 to 4.1 (crossing 1, non-significant) we could not conclude no effect, because a small, underpowered study courts a type II error of missing a real difference.

A difference, not a ratio. Had the outcome been a mean symptom-score difference of 2.0 points with 95% CI −0.5 to 4.5, the no-effect value is 0, the interval crosses it, and the result is non-significant, whatever the point estimate suggests.

COMMON TRAP

Statistical significance is not clinical importance. A trial of 10,000 patients can return p < 0.001 for a 1-point difference on a 60-point depression scale, a difference no patient would notice; conversely a genuinely useful effect in a small study may miss significance purely for want of power. Always read the effect size and its confidence interval, not the p value alone, and anchor the judgement to the minimum clinically important difference.

MNEMONIC

Type I is the FALSE ALARM (reject a true null); Type II is the MISS (retain a false null).

A smoke alarm going off with no fire is a type I error (false positive, probability alpha); a fire the alarm sleeps through is a type II error (false negative, probability beta). Power (1 minus beta) is the alarm actually sounding for a real fire.

HOLD THIS

A 95% CI that crosses 0 (for a difference) or 1 (for a ratio) is non-significant; type I error = alpha = 0.05 (false positive), type II error = beta (false negative), power = 1 minus beta, conventionally 80% or more.

GOOD TO REMEMBER

- **p-value:** the probability of the observed data or more extreme if the null were true; use it to judge compatibility with the null; the significance threshold is alpha = 0.05.
- **Confidence interval (95% CI):** the plausible range for the true population value; use it instead of the p value alone because it shows effect size and precision; non-significant if it crosses 0 (difference) or 1 (ratio RR/OR).
- **Type I error:** a false positive, rejecting a true null; guarded by the significance threshold; its probability is alpha (conventionally 0.05).
- **Type II error:** a false negative, retaining a false null; arises chiefly from too small a sample; its probability is beta.
- **Power:** the ability to detect a true effect; design for it before recruiting; power = 1 minus beta, conventionally 80% or more.
- **Effect size (Cohen's d):** the standardised magnitude of a difference; use it to compare across studies and drive sample size; d = 0.2 small, 0.5 medium, 0.8 large.
- **Sample size / power calculation:** the design-stage arithmetic sizing a study; use it to secure adequate power; its inputs are alpha, power, the minimum clinically important effect size, and the variance.

For the derivations and worked confidence-interval formulae see Altman (1991) and Bland (2015); the interpretation traps are set out plainly in Sterne & Davey Smith (2001). Where these inference tools drive the choice of a specific significance test, that selection is treated in the sibling tests-of-significance material; twin, family and adoption designs that generate the effect estimates fed into these calculations are covered in the Psychiatric Genetics notes, and the reliability and validity of the measuring instrument itself (as distinct from a study's statistical validity) belong to the Psychometry, Assessment and Descriptive Psychopathology notes.

15 · Survival analysis, NNT and ROC

Three tools cluster here because each squeezes a clinically useful single number out of a slightly awkward kind of data. Survival analysis handles data where the outcome is **time to an event** and some patients have not had the event when the study ends. The number needed to treat converts a trial's risk difference into a bedside count of patients. The ROC curve measures how well a diagnostic test separates the sick from the well across every possible cut-off. The examiner tests interpretation, not derivation: what the curve, the count and the area under the curve mean, and the one trap that goes with each (Kaplan & Sadock 2024, Bland 2015).

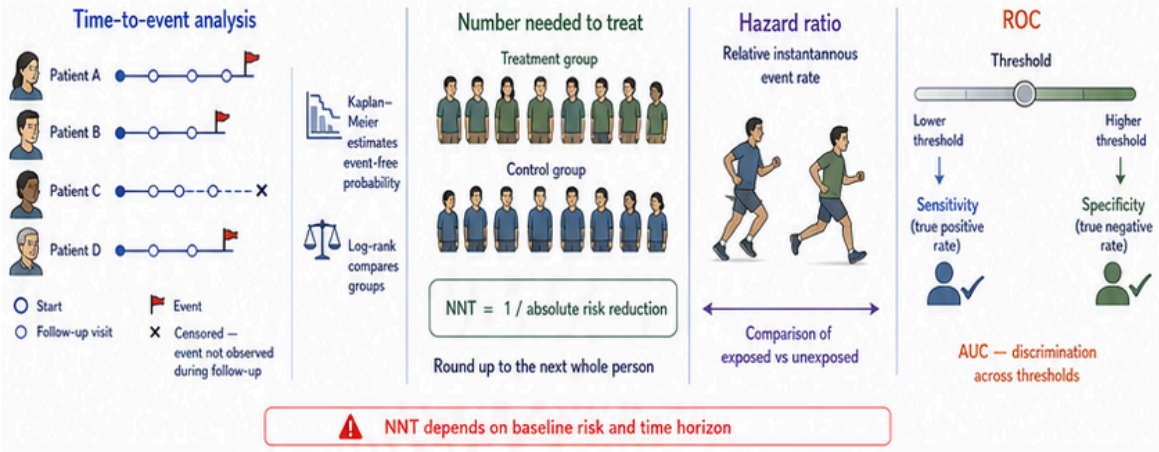


Fig 7.25 Time-to-event, NNT and discrimination.

Why time-to-event needs its own method. If you simply compared the proportion relapsed at two years between two arms, you would throw away everyone who left the study early or who had not relapsed at the cut-off. Survival analysis keeps them by treating their incomplete follow-up as partial information rather than as a missing value to be discarded (Kaplan & Sadock 2024).

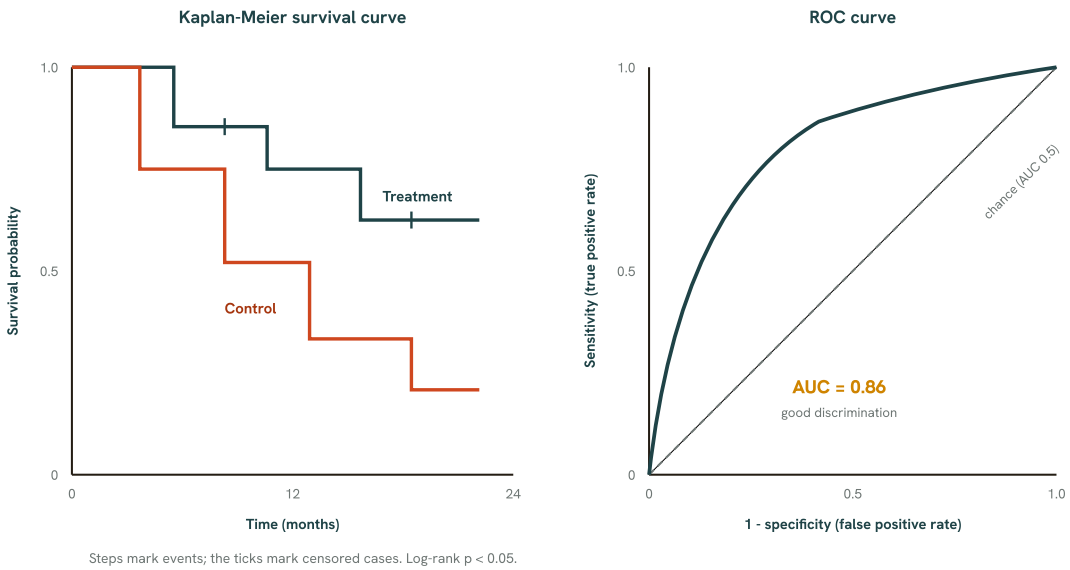


Fig 7.26 Survival and ROC curves. The Kaplan-Meier curve plots the probability of remaining event-free over time, stepping down at each event, with ticks for censored cases; two curves are compared with the log-rank test and summarised by the hazard ratio. The ROC curve plots sensitivity against one minus specificity across every cut-off of a test: the further it bows toward the top-left corner the better, and the area under it (AUC) grades overall discrimination from 0.5 (chance) to 1.0 (perfect).

15.1 Time-to-event data and censoring

What survival data are. Many psychiatric questions live in the time domain: time to onset of drug effect, time in hospital, time to remission or to relapse (Kaplan & Sadock 2024). These are generically **time-to-event** or survival variables; the original event studied was time to death,

which gives the field its name. The two things recorded for each subject are the length of follow-up and whether the event had occurred by the end of it.

Censoring. A subject is censoringed (a censored observation) when the event has not occurred by the time observation stops: the study ends, or the patient is lost to follow-up, or withdraws (Kaplan & Sadock 2024). We know only that their true time-to-event exceeds the time we watched them. This is right-censoring, the common form. Crucially, a censored patient is not the same as a dropout to be deleted: they contribute information for the whole period they were observed, and are only removed from the risk set after the point at which we lose sight of them.

TRAP **Censoring is not ignored loss to follow-up.** Censoring is not the same as loss to follow-up being ignored: Kaplan-Meier accounts for it by using each censored case up to the moment it is censored, then dropping it from the denominator, rather than discarding it or coding it as an event.

15.2 The Kaplan-Meier survival curve

The step curve everyone draws. The kaplan-meier estimator is the nonparametric way to draw the survival function from the data: it makes no assumption about the shape of the underlying distribution (Kaplan & Sadock 2024). It splits time at each point where an event actually occurs and, at each such point, multiplies the running survival probability by the proportion of those still at risk who survived that instant. The probability of surviving beyond time t is therefore the product of the conditional survival probabilities across all preceding intervals, which is why it is a step function that drops only when an event happens, not at fixed calendar intervals.

Reading the curve. The y-axis is the cumulative proportion still event-free; the curve starts at 1.0 and steps down. A small vertical tick on the curve marks a **censored** case (a patient still event-free when last seen). The height where the curve crosses 0.5 gives the **median survival time**, the single summary statistic most often quoted (Kaplan & Sadock 2024). Flatter curve means better survival.

15.3 Comparing two curves: the log-rank test

Is the gap between two curves real? Two survival curves, for example two treatment arms, are compared with the log-rank test, the most commonly used nonparametric comparison (Kaplan & Sadock 2024, Bland 2015). At every event time it compares the number of events observed in each group with the number expected if the two curves shared one underlying survival experience, then sums those observed-minus-expected contributions across all event times into a single chi-square-type statistic. Its null hypothesis is that the two survival distributions are identical. It uses the whole curve, not survival at one arbitrary time-point, and weights every event time equally (the related Gehan and generalized Wilcoxon tests weight early events more).

RULE **Curves to log-rank, effect size to Cox.** Use the log-rank test to ask whether two Kaplan-Meier curves differ; use Cox regression to put a number, the hazard ratio, on how much they differ and to adjust for covariates.

15.4 The hazard ratio from Cox regression

The instantaneous relative risk. The hazard rate is the probability of the event happening at time t given the subject has survived event-free up to t: an instantaneous risk. Cox proportional hazards regression models this time-to-event outcome against covariates without assuming a distributional shape (it is semiparametric), and yields the hazard ratio (Kaplan & Sadock 2024). The hazard ratio is the ratio of the hazard in one group to the hazard in the other: read it like a relative risk that applies at every instant. A hazard ratio of **1.0** means no difference in the rate of events; above 1 the exposure or treatment raises the instantaneous event rate, below 1 it lowers it. The name comes from the **proportionality assumption**: the model assumes the two hazards stay in constant proportion over time (Kaplan & Sadock 2024).

15.5 The number needed to treat

From a risk difference to a headcount. The number needed to treat (nnt) translates a trial result into a clinical unit a resident can quote at the bedside: how many patients must receive the treatment for one extra good outcome, compared with the control (Cooper & Jacoby 2013, Bland 2015). It is the reciprocal of the **absolute risk reduction** (ARR), the difference between the control event rate and the experimental event rate:

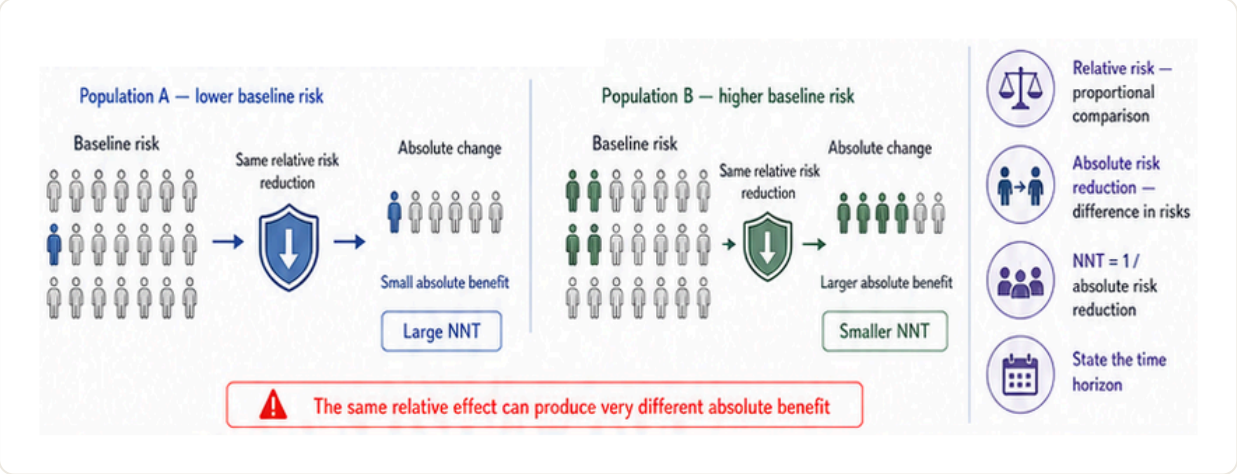


Fig 7.27 Relative effects need absolute context.

Absolute risk reduction (ARR)

Control event rate minus experimental event rate, expressed as a proportion (a difference in the probability of the bad outcome).

Number needed to treat (NNT)

NNT = 1 / ARR, rounded up to the next whole number; the count of patients to treat to prevent one extra bad outcome.

Number needed to harm (NNH)

The mirror image: 1 / absolute risk increase in an adverse outcome; the count of patients to treat before one extra harm occurs.

Direction of merit. A large NNT means many patients must be treated for a single benefit, so the treatment is weak; a small NNT means the benefit comes cheaply, so the treatment is strong. As a rough guide an NNT under **10** denotes a clinically useful treatment effect, and NNTs for

psychiatric interventions are broadly comparable to those in general medicine (Cooper & Jacoby 2013). NNH is best large (harm is rare); NNT is best small.

RULE **Smaller NNT, stronger treatment.** A smaller NNT is a stronger treatment: fewer patients treated per good outcome gained. A small NNT and a large NNH together is the ideal profile.

15.6 A worked NNT

WORKED EXAMPLE

CBT for residual depression (Paykel et al 1999, via Cooper & Jacoby 2013). Patients with residual depressive symptoms were randomised to clinical management alone or clinical management plus cognitive behaviour therapy. Over follow-up the relapse rate was **47%** in the clinical-management (control) arm and **29%** in the CBT arm. The absolute risk reduction is the difference in these relapse rates: ARR = 47% − 29% = **18%** (0.18). The NNT is the reciprocal: NNT = 1 / 0.18 = 5.56, rounded up to **6**. Reading: about six patients with residual depressive symptoms must be treated with CBT to prevent one extra relapse. Since 6 is under 10, this is a clinically worthwhile effect.

15.7 The ROC curve

A test across all its thresholds. A continuous diagnostic test (a rating-scale score, a biomarker level) gives a different sensitivity and specificity at every cut-off you might pick. The roc (receiver operating characteristic) curve plots this whole family of trade-offs on one graph: the **sensitivity** (the true positive rate) on the y-axis against **1 minus specificity** (the false positive rate) on the x-axis, traced across all thresholds (Altman 1991, Bland 2015). Lowering the cut-off catches more true cases (sensitivity rises) at the cost of more false alarms (specificity falls), so the curve sweeps from the bottom-left corner up to the top-right. A test with no discriminating power sits on the diagonal from (0,0) to (1,1); a good test bows up towards the top-left corner, where sensitivity is high and false positives are few.

15.8 The area under the curve (AUC)

One number for overall discrimination. The auc, the area under the ROC curve, summarises the whole curve as a single index of discrimination: the probability that the test will score a randomly chosen affected patient higher than a randomly chosen unaffected one (Altman 1991). Its scale is anchored at two points a resident must hold: an AUC of **0.5** is the diagonal, chance-level discrimination (no better than a coin toss), and an AUC of **1.0** is a perfect test that separates the two groups completely. In between, higher is better, so AUC lets you rank competing tests on one axis.

0.5	1.0	< 10
AUC AT CHANCE	AUC PERFECT TEST	NNT: USEFUL EFFECT

15.9 Choosing a cut-off from the curve

Where to set the threshold. The ROC curve also guides the practical choice of a single operating cut-off (Altman 1991, Bland 2015). The point closest to the top-left corner gives the best overall

balance of sensitivity and specificity, but the clinically right cut-off depends on the costs of the two error types. For a screening test, where missing a case is worse than a false alarm, slide the cut-off to favour **sensitivity** (accept more false positives); for a confirmatory test, where a false positive is costly, favour **specificity**. The curve does not choose for you; it shows the trade-off you are buying at each threshold. The reliability and validity of the underlying instrument itself are covered in the Psychometry, Assessment and Descriptive Psychopathology notes.

TRAP **The diagonal is not a bad test drawn badly.** An ROC curve sitting on the 45-degree line (AUC 0.5) is not an error of plotting: it is a test with zero discriminating ability. Only a curve bowing above the diagonal carries diagnostic information.

HOLD THIS

Kaplan-Meier steps down and keeps censored cases (median survival where it hits 0.5); log-rank compares two curves, Cox gives the hazard ratio (1.0 = no effect); NNT = 1 / ARR and smaller is stronger; ROC plots sensitivity against 1 minus specificity, and AUC runs 0.5 (chance) to 1.0 (perfect).

GOOD TO REMEMBER

- **Survival analysis:** the family of methods for time-to-event data with censoring; use when the outcome is time until an event and some subjects have not had it by study end; the key summary is the median survival time.
- **Censoring:** incomplete follow-up where the event has not yet occurred; use it (do not delete it) whenever a subject is lost, withdraws, or the study ends event-free; it contributes to the risk set only up to the point of censoring.
- **Kaplan-Meier curve:** the nonparametric step estimate of the survival function; use to picture and summarise survival in one or more groups; it drops only at observed event times and marks censored cases with ticks.
- **Log-rank test:** the nonparametric test comparing two or more survival curves; use to ask whether the curves differ overall; null hypothesis is identical survival distributions, and it weights all event times equally.
- **Hazard ratio (Cox regression):** the ratio of instantaneous event rates between groups from a semiparametric model; use to quantify and covariate-adjust the difference between curves; a hazard ratio of 1.0 means no difference.
- **Number needed to treat (NNT):** the count of patients treated per one extra good outcome; use to translate a trial's ARR into clinical terms; NNT = 1 / absolute risk reduction, and under 10 is a useful effect.
- **Number needed to harm (NNH):** the count of patients treated before one extra adverse event; use to size the harm of a treatment; NNH = 1 / absolute risk increase, and larger is safer.
- **ROC curve:** the plot of sensitivity against 1 minus specificity across all thresholds; use to show a continuous test's sensitivity-specificity trade-off and to pick a cut-off; the best-balance point sits nearest the top-left corner.
- **AUC (area under the ROC curve):** a single index of overall discrimination; use to rank or compare diagnostic tests; it runs from 0.5 (chance) to 1.0 (perfect).

For survival methods and Cox regression see Kaplan & Sadock (2024); for ARR, NNT and NNH see Cooper & Jacoby (2013); for ROC and AUC see Altman (1991) and Bland (2015). Genetic

time-to-onset study designs are treated in the Psychiatric Genetics notes, and the disorder-specific efficacy figures these tools summarise appear in the clinical chapters of Paper II.

Epidemiology

16 · Measures of disease frequency and association

Epidemiology begins with two questions and answers each with a number: how common is a disorder, and what raises the chance of getting it. The first question is answered by the **measures of disease frequency**, of which the two workhorses are incidence and prevalence; the second by the **measures of association**, which quantify how much an exposure changes the risk of an outcome (Kaplan & Sadock 2024). The examiner reliably asks you to separate a count of new cases from a count of existing cases, to know which measure of association comes from which study design, and to read an association off a 2x2 table without confusing risk with odds. Get the incidence-versus-prevalence distinction wrong and every downstream inference about causation and burden goes with it.

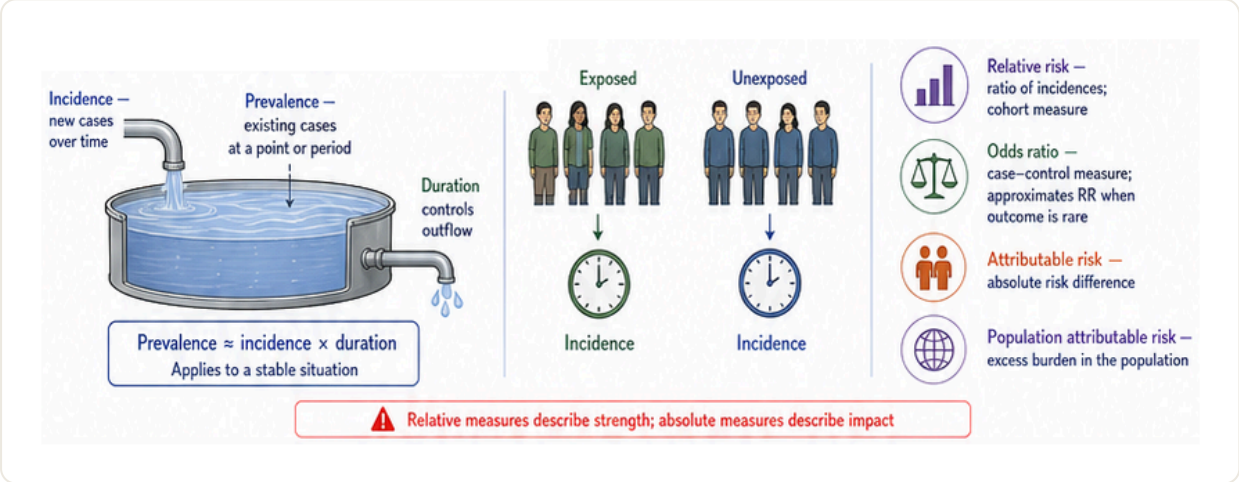


Fig 7.28 Disease frequency and association.

This material owns the measures themselves and the national numbers; the **epidemiology of specific disorders** (the prevalence figures for schizophrenia, mood disorders, and the rest) is developed in the clinical chapters of Paper II. Here we keep the tools, verified formula by formula, and the study design each tool is native to.

16.1 Prevalence: the stock of existing cases

Existing cases in a population at a point or over a period. Prevalence (use "prevalence") is a ratio: the number of people who have the disorder divided by the number in the population, over a designated time window (Kaplan & Sadock 2024). It is a snapshot of the burden of disease, so it counts both old and new cases indiscriminately and depends heavily on how long the disorder lasts. Three elements fix any prevalence estimate: the case definition, the target population, and the time.

Point prevalence

Point prevalence (use "point prevalence"): the proportion of a population who have the disorder at a single specified point in time.

Period prevalence

Period prevalence (use "period prevalence"): the proportion who have the disorder at any time within a stated interval (1-month, 1-year, or lifetime prevalence).

Lifetime prevalence

The proportion who have had the disorder at any point in their lives; useful for risk-factor studies but subject to recall bias.

For mental disorders, point prevalence is hard to pin down because symptoms wax and wane daily, so the **1-month** and **1-year** period prevalences are used in practice; the 1-year figure is what service planners multiply by the population to forecast caseload (Kaplan & Sadock 2024).

16.2 Incidence: the flow of new cases

New cases arising over a period, per population at risk. Incidence (use "incidence") counts only fresh cases: its numerator is the number of new events arising in a specified time period, and its denominator is the population at risk of having that event (Kaplan & Sadock 2024). People who already have the disorder at the start are removed from the denominator because they are, by definition, no longer at risk of developing it. Incidence is the measure of choice for a first-onset question, for example the number of new cases of post-traumatic stress disorder after a natural disaster.

Cumulative incidence

Cumulative incidence (use "cumulative incidence"): new cases divided by the number of disease-free people at risk at the start of the period; a proportion (risk), so it needs a stated time period to mean anything.

Incidence rate

Incidence rate (use "incidence rate"): new cases divided by the total person-time at risk; a true rate with units of per person-year, robust to people entering and leaving the population.

Person-time

The sum, over all individuals, of the time each was actually at risk until they became a case or were lost to follow-up; the denominator of the incidence rate.

Because most mental disorders are rare per year, estimating incidence needs large populations at risk followed for long periods, and most incidence rates are quoted over a 1-year window (Kaplan & Sadock 2024).

RULE **Incidence is a rate of the new, prevalence is a stock of the existing.** Ask "new cases over a period" for incidence, "all cases at a moment" for prevalence.

16.3 The bridge: prevalence is roughly incidence times duration

The equation that ties the two frequency measures together. Prevalence, incidence, and mean duration are mathematically related: the prevalence of a disorder is proportional to its incidence multiplied by its mean duration, written **prevalence is roughly incidence times duration** (P is

proportional to I x d) for a stable, low-prevalence condition (Kaplan & Sadock 2024). The consequence is the single most examined trap in this topic. Prevalence reflects not only how many new cases appear but also how long cases stay ill, so anything that lengthens duration inflates prevalence even when incidence is flat.

TRAP **Prevalence rises with longer illness duration even if incidence is unchanged.** A treatment that prolongs life without curing (the AIDS example) raises prevalence; a cure lowers it. Rising prevalence never by itself proves rising incidence.

COMMON TRAP

Do not read a climbing prevalence as more people falling ill. Because prevalence is roughly incidence times duration, better survival or chronification lifts prevalence with incidence untouched. When you need to tell a genuine rise in new cases apart from improved survival, you must use an incidence measure, not prevalence.

16.4 From frequency to association: the 2x2 table

Every measure of association is one ratio read off this grid. The **measures of association** compare disease frequency between an exposed and an unexposed group, and all of them are computed from a single 2x2 table that cross-tabulates exposure against outcome (Kaplan & Sadock 2024). Fix the layout first, populate the four cells with absolute counts, and check the marginal totals before you divide. In the standard orientation the exposed row holds cells a and b, the unexposed row cells c and d.

GROUP	DISEASE PRESENT	DISEASE ABSENT	ROW TOTAL
Exposed	a	b	**a + b**
Unexposed	c	d	**c + d**

Risk in the exposed reads across the top row, a / (a + b); risk in the unexposed reads across the bottom row, c / (c + d).

16.5 Relative risk: the ratio of two incidences, from a cohort

How many times more likely the exposed are to develop disease. The relative risk (use "relative risk") is the ratio of two incidences: the incidence in the exposed divided by the incidence in the unexposed (Kaplan & Sadock 2024). Because it needs the actual risk (incidence) in each group, it can only be computed when you have followed disease-free people forward and watched new cases arise, that is, from a cohort study. A relative risk greater than 1 marks the exposure as a risk factor; less than 1, a protective factor; exactly 1, no association.

Formula

Relative risk = incidence in exposed / incidence in unexposed = [a / (a + b)] / [c / (c + d)].

Design

Cohort study (follows exposed and unexposed forward), because only a cohort yields incidence directly.

Reads

A risk ratio: "the exposed are RR times as likely to develop the disorder as the unexposed."

RULE **Relative risk comes from a cohort, the odds ratio from a case-control.** If the design gives you incidence you can quote a relative risk; if it starts from cases and controls you are limited to an odds ratio.

16.6 Odds ratio: the case-control measure that approximates RR when disease is rare

The ratio of the odds of exposure, computed when you cannot measure incidence. The odds ratio (use "odds ratio") is used when the study begins with cases and controls rather than exposed and unexposed cohorts, so incidence and therefore relative risk cannot be measured directly (Kaplan & Sadock 2024). It compares the odds of disease in the exposed (a / b) with the odds of disease in the unexposed (c / d), which reduces to the cross-product ad / bc. Like the relative risk it varies around 1: above 1 an association with disease, below 1 an association with not having disease, exactly 1 no association.

Formula

Odds ratio = (a / b) / (c / d) = ad / bc (the cross-product ratio).

Design

Case-control study (starts from diseased cases and disease-free controls, then looks back at exposure).

Key property

The odds ratio approximates the relative risk when the outcome is rare (the rare-disease assumption), so for uncommon disorders a case-control odds ratio stands in for a cohort relative risk.

16.7 Worked read of a 2x2: relative risk and odds ratio side by side

WORKED EXAMPLE

Setup. A cohort of 200 exposed and 200 unexposed people is followed. Among the exposed, 40 develop the disorder and 160 do not, so a = 40, b = 160. Among the unexposed, 10 develop it and 190 do not, so c = 10, d = 190.

Relative risk. Incidence in exposed = a / (a + b) = 40 / 200 = 0.20. Incidence in unexposed = c / (c + d) = 10 / 200 = 0.05. Relative risk = 0.20 / 0.05 = **4.0**, so the exposed are four times as likely to develop the disorder.

Odds ratio. Odds of disease in exposed = a / b = 40 / 160 = 0.25. Odds in unexposed = c / d = 10 / 190 = 0.0526. Odds ratio = ad / bc = (40 x 190) / (160 x 10) = 7600 / 1600 = **4.75**.

The lesson. With a disease this common (20 percent in the exposed) the odds ratio (4.75) overstates the relative risk (4.0): the odds ratio always lies further from 1 than the risk ratio. Make the disease rare (say 5 new cases in the exposed rather than 40) and the two converge, which is exactly the rare-disease approximation in action.

4.0	4.75	1
RELATIVE RISK (COHORT)	ODDS RATIO (CROSS-PRODUCT)	VALUE MEANING NO ASSOCIATION

16.8 Attributable risk and the population attributable risk

The excess risk, not the ratio of risks. Where relative risk and odds ratio are ratios, the attributable risk (use "attributable risk") is a difference: the excess risk of disease in the exposed

that can be attributed to the exposure, calculated as the incidence in the exposed minus the incidence in the unexposed (Kaplan & Sadock 2024). It answers "how much extra disease does this exposure add", and expressed as a fraction of the exposed incidence it becomes the attributable fraction, the share of disease in exposed people that the risk factor explains.

Attributable risk

Excess risk in the exposed = incidence in exposed minus incidence in unexposed.

Population attributable risk

The excess disease in the whole population attributable to the exposure; it depends on how common the exposure is, so a rare exposure yields a small population attributable risk however strong its relative risk.

Public-health use

If the exposure is truly causal, the population attributable risk estimates the disease reduction achievable by removing the exposure.

In the worked cohort, attributable risk = 0.20 minus 0.05 = **0.15**, meaning 15 excess cases per 100 exposed persons are attributable to the exposure; the ratio measures (RR, OR) tell you the strength of association, the attributable measures tell you the burden.

16.9 The measures assembled: formula, design, interpretation

One table to hold the whole toolkit. The examiner wants you to match each measure to its formula, the study design it is native to, and how to read it (Kaplan & Sadock 2024, Bland 2015).

MEASURE	FORMULA	DESIGN IT COMES FROM	INTERPRETATION
Point prevalence	cases at a point / population	**Cross-sectional survey**	Burden now; stock of existing cases
Period prevalence	cases in interval / population	**Cross-sectional / repeated survey**	Burden over an interval (1-month, 1-year, lifetime)
Cumulative incidence	new cases / at-risk at start	**Cohort**	Risk of new disease over the period
Incidence rate	new cases / person-time at risk	**Cohort**	Speed of new-case occurrence, per person-year
Relative risk	incidence exposed / incidence unexposed	**Cohort**	How many times more likely disease is in exposed; RR > 1 harmful
Odds ratio	ad / bc	**Case-control**	Approximates RR when disease is rare; OR > 1 associated with disease
Attributable risk	incidence exposed minus incidence unexposed	**Cohort**	Excess (extra) risk in the exposed due to exposure

MEASURE	FORMULA	DESIGN IT COMES FROM	INTERPRETATION
Population attributable risk	excess disease in population from exposure	**Cohort / population data**	Disease preventable by removing exposure; depends on exposure prevalence

Ratio measures (RR, OR) give strength of association; difference measures (attributable risk) give the excess burden; frequency measures (prevalence, incidence) give how common the disorder is.

16.10 The national numbers this material owns

Where the population figures come from. The flagship Indian frequency estimate is the National Mental Health Survey of India (2015 to 2016), a cross-sectional survey that reported a current weighted prevalence of any mental disorder of about **10.6** percent and a lifetime prevalence near **13.7** percent, with a treatment gap for mental disorders exceeding **70** percent (Gururaj et al 2016). These are prevalence numbers, a stock of existing cases at survey time, not incidence; they belong here as measures of frequency, while the disorder-by-disorder breakdown is carried in the clinical chapters of Paper II.

INDIA

The National Mental Health Survey of India (2015 to 2016) gives a current weighted prevalence of any mental disorder of about **10.6** percent (lifetime near **13.7** percent) and a treatment gap above **70** percent. Read these as point/period prevalence figures: they measure how many people have a disorder now, and because prevalence is roughly incidence times duration they cannot on their own tell you whether new cases are rising.

HOLD THIS

Incidence counts new cases over a period per population at risk; prevalence counts existing cases and equals roughly incidence times duration; relative risk comes from a cohort (incidence exposed / incidence unexposed) and the odds ratio (ad / bc) from a case-control, approximating RR only when the disease is rare.

MNEMONIC

PRIDE: Prevalence Rises with Increased Duration of Existing cases

Prevalence **R**ises with **I**ncreased **D**uration of **E**xisting cases. Because prevalence is roughly incidence times duration, longer illness inflates prevalence with incidence flat; incidence, by contrast, only ever counts the genuinely new.

PEARL

Match the measure to the design before you compute. A cohort hands you incidence, so you may quote a relative risk and an attributable risk. A case-control starts from cases and controls, so incidence is unavailable and you are restricted to the odds ratio, which you trust as a stand-in for relative risk only when the outcome is rare. Never quote a relative risk from a case-control study.

GOOD TO REMEMBER

- **Prevalence:** existing cases in a population over a time window; use it for burden and service planning; prevalence is roughly incidence times duration (P is proportional to I x d). Point prevalence = at one instant; period prevalence = over an interval.
- **Incidence:** new cases over a period per population at risk; use it for first-onset questions and to separate real rises from better survival; cumulative incidence = new cases / at-risk at start, incidence rate = new cases / person-time.
- **Relative risk:** how many times more likely disease is in the exposed; use it from a cohort; RR = incidence in exposed / incidence in unexposed; RR > 1 harmful, < 1 protective, = 1 no association.
- **Odds ratio:** the case-control measure of association; use it when incidence cannot be measured; OR = ad / bc; approximates the relative risk only when the outcome is rare.
- **Attributable risk:** the excess risk in the exposed caused by the exposure; use it to size the burden a risk factor adds; attributable risk = incidence in exposed minus incidence in unexposed; the population attributable risk scales this to the whole population and shrinks when the exposure is rare.

These measures are the shared currency of every observational and experimental design; the prevalence and incidence of individual psychiatric disorders, and the risk factors quantified by these ratios for each condition, are set out in the clinical chapters of Paper II, while the reliability and validity of the instruments used to define a case (as distinct from the frequency measures here) are covered in the Psychometry, Assessment and Descriptive Psychopathology notes.

17 · The National Mental Health Survey and the Indian picture

Every design and test taught earlier exists so that a number can be trusted. This topic is where those methods are spent on a single high-yield application: the National Mental Health Survey (NMHS) of India, 2015 to 2016, led by NIMHANS (Gururaj et al 2016). It is the one dataset an examiner expects an Indian resident to quote by heart, and it is the standing answer to any viva question that begins "what do we know about the burden of mental illness in India". Read it not as a table of prevalences to memorise blindly but as the country-level payoff of the **epidemiology of** mental disorders: a cross-sectional multistage survey applying the sampling logic and cross-sectional design covered earlier in this chapter.

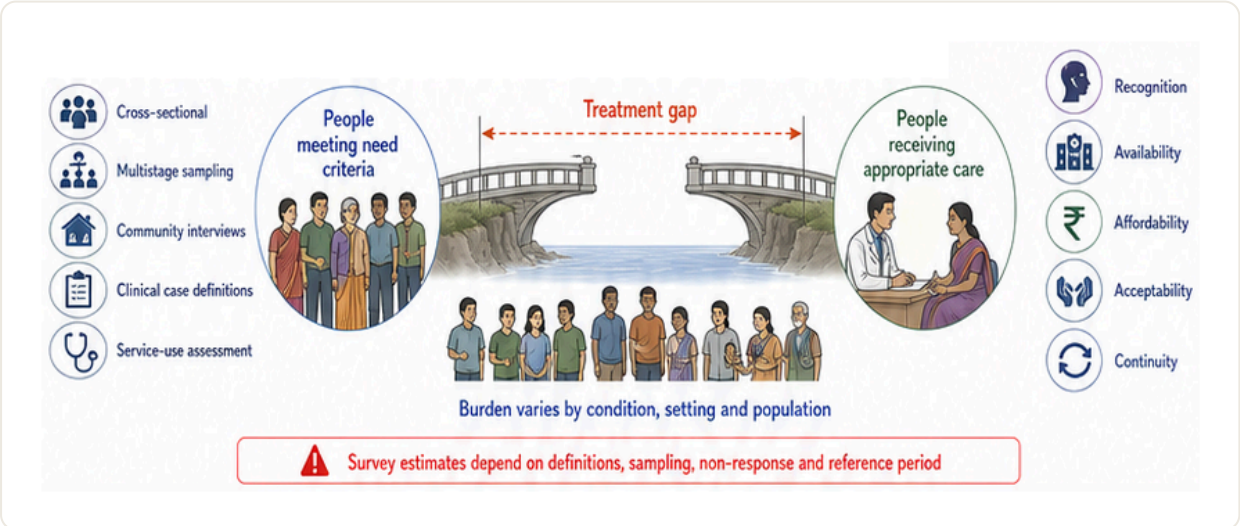


Fig 7.29 India's National Mental Health Survey: burden, care and gap.

The examiner's real interest, and the policy headline, is not how common illness is but how few of the ill are treated. The treatment gap, the proportion of people with a diagnosable disorder who receive no care, is the number that reframes Indian psychiatry from a clinical problem into a public-health one, and it is where the marks sit. Hold the prevalences, but lead with the gap.

17.1 What the NMHS is, and why it is the India device

The NMHS is India's first large multi-state national mental-health epidemiology survey. The **national mental health survey** was conducted across 12 states of India between 2015 and 2016, coordinated by the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, and published as NIMHANS Publication No. 129 (Gururaj et al 2016). Its purpose was to estimate the prevalence of mental disorders, describe their patterns and outcomes, and quantify the treatment gap and disability, so that mental-health policy and the District Mental Health Programme could be planned on **indian data** rather than borrowed Western figures. When a question asks for the burden of mental illness in India, this is the citation.

17.2 Methodology: a cross-sectional multistage survey

The NMHS is a prevalence (cross-sectional) survey built on multistage sampling. Methodologically the NMHS is an application of two designs taught earlier: it is a **cross-sectional** design (it measures disorder and non-disorder at one point in time, so it yields prevalence, not incidence, and cannot by itself establish that any exposure came first) delivered through a multistage random sampling frame (state, then district, then taluk or town, then village or ward, then household, then individual) so that a manageable sample can stand in for a vast and stratified population. For the anatomy of the sampling frame see the Sampling methods topic; for why a one-time snapshot gives prevalence and not causal direction see the Observational study designs topic in this chapter. Diagnoses were made with a structured diagnostic instrument (the MINI 6.0.0), the same family of fully structured interviews that anchors modern population psychiatry.

RULE **A cross-sectional survey gives prevalence, never incidence.** The NMHS tells you how many people are currently ill, not how many newly fall ill per year.

17.3 The headline prevalences: current and lifetime

Roughly one Indian in ten currently has a mental disorder; nearly one in seven has had one in their lifetime. The NMHS put the **current** prevalence of mental disorders (excluding tobacco use in most summaries) at **10.6%** (10.56% precisely) and the lifetime prevalence at **13.7%** (13.67%; Gautham et al 2020), drawn from 34,802 adults interviewed across 12 states and translating to an estimated 150 million Indians affected. Read plainly: about one adult in ten is unwell now, and close to one in seven has been unwell at some point. These two figures are the spine of the topic; quote them together and always with their source and survey years.

10.6%	13.7%
CURRENT PREVALENCE, ANY MENTAL DISORDER	LIFETIME PREVALENCE, ANY MENTAL DISORDER

TRAP **Never quote a prevalence bare.** A figure without its year and its source (NMHS 2015 to 2016) is unciteable and marks nothing; pair every number with survey and year.

17.4 The treatment gap: the policy headline

The Indian story is not that illness is common but that care is scarce. The **treatment gap** is the percentage of people who meet criteria for a disorder yet receive no treatment for it. Across mental disorders in India the NMHS found the overall treatment gap to be **84.5%** (Gautham et al 2020), varying widely by disorder. This is the single most examinable NMHS fact, because it is what drives policy: it is the argument for the National Mental Health Programme, task-shifting to primary care, and closing the psychiatrist shortfall (India has fewer than 10,000 psychiatrists against a desirable minimum of about 3 per 100,000 population; Kaplan and Sadock 2024).

RULE **Lead with the gap, not the prevalence.** The treatment gap, not prevalence alone, is the Indian policy headline; it is what an examiner is testing.

17.5 How the gap varies by disorder: the substance-use picture

The gap is widest for the substance-use and tobacco disorders. The treatment gap is not uniform: it is largest where stigma and normalisation are greatest. For substance use disorders overall the NMHS found a treatment gap of about **91.1%**, comprising **86.3%** for alcohol use disorder, **91.8%** for tobacco use disorder, and **72.9%** for other substance use disorders (Clinical Methods in Psychiatry 2024). The lesson to carry into the clinic and the exam is that the people least likely to be in treatment are precisely those with the addictions, which reframes screening and opportunistic case-finding as the front line.

91.1%	86.3%	91.8%	72.9%
TREATMENT GAP, SUBSTANCE USE DISORDERS	TREATMENT GAP, ALCOHOL USE DISORDER	TREATMENT GAP, TOBACCO USE DISORDER	TREATMENT GAP, OTHER SUBSTANCES

NMHS treatment gaps for the substance-use disorders, the group in which the gap is widest (Clinical Methods in Psychiatry 2024).

17.6 Setting India beside the World Mental Health survey frame

The NMHS is India's contribution to a global epidemiological project, not an isolated survey. The World Mental Health Survey Initiative is a suite of surveys conducted throughout the world using comparable sampling and diagnostic instruments (Tasman Psychiatry 2024), carried out in representative community samples in 17 countries across Africa, the Americas, Asia, Europe and the Middle East (Kaplan and Sadock 2024). Its two enduring lessons frame the Indian numbers: mental disorders are common everywhere, and the treatment gap is substantial worldwide and worst in low-income countries. The NMHS is best read as the Indian instance of exactly this pattern, using the same third-generation survey methodology (the ECA, the NCS and NCS-R, and the World Mental Health Survey Initiative, all built on structured instruments such as the CIDI; Tasman Psychiatry 2024). This is why "the treatment gap is global" is a defensible one-line summary and why India's overall gap of 84.5% is not an outlier but an intensification of the global picture.

WORKED EXAMPLE: READING A TREATMENT GAP

A treatment gap is a simple proportion. If a survey identifies 1,000 people who meet criteria for alcohol use disorder and finds that 137 of them have received any treatment for it, the treated proportion is 137 divided by 1000, which is 13.7%, so the treatment gap is 100% minus 13.7%, equals **86.3%**. That is exactly the NMHS alcohol-use-disorder figure. The arithmetic is trivial; the point of the calculation is that the gap is nothing more than one minus the proportion treated, and that a change in either the numerator (who counts as treated) or the denominator (who counts as a case) will move it. Always ask how "treated" and "case" were defined before comparing two gaps.

COMMON TRAP

Do not confuse the NMHS with the separate national drug-use survey. The frequently quoted figure that 14.6% of Indians aged 10 to 75 years use alcohol comes from the national survey on the magnitude of substance use in India, not from the NMHS; it is a use figure, not a disorder prevalence, and not a treatment gap. Mixing the two is a classic viva error. Keep the NMHS for disorder prevalence and treatment gap, and cite the substance-use magnitude survey separately if you quote its use figures.

INDIA

The whole topic is the India device for this chapter. The NMHS 2015 to 2016 (NIMHANS, 12 states) gives the numbers a resident must own: current prevalence **10.6%**, lifetime prevalence **13.7%**, and an overall treatment gap of **84.5%**, widest for the substance-use and tobacco disorders. It is the epidemiological justification for the District Mental Health Programme and for task-shifting mental-health care to primary care, given India's psychiatrist shortfall. When any Paper II clinical chapter needs an Indian prevalence for a specific disorder, the NMHS is the source to cite, but the disorder-specific prevalence must be looked up and quoted with its year, not guessed.

PEARL

Prevalence answers "how common", the treatment gap answers "how neglected". In India the second question carries the marks and the policy weight. A resident who can state the gap and explain why it drives task-shifting has understood the survey; one who only recites prevalences has memorised it.

MNEMONIC

GAP: Gururaj, All-India 12 states, Prevalence 10.6 now.

Gururaj (the lead author, Gururaj et al 2016) fixes the citation; All-India across 12 states fixes the scope; Prevalence 10.6% current (with 13.7% lifetime) fixes the headline number, so the letters of GAP also remind you that the gap itself is the point.

HOLD THIS

NMHS 2015 to 2016: current prevalence of any mental disorder 10.6%, lifetime 13.7%, and an overall treatment gap of 84.5%, which is the Indian policy headline.

GOOD TO REMEMBER

- **National Mental Health Survey (NMHS):** India's cross-sectional multistage prevalence survey (NIMHANS, 12 states, 2015 to 2016); use it for any Indian burden or treatment-gap figure; the two numbers to hold are current prevalence 10.6% and lifetime 13.7%.
- **Treatment gap:** percentage of people with a disorder who receive no care; 84.5% overall in India (widest for substance-use and tobacco); compute it as 100% minus the proportion treated.
- **World Mental Health Survey Initiative:** global suite of surveys using comparable sampling and structured diagnostic instruments (CIDI) across 17 countries; use it as the comparative frame that shows the treatment gap is global and worst in low-income settings.
- **Cross-sectional multistage design:** the NMHS method; use when you need population prevalence at one time point; remember it yields prevalence not incidence, and the one formula to know is prevalence equals cases divided by population sampled.

18 · Principles of screening

Screening is prevention masquerading as a test. **Screening** means testing apparently well people to detect disease early, before symptoms declare themselves, in the belief that earlier detection buys better outcomes (Wilson & Jungner 1968). The examiner rarely wants the mechanics of any one test; the question is whether a screening programme is justified at all, and whether an impressive-looking survival figure is real or an artefact. Two bodies of knowledge answer that: the Wilson and Jungner criteria, which decide when to screen, and the three screening biases, which explain why screening flatters itself. Master both and every screening vignette resolves cleanly (Wilson & Jungner 1968; Kaplan & Sadock 2024).

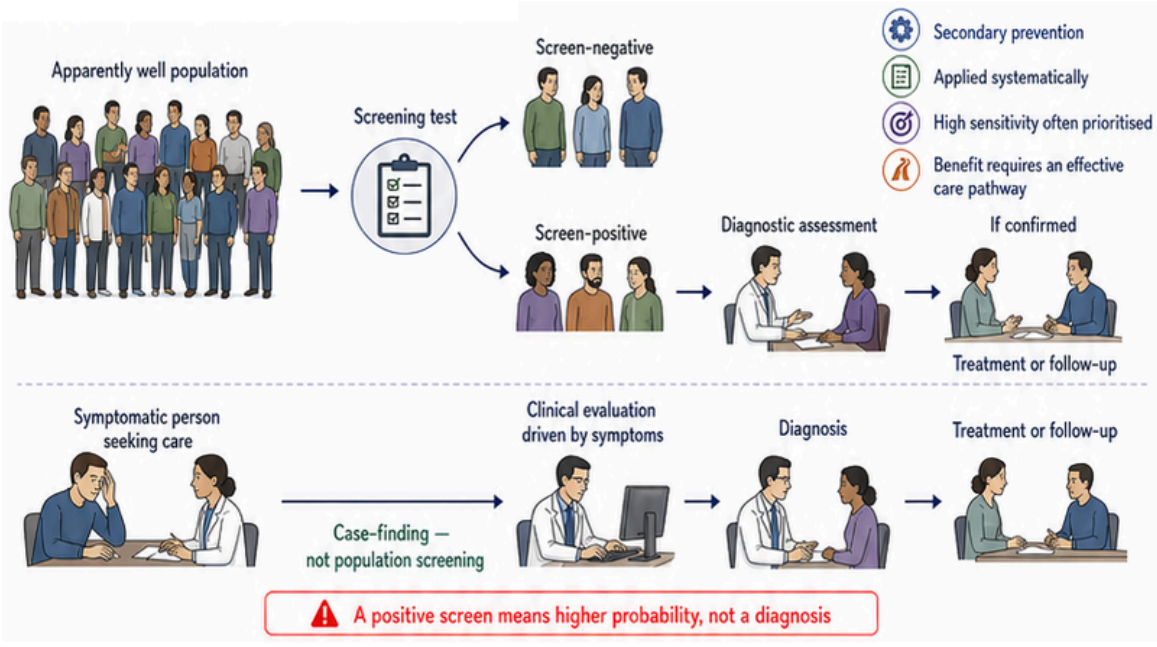


Fig 7.30 Screening is not diagnosis.

One framing distinction anchors the topic before the detail. Screening is applied to people with no complaint, so the base rate of true disease is low and the ethical bar is high: you are intervening on the well, and the harm of a false positive (anxiety, further invasive tests, overtreatment) falls on someone who was never going to be ill. That is the opposite of diagnostic testing, which is applied to the symptomatic, where prevalence is higher and the person has already sought help. This low pre-test probability is exactly why a screening test's positive predictive value collapses in the general population, a point developed in the Diagnostic test statistics topic and restated at 18.5.

18.1 What screening is, and how it differs from diagnosis

Testing apparently well people to detect disease early. Screening is the systematic application of a test to an asymptomatic population to identify those likely to have (or to be at high risk of) a disease, who are then referred for definitive diagnosis and treatment (Wilson & Jungner 1968). Two features define it. First, the target is the well, not the ill, so a screen is never itself a diagnosis: a positive screen selects people for a confirmatory diagnostic test, it does not label them with the disease. Second, the justification is downstream benefit, so a programme is only worth running if earlier detection actually changes the outcome, not merely the timing of the label. The distinction from case-finding (opportunistically testing patients already attending for another reason) and from surveillance is worth holding, but the core contrast the examiner wants is screen (asymptomatic, provisional) versus diagnose (symptomatic, definitive).

18.2 The Wilson and Jungner criteria (1968): the condition

Screen only a disease worth catching early. The classic Wilson and Jungner criteria, published for the World Health Organization in 1968, group the requirements of a sound screening programme, and the first group concerns the condition itself (Wilson & Jungner 1968). The condition must be an **important health problem** (common enough, or serious enough, to justify a population effort); it must have a **recognisable latent or early symptomatic stage** at which the screen can catch it before it declares clinically; and its **natural history must be adequately understood**, including the progression from latent to overt disease, so that we know that intercepting the latent stage genuinely alters the course. A disease with no detectable pre-clinical window, or one whose natural history is a mystery, fails at this first hurdle.

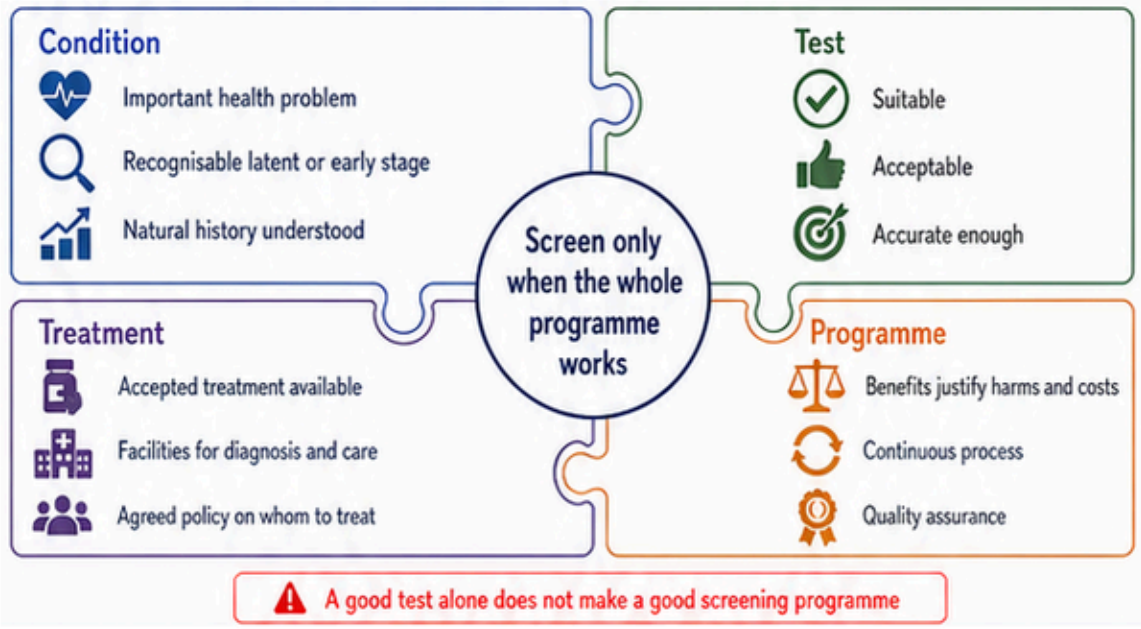


Fig 7.31 Wilson and Jungner: when is screening worth doing?.

18.3 The Wilson and Jungner criteria: the test, the treatment and the programme

A suitable test, an accepted treatment, and an organised, cost-effective programme. The remaining Wilson and Jungner groups concern the test, the treatment and the programme (Wilson & Jungner 1968). The **test** must be suitable (valid, with good sensitivity and specificity), simple, safe and acceptable to the population, since a screen the public will not attend screens no one. The **treatment** must exist and be accepted: there must be an effective, agreed treatment for patients found, together with the facilities to diagnose and treat them, because detecting a disease you cannot help merely inflicts foreknowledge. The **programme** must be organised: an agreed policy on whom to treat (an agreed cut-off and referral pathway), a cost that is balanced against benefit for the whole system (cost-effectiveness), and, critically, screening understood as a continuing process, not a one-off campaign, repeated at an interval matched to the disease's natural history. Later frameworks (the UK National Screening Committee, and a 2008 WHO update) refine these, but the 1968 list remains the examinable canon.

RULE **Screen with a sensitive test, confirm with a specific one.** The first-line screen is tuned for high sensitivity to miss few true cases; every positive is then re-tested with a specific diagnostic test to weed out the false positives.

18.4 The sensitivity-specificity trade-off in a screening test

A screening test is deliberately tuned for high sensitivity. Because the cost of missing a true case (a false negative reassurance) is usually judged worse than the cost of a false alarm, the sensitivity of a screening test is set high, at the price of lower specificity and therefore more false positives (Kaplan & Sadock 2024). Those positives are not treated on the strength of the screen; they pass to a second, more **specific** diagnostic test that confirms or excludes the disease. This two-stage architecture, a sensitive sieve followed by a specific confirmation, is the standard

design of a screening pathway (for example a sensitive immunoassay confirmed by a specific test, or a screening questionnaire confirmed by a structured clinical interview). Moving the cut-off trades the two errors against each other: a more lenient threshold raises sensitivity and lowers specificity; a stricter one does the reverse. The receiver operating characteristic curve, treated in its own topic, is the formal picture of that trade-off.

18.5 Low prevalence wrecks the positive predictive value

In an asymptomatic population, most positives are false. Sensitivity and specificity are intrinsic to the test and do not move with prevalence, but the positive predictive value (the chance a screen-positive person truly has the disease) is a hostage to prevalence: as prevalence falls, PPV falls (Kaplan & Sadock 2024). Screening operates precisely where prevalence is lowest, the general well population, so even an excellent test throws up a flood of false positives, and a positive screen means far less than the same result in a symptomatic clinic. The full 2x2 worked calculation (a good test whose PPV collapses from about **50%** at **10%** prevalence to roughly **8%** at **1%** prevalence) is carried in the Diagnostic test statistics topic; here, hold the consequence: a programme that looks superb in a high-risk clinic can generate mostly false alarms once rolled out to the low-prevalence general population, which is why the confirmatory specific test is not optional.

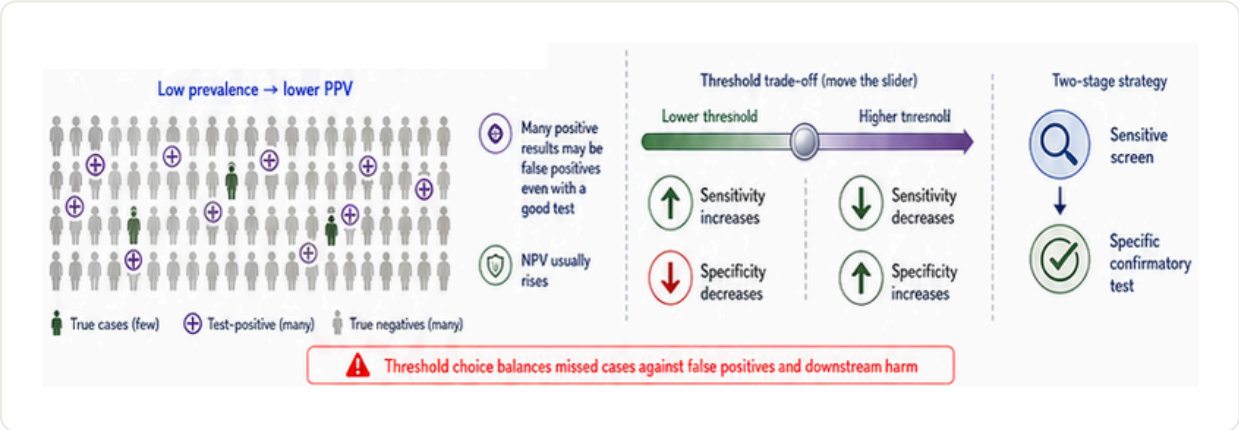


Fig 7.32 Low prevalence and the screening threshold.

18.6 Lead-time bias: earlier does not mean longer

Diagnosing earlier lengthens apparent survival without postponing death. Lead-time bias is the spurious improvement in measured survival that arises simply because screening advances the moment of diagnosis (Kaplan & Sadock 2024). Survival is timed from diagnosis to death; if a screen detects the disease two years before it would have surfaced clinically, but the patient dies at exactly the same moment as they would have unscreened, then the survival clock has been started earlier and reads two years longer, even though no survival time was actually gained. The disease was found sooner, so the patient merely spends longer knowing they have it. Any screening series compared with a clinically-diagnosed series will show longer survival for this reason alone, before any real benefit is considered. The defence is to judge screening by mortality (deaths in the whole screened population versus the unscreened) rather than by survival-from-diagnosis, and to use a randomised trial with mortality as the endpoint.

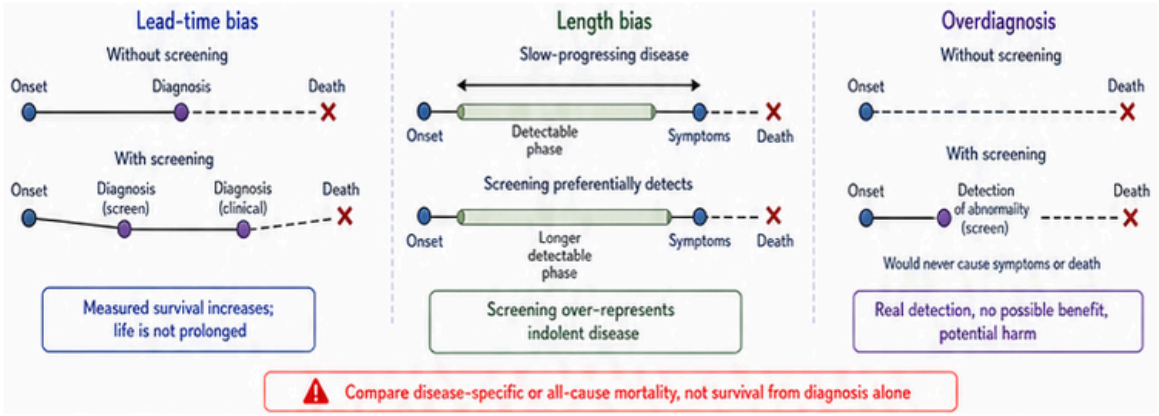


Fig 7.33 Screening biases: apparent benefit without true benefit.

TRAP **Improved survival in a screening series can be pure lead-time bias.** Longer survival-from-diagnosis after screening does not prove lives are saved; only a fall in population mortality does.

18.7 Length bias: the screen catches the indolent

Screening preferentially catches slow, indolent disease. Length bias (also called length-time bias) arises because a periodic screen is more likely to catch diseases that spend a long time in the detectable pre-clinical phase, and those slow-growing cases are, by their nature, the more indolent, better-prognosis ones (Kaplan & Sadock 2024). Fast, aggressive disease passes quickly from undetectable to symptomatic and often surfaces clinically in the gap between screening rounds, so it is under-represented among screen-detected cases. The screened group is therefore enriched for slow, benign disease and looks to do better, but the advantage is a sampling artefact, not a treatment effect. Length bias explains part of the apparent good prognosis of screen-detected cancers and is a cousin of lead-time bias: both make the screened group appear to fare better without any real extension of life.

18.8 Overdiagnosis: the extreme of length bias

Detecting disease that would never have caused harm. Overdiagnosis is the detection, by screening, of a genuine abnormality that met the pathological definition of disease but that would never have progressed to cause symptoms or death in the person's lifetime (Kaplan & Sadock 2024). It is the limiting case of length bias: the disease is so indolent that the patient would have died of something else first. Overdiagnosis is not misdiagnosis, the lesion is real, but the diagnosis is useless or harmful, because the person is then subjected to the anxiety, investigation and treatment of a disease that was never going to trouble them (overtreatment). It inflates apparent survival and incidence figures (more cases detected, all surviving) while doing pure harm to the individual. It is the strongest ethical argument for restraint in screening and the reason every programme must weigh benefit against the harm done to those who could never have benefited.

WORKED EXAMPLE

Two towns, identical disease biology. Town A is screened, Town B is not. Screen-detected patients in Town A are diagnosed on average 3 years earlier and their mean survival-from-diagnosis is 8 years; Town B's clinically-diagnosed patients survive 6 years from diagnosis. It looks like screening added 2 years. But every patient in both towns dies at the same age: the 2-year gap is exactly the lead time (3 years advanced diagnosis, offset by the different case mix), so it is lead-time bias, not benefit. On top of that, Town A's screened cases include several slow, indolent tumours that Town B's clinical presentation would have missed (they surfaced between rounds or never), so Town A's series is further enriched by length bias, and a handful of those lesions would never have harmed anyone at all (overdiagnosis). The only honest comparison is total mortality across each whole town, which shows no difference. Survival-from-diagnosis was the wrong yardstick.

18.9 Judging a screening programme honestly

Mortality in a randomised trial, not survival in a case series. Because lead-time, length and overdiagnosis all inflate survival-from-diagnosis, the correct evaluation of screening compares disease-specific (and ideally all-cause) mortality between a screened and an unscreened population, allocated at random so the two arms are otherwise alike (Kaplan & Sadock 2024). Randomisation defeats length bias (both arms get the same case mix) and the mortality endpoint defeats lead-time bias (the clock is not reset by earlier diagnosis). The benefits of a programme are then weighed against its harms, the false positives and their cascade of tests, the overdiagnosed and overtreated, the cost, and the anxiety inflicted on the well, exactly the balance the Wilson and Jungner programme criteria demand. A screening test that improves survival figures but not population mortality has proved nothing.

HOLD THIS

Screen with a sensitive test and confirm with a specific one; and never trust survival-from-diagnosis in a screened series, because lead-time bias, length bias and overdiagnosis all inflate it, so judge screening only by mortality in a randomised comparison.

BIAS	WHAT HAPPENS	WHY THE SCREENED GROUP LOOKS BETTER	DEFENCE
Lead-time bias	**Diagnosis advanced, death unchanged**	Survival is timed from an earlier diagnosis, so it reads longer without any life gained	Use mortality, not survival-from-diagnosis; randomised trial
Length bias	**Slow disease oversampled**	Periodic screens preferentially catch indolent, long-pre-clinical, good-prognosis cases	Randomised allocation equalises case mix between arms
Overdiagnosis	**Non-progressive disease detected**	Real but harmless lesions are counted as cured cases, inflating incidence and survival	Weigh benefit against overtreatment harm; long-term mortality

The three screening biases: each makes a screened series look better than it is; the hit column is the mechanism to name in a stem.

1968	3	8%
WILSON & JUNGNER YEAR	SCREENING BIASES TO NAME	PPV AT 1% PREVALENCE

COMMON TRAP

Two errors the examiner rewards. First, quoting improved five-year survival as proof that a screen saves lives: that figure is exactly what lead-time and length bias inflate, and only a fall in population mortality is proof. Second, treating a positive screen as a diagnosis: a screen is a sensitive sieve, not a specific verdict, and in a low-prevalence population most of its positives are false until a specific confirmatory test says otherwise.

MNEMONIC

The three biases spell L-L-O: Lead-time, Length, Overdiagnosis.

Lead-time advances the diagnosis clock; Length over-samples slow disease; Overdiagnosis catches disease that never mattered. All three inflate the screened group's apparent survival; none of them extends a single life; only population mortality tells the truth.

INDIA

In a low-resource, high-population setting the Wilson and Jungner programme criteria bite hardest: a screen is only defensible if the confirmatory diagnostic test and the accepted treatment are actually available and affordable at scale, and if the programme can be sustained as a continuing process rather than a one-off camp. Screening for a condition whose treatment or follow-up cannot be delivered breaches the treatment and programme criteria and merely generates anxiety and cost.

GOOD TO REMEMBER

- **Screening:** testing apparently well (asymptomatic) people to detect disease early; a sensitive sieve that selects people for a confirmatory diagnostic test, never a diagnosis itself; justified only if earlier detection improves the outcome, not just its timing.
- **Wilson & Jungner criteria (1968):** when to screen; four groups, the condition (important, recognisable latent stage, understood natural history), the test (suitable, acceptable), the treatment (accepted treatment plus facilities), and the programme (agreed policy on whom to treat, cost-effective, a continuing process); the WHO canon for a justified programme.
- **Screening test trade-off:** tuned for high sensitivity, accepting more false positives, then confirmed by a specific diagnostic test; the one number to hold is that PPV falls as prevalence falls, so most positives in the general population are false.
- **Lead-time bias:** earlier diagnosis lengthens apparent survival without postponing death; suspect it whenever survival-from-diagnosis improves; defeated by using mortality as the endpoint in a randomised trial.
- **Length bias:** screening preferentially catches slow, indolent, good-prognosis disease; suspect it when screen-detected cases look benign; defeated by randomised allocation equalising case mix.
- **Overdiagnosis:** detecting disease that would never have caused harm; the extreme of length bias; the strongest argument for restraint; weighed against benefit through long-term population mortality.

Discriminate

19 · Discriminate: pick the design, pick the test

This is the payoff. Every research vignette in the examination reduces to two acts of discrimination: **which design** answers the question that was asked, and **which test** reads the data that came back. The first act is **choosing a** study design from a clinical question; the second is **test selection** from the shape of the data. The examiner rarely asks you to compute anything by hand. What is tested is whether you can move cleanly from a one-line stem to the right design, and from a described dataset to the correct statistical test, and whether you know why the wrong pick is wrong (Bland 2015; Altman 1991; Johnstone et al 2010). This topic sets out the two selectors side by side, because in practice a question flows through both in turn: the design fixes what data you will have, and that data fixes which test is legitimate.

Think of it as two interleaved lookup tables. PART A, the study-design chooser, turns a **research question** into a design, and its axis is the *nature of the question*: prevalence, a rare outcome, a rare exposure, an intervention, the totality of evidence, or meaning and experience. PART B, the statistical-test chooser, turns the data into a test, and its axes are the *data type* (categorical versus continuous), the *number of groups* (one, two, three or more), and whether the observations are *paired or unpaired*. Hold both grids and almost every methods stem falls open.

data type \ comparison	Two groups unpaired	Two groups paired	Three or more groups	Association of two variables
Continuous, normal (parametric)	Independent t-test	Paired t-test	ANOVA (then post-hoc)	Pearson r linear regression
Ordinal or non-normal (non-parametric)	Mann-Whitney U	Wilcoxon signed-rank	Kruskal-Wallis	Spearman rho
Categorical counts (proportions)	Chi-square (Fisher if small)	McNemar	Chi-square	Chi-square logistic regression

Fig 7.34 Choosing the right statistical test. Read down to the type of your outcome data and across to the comparison you are making, and the cell names the test. Continuous normal data take the parametric tests (t-test, ANOVA, Pearson); ordinal or non-normal data take their non-parametric twins (Mann-Whitney, Wilcoxon, Kruskal-Wallis, Spearman); categorical counts take the chi-square family. This one grid, read with the study-design chooser, is the practical heart of the whole subject.

19.1 The design-choice logic: read the question, not the data

The question dictates the design. Before any data exist, the **design-choice** is settled by what the investigator wants to know and by what is rare or costly to observe (Bland 2015). Four sub-questions run in order. First, is this an *intervention* question (does a treatment work?) or an *observation* question (is this exposure associated with this outcome?): intervention licenses a trial, observation sends you to the observational family. Second, for observation, what is the *direction of enquiry*: from outcome back to exposure, or from exposure forward to outcome? Third, what is *rare*, the outcome or the exposure, since that decides between the two comparative designs. Fourth, does the question ask about the *current burden*, the *totality of the evidence*, or the lived *meaning* of an experience, each of which has its own home. The exact-string task here is naming **which design** fits the vignette.

RULE **Match the question to the design.** A prevalence question to cross-sectional, a rare outcome to case-control, a rare exposure or incidence question to cohort, an efficacy question to a randomised controlled trial, an evidence-synthesis question to systematic review and meta-analysis, a meaning question to qualitative.

19.2 PART A: the study-design chooser

Question in, design out. This is the first selector: read the clinical question in the left column and land on the design in the hit column (question to design). Rarity and temporality do most of the sorting; the last three rows sit apart because they answer questions of totality of evidence and of meaning rather than of individual-level association (Bland 2015; Altman 1991; Greenhalgh 2019).

RESEARCH QUESTION (THE VIGNETTE)	DIRECTION / UNIT	DESIGN TO PICK	MEASURE IT YIELDS
How common is the condition right now?	Snapshot, one time point	**Cross-sectional**	Prevalence, prevalence ratio
What are the risk factors for a rare outcome (or a long-latency disease)?	Outcome to exposure (backward)	**Case-control**	Odds ratio (OR)
What are the effects of a rare exposure, or the incidence of an outcome?	Exposure to outcome (forward)	**Cohort**	Incidence; relative risk (RR)
Must I prove the exposure preceded the outcome (temporality)?	Exposure to outcome, real time	**Prospective cohort**	Incidence; relative risk (RR)
Does this intervention actually work (efficacy)?	Investigator allocates exposure	**Randomised controlled trial**	Risk ratio, absolute risk reduction, NNT
What does the totality of the evidence say?	Studies as the unit	**Systematic review and meta-analysis**	Pooled effect size (95% CI)

RESEARCH QUESTION (THE VIGNETTE)	DIRECTION / UNIT	DESIGN TO PICK	MEASURE IT YIELDS
What is the meaning or lived experience of this?	Words, not numbers	**Qualitative**	Themes; no effect measure
Only aggregate, population-level data are available?	Group is the unit	**Ecological (mind the fallacy)**	Correlation of population rates

Study-design chooser: read the research question, pick the design (question to design); rarity and temporality do the sorting.

TRAP **Rare exposure is not rare outcome.** A case-control study is efficient for a rare *outcome*, a cohort for a rare *exposure*; swapping them is the classic design-choice error.

19.3 The intervention branch: the randomised controlled trial

When the question is efficacy. If the vignette asks whether a treatment *works*, and the investigator can *allocate* the exposure, the answer is the randomised controlled trial (Bland 2015). Randomisation is what separates it from every observational design: allocating treatment by chance balances known and unknown confounders across arms, so a difference in outcome can be attributed to the intervention. The other pillars, allocation concealment, blinding, and intention-to-treat analysis, protect that internal validity downstream. It is the strongest single design for a causal claim about an intervention, which is why the efficacy question routes here and nowhere else.

19.4 The evidence-synthesis branch: systematic review and meta-analysis

When the question is the totality of evidence. If the vignette asks what *all* the studies together show, the design is a systematic review, and where the studies are combined numerically, a meta-analysis (Greenhalgh 2019). A systematic review answers a focused question with a pre-specified, reproducible search and appraisal of every eligible study; the meta-analysis then pools their effect sizes into a single weighted estimate with a narrower confidence interval than any one study could give. It sits at the apex of the evidence hierarchy because it is the design whose unit of analysis is the study itself. Its validity depends wholly on the quality of the studies it pools and on whether publication bias has hidden the negative ones.

19.5 The meaning branch: qualitative designs

When the question is meaning, not magnitude. If the vignette asks about *why*, about experience, or about the meaning people attach to an illness or a service, no numerical design fits: the answer is a qualitative design (Greenhalgh 2019). Qualitative research works in words, gathered by in-depth interview, focus group or observation, and analysed by approaches such as thematic analysis, grounded theory or interpretative phenomenological analysis. It yields themes and understanding, not an effect size or a p-value, and it is judged by trustworthiness criteria (credibility, transferability, dependability, confirmability) rather than by statistical power. It is the correct pick whenever the stem asks about lived experience or meaning, and the wrong pick whenever the stem asks how many or how much.

19.6 The test-selection logic: read the data

The data dictate the test. Once a design has produced data, **test selection** turns on three facts and three facts only (Johnstone et al 2010; Altman 1991). First, the *data type*: is the outcome categorical (counts in categories) or continuous (measured on a scale), and if continuous, is it approximately normal? Second, the *number of groups* being compared: one, two, or three or more? Third, are the observations *paired* (the same subjects measured twice, or matched pairs) or *unpaired* (independent groups)? Read those three off the stem and the **statistical test** is fixed. The parametric tests (which assume an underlying normal distribution and compare means) each have a non-parametric twin (which works on ranks and assumes no distribution) for ordinal or non-normal data.

RULE **Data type x groups x pairing.** Those three coordinates alone pick the statistical test; continuous-normal goes parametric, ordinal or non-normal goes to the rank-based twin, categorical goes to chi-square.

19.7 PART B: the statistical-test chooser

Data in, test out. This is the second selector. Read across the data type, the number of groups, and the pairing to reach the correct **statistical test** in the hit column. Two independent continuous-normal groups give the independent t-test; two paired give the paired t-test; three or more give ANOVA; their non-parametric twins are Mann-Whitney, Wilcoxon and Kruskal-Wallis; two categorical variables give chi-square; an association of two continuous variables gives Pearson (or Spearman if ordinal or non-normal) (Johnstone et al 2010; Altman 1991).

DATA TYPE	NUMBER OF GROUPS	PAIRED OR UNPAIRED	CORRECT STATISTICAL TEST
Continuous, normal	One sample vs known value	n/a (single sample or a pairwise association)	**One-sample t-test**
Continuous, normal	Two	Unpaired (independent)	**Independent t-test**
Continuous, normal	Two	Paired / matched	**Paired t-test**
Continuous, normal	Three or more	Unpaired (independent)	**ANOVA (one-way)**
Continuous, normal	Three or more	Paired / repeated	**Repeated-measures ANOVA**
Continuous, non-normal / ordinal	Two	Unpaired (independent)	**Mann-Whitney U**
Continuous, non-normal / ordinal	Two	Paired / matched	**Wilcoxon signed-rank**
Continuous, non-normal / ordinal	Three or more	Unpaired (independent)	**Kruskal-Wallis**
Continuous, non-normal / ordinal	Three or more	Paired / repeated	**Friedman test**

DATA TYPE	NUMBER OF GROUPS	PAIRED OR UNPAIRED	CORRECT STATISTICAL TEST
Categorical (counts)	Two variables, two or more groups	Unpaired	**Chi-square test**
Categorical (counts), small cells	Two variables, 2x2	Unpaired	**Fisher exact test**
Categorical (counts)	Two variables, 2x2	Paired / before-after	**McNemar test**
Two continuous variables	Association (normal)	n/a (single sample or a pairwise association)	**Pearson correlation**
Two continuous / ordinal variables	Association (non-normal)	n/a (single sample or a pairwise association)	**Spearman rank correlation**

Statistical-test chooser: data type by number of groups by paired/unpaired, resolving to the correct parametric test or its non-parametric twin (categorical drops to Fisher exact when any expected cell is under 5).

TRAP **Three groups is not a job for the t-test.** Running a t-test on every pair of three or more groups inflates the type I error; use ANOVA (or Kruskal-Wallis) once, then post-hoc tests.

19.8 The two-selector worked walk-through

WORKED EXAMPLE

Design, then test, in one vignette. A team asks whether a new brief psychotherapy lowers depression scores more than treatment as usual. The question is *efficacy* and the investigator can *allocate* the therapy, so PART A resolves to a randomised controlled trial. The trial randomises 120 patients to two arms and records the continuous HAM-D score at 12 weeks. Now PART B: the outcome is *continuous*, roughly *normal*, there are *two* groups, and they are *independent* (different patients in each arm), which lands on the independent t-test. Say instead each patient's HAM-D is compared before and after within the same arm: that is *two paired* measurements, so the test becomes the paired t-test. Add a third arm and compare all three endpoints at once and it becomes a one-way ANOVA. Read a 2x2 of responders vs non-responders across the two arms instead, and the counts route to a chi-square test. One vignette, both selectors, four different tests depending only on data type, group number and pairing.

19.9 The classic mix-ups the examiner sets

Four errors sit at the seam of the two selectors. Each is a discrimination the stem deliberately blurs (Bland 2015; Altman 1991).

Odds ratio vs relative risk

A case-control study yields only an odds ratio; the relative risk needs a cohort with a denominator followed over time. The OR approximates the RR only when the outcome is rare.

Sensitivity vs positive predictive value

Sensitivity is a property of the test (proportion of the diseased it catches) and is prevalence-independent; PPV is a property of the setting (proportion of positives who are truly diseased) and falls as prevalence falls.

t-test where ANOVA is needed

Multiple pairwise t-tests across three or more groups inflate the false-positive rate; one ANOVA with post-hoc correction is the legitimate route.

Correlation claimed as causation

A significant Pearson or Spearman correlation quantifies association, not cause; only a design that controls confounding and establishes temporality (ideally a trial) supports a causal claim.

COMMON TRAP

These four mix-ups recur every year. Reporting a *relative risk* from a case-control study (it gives an odds ratio); reading a high *sensitivity* as a high *positive predictive value* (they diverge as prevalence changes); running a *t-test* across three or more groups where *ANOVA* is required (multiplicity inflates type I error); and reading a *correlation* as *causation* (association is not cause). Each is a failure to discriminate at exactly the point the two selectors meet.

19.10 The rare-disease bridge between the two selectors

PEARL

The two selectors are linked by the rare-disease assumption. When the outcome is rare, the odds ratio from a case-control design (PART A) closely approximates the relative risk you would have obtained from a cohort, and the chi-square that tests that 2x2 table (PART B) behaves well because expected cell counts stay large enough. As the outcome becomes common, both approximations fray: the OR exaggerates the RR, and small or lopsided cells push you toward the Fisher exact test. Rarity, the same axis that steers the design choice, quietly governs which test is trustworthy on the data that design returns.

MNEMONIC

QUESTION picks the DESIGN; DATA picks the TEST.

Two selectors, two inputs. Read the **question** (prevalence, rare outcome, rare exposure, efficacy, totality of evidence, meaning) to pick the design; read the **data** (type x number of groups x paired?) to pick the test. Never read the data to pick the design or the question to pick the test.

HOLD THIS

The question picks the design (prevalence to cross-sectional, rare outcome to case-control, rare exposure or incidence to cohort, efficacy to RCT, totality of evidence to systematic review and meta-analysis, meaning to qualitative); the data pick the test (data type x number of groups x paired/unpaired: two continuous-normal independent to independent t-test, paired to paired t-test, three or more to ANOVA, their twins Mann-Whitney / Wilcoxon / Kruskal-Wallis, two categorical to chi-square, two continuous associated to Pearson or Spearman).

GOOD TO REMEMBER

- **Cross-sectional:** the design for a prevalence question; use it to count current cases in a snapshot; yields prevalence = existing cases / population at that time.
- **Case-control:** the design for a rare outcome's risk factors; use it to look back from cases and controls to exposure; yields the odds ratio, OR = (odds of exposure in cases) / (odds of exposure in controls).
- **Cohort:** the design for a rare exposure's effects or for incidence; use it to follow exposed vs unexposed forward; yields incidence and relative risk, RR = (incidence in exposed) / (incidence in unexposed).
- **Randomised controlled trial:** the design for an intervention's efficacy; use it when the investigator can allocate the treatment; randomisation balances confounders and yields a risk ratio, absolute risk reduction and NNT = 1 / absolute risk reduction.
- **Systematic review and meta-analysis:** the design for the totality of evidence; use it to pool a focused question across all eligible studies; yields a single weighted pooled effect size with a 95% confidence interval.
- **Qualitative:** the design for meaning and experience; use it when the stem asks why or about lived experience; yields themes, judged by trustworthiness, with no effect measure or p-value.
- **Independent t-test:** the test for two independent continuous-normal groups; use it to compare two group means; two-sample t has n1 + n2 − 2 degrees of freedom.
- **Paired t-test:** the test for two paired continuous-normal measurements; use it for before-after or matched pairs; it tests the mean of the within-pair differences.
- **ANOVA:** the test for three or more continuous-normal group means; use it to avoid multiple t-tests; its statistic is F = MS(between) / MS(within).
- **Mann-Whitney / Wilcoxon / Kruskal-Wallis:** the non-parametric twins of the independent t-test, paired t-test and ANOVA respectively; use them on ordinal or non-normal data; they work on ranks, not means.
- **Chi-square:** the test for the association of two categorical variables; use it on absolute counts, never percentages; statistic = sum of (O − E)squared / E, dropping to the Fisher exact test when any expected cell is under **5**.
- **Pearson / Spearman:** the test for the association of two continuous variables; use Pearson when both are normal, Spearman (rank-based) when ordinal or non-normal; each returns a correlation coefficient r between −1 and +1, which is association and not causation.

For design selection and worked derivations see Bland (2015), Altman (1991) and Johnstone et al (2010); for the qualitative and evidence-synthesis branches see Greenhalgh (2019). Twin, family and adoption designs used to partition genetic and environmental variance are treated separately in the Psychiatric Genetics notes; the reliability and validity of a psychometric instrument, as distinct from the validity of a study design, are covered in the Psychometry, Assessment and Descriptive Psychopathology notes; the disorder-specific applications of these designs and tests appear in the clinical chapters of Paper II.

Apply and consolidate

20 · Apply: four worked appraisal vignettes

Everything in the research-methods and biostatistics material converges on a single skill the examiner can actually test in an OSCE station or a short-answer stem: put a piece of evidence in

front of the candidate and ask them to read it correctly. This topic drills that skill through four short worked appraisal vignettes, each a compact scenario followed by the reasoning and then the read. The four moves recur across every viva: read a **forest plot**, choose the right statistical test for a described dataset, compute an index from a diagnostic **2x2 table**, and interpret a **p-value** and a **confidence interval** without over-claiming (Bland 2015, Altman 1991).

How to use these. Treat each vignette as a self-contained worked example: cover the read, work the reasoning yourself, then check. The arithmetic in vignette three is fully worked and verified so you can reproduce it under pressure; the other three are conceptual reads where the trap is almost always the same, over-trusting a result the data cannot support (Sackett et al 2000). Every number quoted below has been checked by hand.

20.1 Vignette one: read a forest plot

WORKED EXAMPLE

Case: A meta-analysis pools eight randomised trials of an add-on agent for depression. Each trial is a horizontal line (its point estimate and 95% confidence interval) stacked down the plot; a vertical line marks the no-effect value, and a diamond at the foot marks the pooled estimate. The pooled diamond sits to the left of the no-effect line but its right tip just crosses it. The reported heterogeneity is I-squared = **72%**.

Reasoning. Each study line's width shows that study's precision; a wider line is a smaller or noisier trial. The forest plot diamond is the fixed or random-effects pooled estimate, and its width is the 95% confidence interval of that pooled estimate. Whether the diamond crosses the vertical no-effect line is the whole verdict: for a ratio measure (odds ratio, relative risk) the no-effect value is **1**; for a difference measure (mean difference) it is **0**. Here the diamond crosses the null line, so the pooled effect is not statistically significant at the 0.05 level even though the central estimate favours the drug.

The read. A diamond that crosses the null line means the meta-analysis has not demonstrated a significant pooled effect. Then heterogeneity changes your confidence in that pooled number: I-squared of 72% is high (a common ladder reads under 25% as low, around 50% as moderate, over 75% as high), meaning most of the variation across trials is real between-study difference, not chance. High heterogeneity means the single diamond hides genuinely different underlying effects, so the pooled estimate is less trustworthy and a random-effects model with wider intervals is the honest summary (Higgins et al 2003, Bland 2015).

RULE **Cross the null, lose significance.** A forest-plot diamond touching the no-effect line (1 for ratios, 0 for differences) means a non-significant pooled result.

TRAP **Pooling despite high heterogeneity.** A tidy diamond over an I-squared of 72% is a false comfort: the trials disagree, so the single number oversimplifies.

20.2 Vignette two: choose the test

WORKED EXAMPLE

Case: A trial randomises patients to three treatment arms (drug A, drug B, placebo) and measures a continuous symptom score, the change on a depression rating scale, at eight weeks. The question is whether mean symptom change differs across the three arms. In this vignette the score is roughly normally distributed within each arm and variances are comparable.

Reasoning. Walk the chooser: the outcome is continuous, the groups are independent (different patients per arm), and there are three groups, not two. Three independent groups on a normal continuous outcome is the textbook indication for one-way ANOVA (analysis of variance), whose F statistic is the ratio of between-group to within-group variance (Johnstone et al 2010). A significant ANOVA then licenses post-hoc pairwise comparisons (Tukey or Bonferroni) to locate which arms differ.

Why a t-test would be wrong. A t-test compares only two means. To cover three arms you would run three separate t-tests (A vs B, A vs placebo, B vs placebo), and each carries its own **0.05** chance of a false positive, so the family-wise error inflates well above 5%. ANOVA tests all three at once at a single controlled alpha, which is exactly why it exists.

The non-parametric twin. If the same score were skewed or ordinal (assumptions of normality failing), swap ANOVA for its rank-based twin, the Kruskal-Wallis test, which compares three or more independent groups on medians rather than means. The two-group non-parametric equivalent (had there been only two arms) would have been Mann-Whitney U in place of the t-test.

TRAP **Serial t-tests for three arms.** Three pairwise t-tests inflate the false-positive rate; use ANOVA (or Kruskal-Wallis if non-normal) for three or more groups.

20.3 Vignette three: compute from a 2x2

WORKED EXAMPLE

Case: A brief screening questionnaire for a disorder is validated against a structured interview (the reference standard) in a clinic of 1000 attenders where the disorder prevalence is 10%. The 2x2 table comes out as below. Work out the sensitivity and the positive predictive value, then say what happens to the PPV if the same test is used where the disorder is rarer.

SCREEN RESULT	DISORDER PRESENT	DISORDER ABSENT	ROW TOTAL
Screen positive	80 (a)	90 (b)	**170**
Screen negative	20 (c)	810 (d)	**830**
Column total	100	900	**1000**

Prevalence 10%: 100 diseased, 900 non-diseased among 1000 attenders.

Sensitivity. Read down the disorder-present column: sensitivity = a / (a + c) = 80 / (80 + 20) = 80 / 100 = **0.80**, that is 80%. The screen detects 80% of true cases; it misses 20% (the false-negative rate).

Positive predictive value. Read across the screen-positive row: PPV = a / (a + b) = 80 / (80 + 90) = 80 / 170 = 0.4706, about **47%**. So even with 80% sensitivity and (from d / (b + d) = 810 / 900) 90% specificity, fewer than half of those who screen positive truly have the disorder in this clinic.

If prevalence falls. Sensitivity and specificity are intrinsic to the test and do not move. But re-run the same 80% sensitive, 90% specific test where prevalence is only 1%: among 10000 people, 100 are diseased and 9900 are not. True positives = 80, but false positives now = 9900 x 0.10 = 990, so PPV = 80 / (80 + 990) = 80 / 1070 = 0.0748, about **7.5%**. The very same test turns roughly nine of every ten positives into false alarms once the disorder is rare. That is why a screen that looks good in a high-risk clinic floods the general population with false positives (Wilson & Jungner 1968, Altman 1991).

80%	47%	7.5%
SENSITIVITY	PPV AT 10% PREVALENCE	PPV AT 1% PREVALENCE

RULE **PPV chases prevalence.** Sensitivity and specificity stay fixed; PPV falls as the disorder becomes rarer because false positives swamp the positive row.

20.4 Vignette four: interpret a p-value and a CI

WORKED EXAMPLE

Case: A cohort study reports that an exposure is associated with a disorder at an odds ratio of 1.8 with a 95% confidence interval of 1.2 to 2.7 (p = 0.01). A parallel trial reports a mean difference in symptom score of 1.5 points (95% CI 0.2 to 2.8, p = 0.03) on a scale where clinicians regard 5 points as the smallest change a patient would notice.

Reasoning: the odds ratio. The point estimate 1.8 means the odds of the disorder are 1.8 times higher in the exposed. The 95% confidence interval 1.2 to 2.7 is the range of values compatible with the data; the interpretation is that if the study were repeated many times, 95% of such intervals would contain the true value. Because the interval does not include the no-effect value of **1**, the association is statistically significant, which agrees with the reported p of 0.01 (below the 0.05 threshold). For a ratio measure, crossing 1 and having p above 0.05 are the same statement.

Reasoning: the mean difference. Its no-effect value is **0**. The CI 0.2 to 2.8 excludes 0, so the 1.5-point difference is statistically significant (p = 0.03). But the whole interval lies below the 5-point threshold that patients can actually feel. So the result is statistically significant yet clinically trivial: a real but tiny effect, made detectable only by a large sample. Statistical significance answers "is this likely a chance finding?"; clinical significance answers "is the effect big enough to matter to a patient?", and the two can diverge in either direction (Bland 2015, Altman 1991).

The read. Correct the p-value too: p = 0.01 is the probability of data this extreme if the null were true, not the probability that the null is true and not the size of the effect. A narrow CI that excludes the null and clears the clinical threshold is the strongest result; a CI that excludes the null but sits below it, as here, is significant but not meaningful.

TRAP **Significant equals important.** A p under 0.05 with a CI excluding the null can still be clinically trivial if the effect sits below the minimal important difference.

20.5 The four appraisal moves as one habit

One question runs through all four vignettes. Does this evidence support the claim being made of it, or is someone over-reading it? In the forest plot the check is whether the diamond clears the null and whether heterogeneity undermines the pool; in the test-choice vignette it is whether the analysis matched the data structure or inflated error with serial comparisons; in the 2x2 it is whether a positive result means much given the prevalence; in the p-value and CI it is whether statistical significance was mistaken for clinical importance (Sackett et al 2000, Bland 2015). Learn to ask that one question and every appraisal station collapses to a short, safe read. In each worked example the vignette stem (marked case:) is deliberately terse, because the examiner wants the read, not a recital of the scenario.

HOLD THIS

Diamond crossing the null equals non-significant; three groups need ANOVA (Kruskal-Wallis if non-normal), never serial t-tests; PPV falls with prevalence while sensitivity and specificity hold; and a CI excluding the null is statistically significant but only clinically significant if the effect clears the minimal important difference.

MNEMONIC

READ: Reach for the null line, Elect the right test, Anchor to prevalence, Distinguish significances.

Reach: does the forest-plot diamond (or the CI) cross the no-effect value? **E**lect: match the test to data type by group count by paired status. **A**nchor: read predictive values against the population's prevalence. **D**istinguish: statistical significance is not clinical significance.

GOOD TO REMEMBER

- **Forest plot:** the graphic summary of a meta-analysis; use it to read pooled effect and heterogeneity at a glance; the diamond crossing the null line (1 for ratios, 0 for differences) means non-significant, and I-squared over 75% is high heterogeneity.
- **I-squared (heterogeneity):** the percentage of total variation across trials due to real between-study difference rather than chance; use to judge how much to trust a pooled estimate; roughly under 25% low, around 50% moderate, over 75% high.
- **ANOVA:** the parametric test for three or more independent group means on a normal continuous outcome; use instead of multiple t-tests to control error; statistic is F = between-group variance / within-group variance.
- **Kruskal-Wallis:** the non-parametric twin of one-way ANOVA; use for three or more independent groups when normality fails; it compares ranks, so report medians.
- **Sensitivity:** the proportion of true cases the test correctly flags; use to rule out disease when negative (SnNOUT); formula = a / (a + c), read down the disease-present column and independent of prevalence.
- **Positive predictive value (PPV):** the proportion of test-positives who truly have the disorder; use to judge how much a positive result means in this population; formula = a / (a + b), and it falls as prevalence falls.
- **Odds ratio with 95% CI:** a ratio measure of association read together with its interval; use to test significance and precision at once; significant when the CI excludes the no-effect value of 1.
- **Confidence interval:** the range of values compatible with the data at 95%; use to test significance (does it cross the null?) and to gauge precision; a narrow interval excluding the null that also clears the clinical threshold is the strongest result.
- **p-value:** the probability of data at least this extreme if the null hypothesis were true; use against a pre-set threshold (conventionally 0.05); it is not the probability the null is true and not a measure of effect size.

21 · Consolidate: mnemonic, retrieval and synthesis

Everything in these notes reduces to one reflex the examiner is testing: an abstract lands, and you must place its **design**, judge how its **data** were analysed, and read its **disease frequency** or effect. That is the whole "THREE D's" seed planted at the start, Design then Data then Disease-frequency, and this closing topic ties the three bands into a single memorisable spine so that naming a study, choosing its test, and quoting its measure become one continuous move rather than three separate recalls (Kaplan & Sadock 2024).

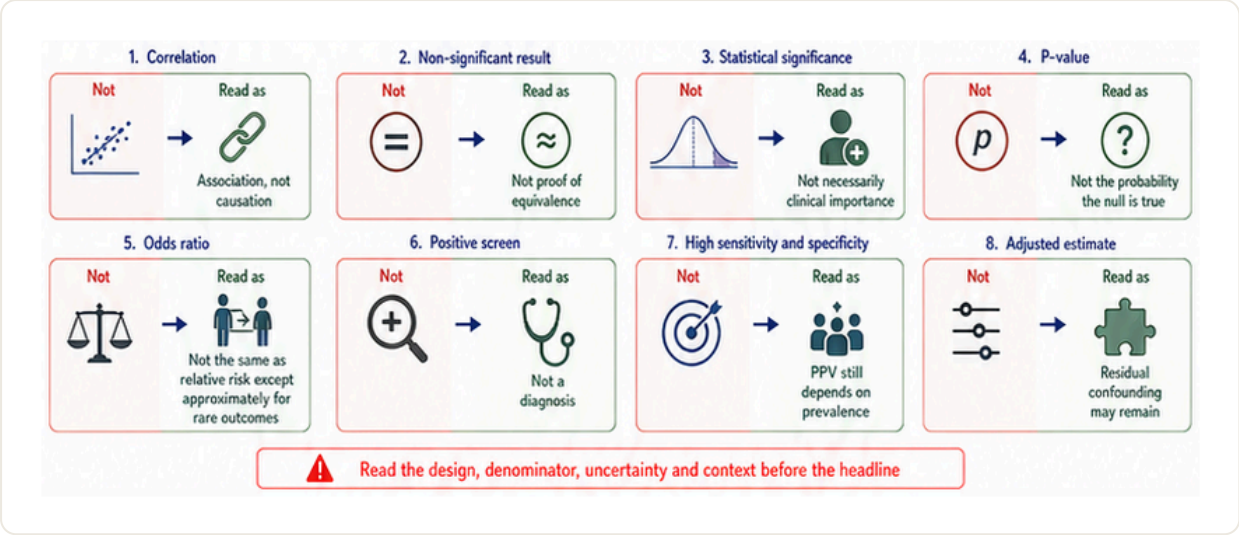


Fig 7.35 Research claims: eight common misreads.

How to use this page. Read the master mnemonic once to fix the skeleton, then close the book and work the recall prompts before you look anything up, then rebuild the whole picture as a branching map from memory. A note read passively fades in days; a note recalled and redrawn under mild difficulty is the version that survives to the viva (Bland 2015). Consolidation is not extra content, it is the retrieval scaffold that makes the preceding content stick.

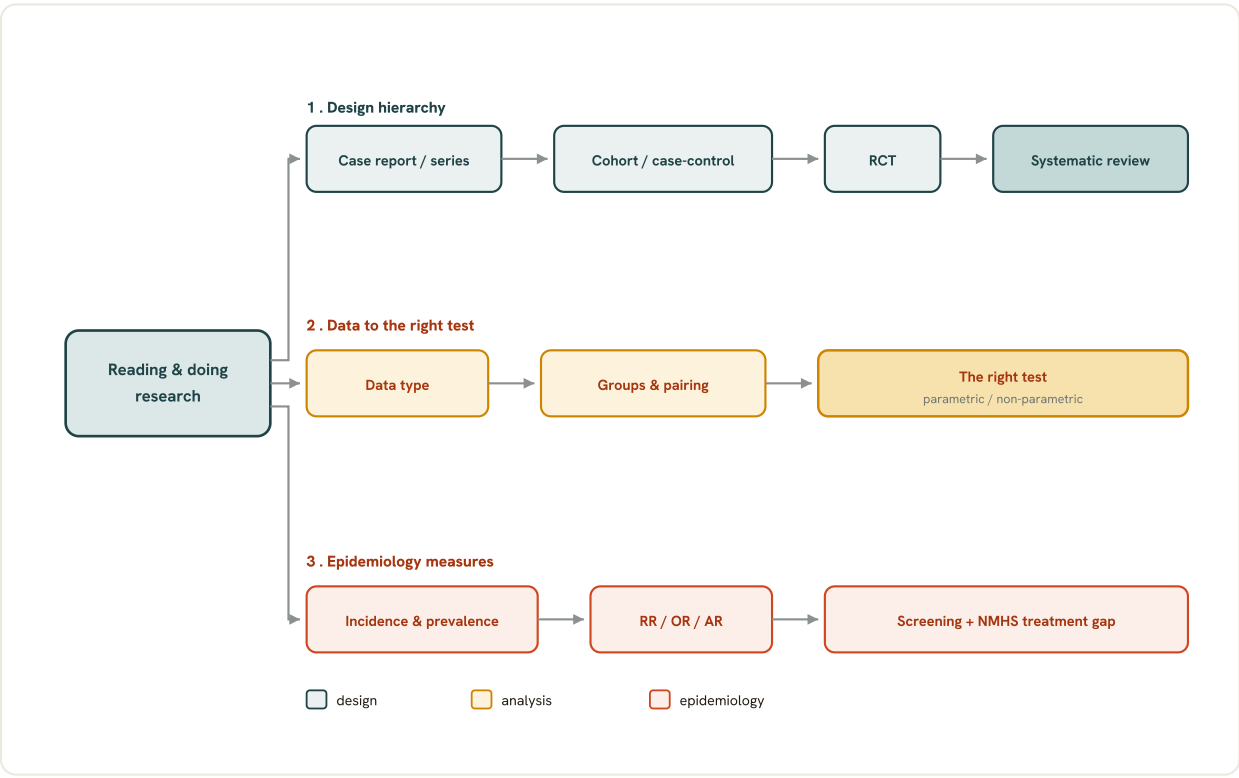


Fig 7.36 The whole-chapter synthesis map. Three branches run out from one hub: the design hierarchy that ranks the strength of a study, the analysis path that takes a dataset from its measurement scale through the number of groups to the correct test, and the epidemiology measures that quantify how common a disorder is and how strongly an exposure raises its risk. Cover the boxes and redraw the three branches from memory as the final retrieval check.

21.1 The master mnemonic: one chain from design to test to measure

The whole document on a single hook. The three bands each get a memory anchor, and the three anchors nest under the "THREE D's" seed so that one cue unpacks the entire note. The design hierarchy runs from the weakest, most abundant evidence at the base up to the strongest, scarcest evidence at the apex; the analysis path runs from the type of data you hold to the one correct test; the epidemiology measures split into the two frequency counts and the two ratio measures of association. Learn the box below and you can reconstruct every earlier topic from its first letter.

MNEMONIC

THREE D's -> "REACH the top, DANCE to the test, FOUR frequencies." (Design climb: Reports, Enquiry cross-sectional, Analyse case-control, Cohort, RCT, Higher-order review. Data path: Discrete-or-continuous, count of groups, Are-they-paired, Normal-or-not, then Choose. Epidemiology: Incidence, Prevalence, Relative risk, Odds ratio.)

Unpack it band by band. **REACH** is the design climb up the evidence pyramid: **R**eports (case report and case series, the base), **E**nquiry-at-a-point (cross-sectional survey, gives prevalence), **A**nalyse-backwards (case-control, gives an odds ratio), **C**ohort (follows forward, gives incidence and relative risk), then the RCT, then the **H**igher-order synthesis (systematic review and meta-analysis, the apex): case report to cohort to RCT to systematic review, base to apex. **DANCE** is the data-to-test path: is the outcome **D**iscrete (categorical) or continuous; how many groups; **A**re they paired or unpaired; is the distribution **N**ormal (parametric) or not; then **C**hoose the cell of the test grid and **E**xecute. **FOUR frequencies** is the epidemiology quartet in reading order: **I**ncidence (new cases, from a cohort), **P**revalence (existing cases, from a cross-sectional survey), **R**elative risk (ratio of two incidences, from a cohort), **O**dds ratio (cross-product, from a case-control). One seed, three chains, the whole note: that is the payoff of the "THREE D's" you were handed at the start.

RULE **Name, test, measure, in that order.** For any abstract, say the design first, then the statistical test its data demanded, then the frequency or effect it reports; the three D's force the sequence so nothing is skipped.

21.2 The three chains laid side by side

What each letter is standing in for. A mnemonic is only worth its unpacking, so the table sets the three chains against each other: the design climb, the analysis path, and the epidemiology quartet, each with the one fact that letter must trigger. Read down any column to rehearse a band; read across to see how a single vignette moves design to test to measure.

BAND (THE D IT SERVES)	THE CHAIN, IN ORDER	THE ONE FACT EACH LINK MUST FIRE
Design climb (Design)	Case report -> cross-sectional -> case-control -> cohort -> RCT -> systematic review	**Trustworthiness rises with control of bias; base is weak and abundant, apex is strong and scarce**
Analysis path (Data)	Data type -> number of groups -> paired or unpaired -> normal or not -> the test	**Categorical vs numerical is the top fork; parametric only when numerical and roughly normal**
Epidemiology quartet (Disease-frequency)	Incidence -> prevalence -> relative risk -> odds ratio	**Incidence and RR need a cohort; prevalence needs a cross-sectional survey; OR is the case-control stand-in**

The three chains under the "THREE D's" seed: one column per band, read across to trace a vignette from design to test to measure.

TRAP **Quoting the wrong measure for the design.** A case-control study cannot yield a relative risk and a cross-sectional survey cannot yield an incidence; if you misname the design you will misname the measure, which is why the chain fixes them together.

21.3 The analysis path in one glance: data type to the right test

The middle chain, filled in. The DANCE letters resolve to a grid whose rows are the group-and-pairing situation and whose columns are the data type. The parametric column (interval or ratio, roughly normal) is the discriminator: pick it only when the data earn it, otherwise drop one column left to the non-parametric equivalent (Bland 2015; Altman 1991). This is the single most examined "choose the test" table, so hold it whole.

GROUPS & PAIRING	CATEGORICAL (NOMINAL)	ORDINAL / NON-NORMAL	INTERVAL OR RATIO (PARAMETRIC)
One sample vs known value	Chi-square goodness-of-fit	Sign test	**One-sample t-test**
Two groups, independent (unpaired)	Chi-square test of association	Mann-Whitney U	**Independent two-sample t-test**
Two groups, paired / matched	McNemar test	Wilcoxon signed-rank	**Paired t-test**
Three or more groups, independent	Chi-square test	Kruskal-Wallis	**ANOVA (one-way), F-test**
Three or more groups, repeated / paired	Cochran's Q	Friedman test	**Repeated-measures ANOVA**
Association between two variables	Chi-square / phi coefficient	Spearman rank correlation	**Pearson correlation**

The DANCE grid: data type across the top, group and pairing down the side, the correct test in the cell; parametric column highlighted.

21.4 The epidemiology quartet, worked once so the numbers stick

The disease-frequency chain, with its arithmetic. The two frequency counts and the two association ratios are best fixed by one 2x2 read that produces both a relative risk and an odds ratio, because seeing the two diverge is what stops you quoting one for the other. Take a cohort of 100 exposed and 100 unexposed people followed forward.

WORKED EXAMPLE

Of 100 exposed, 20 develop the disorder (incidence in exposed = 20/100 = 0.20); of 100 unexposed, 5 develop it (incidence in unexposed = 5/100 = 0.05). The relative risk = incidence in exposed / incidence in unexposed = 0.20 / 0.05 = **4.0**. The odds ratio = ad/bc = (20 x 95) / (80 x 5) = 1900/400 = **4.75**. The attributable risk = incidence in exposed minus incidence in unexposed = 0.20 minus 0.05 = **0.15**, that is 15 excess cases per 100 exposed. Note the odds ratio (4.75) sits further from 1 than the relative risk (4.0) because the disorder is common here (20 percent); make it rare and the two converge, which is the rare-disease approximation. Prevalence would come from a different design entirely, a cross-sectional snapshot, and rises with duration since prevalence is roughly incidence times duration (Kaplan & Sadock 2024).

TRAP **The odds ratio always lies further from 1 than the relative risk.** With a common outcome the OR exaggerates the RR; only when the outcome is rare do they converge, so never read a case-control OR as a relative risk when the disorder is frequent.

21.5 Retrieval practice: close the book and answer these first

Test yourself before you re-read. The evidence for durable memory is unambiguous: active recall beats re-reading, and spaced retrieval practice beats massed review (Bland 2015). So the instruction is literal, cover the answers, attempt each prompt aloud or on paper, and only then check against the earlier topics. The prompts below span all three bands, design then data then disease-frequency, and none of them prints its answer.

RETRIEVAL PRACTICE, COVER THE ANSWERS

1. Name the six rungs of the study-design hierarchy from base to apex, and state what makes the apex more trustworthy than the base.
2. Which single design feature separates the whole observational family from a randomised controlled trial?
3. A vignette gives you a rare, long-latency outcome and asks for the most efficient design: which do you pick, and which measure of association does it yield?
4. State the direction of enquiry for a cohort study versus a case-control study, and the measure each produces.
5. What is the top fork of the data-to-test path, and why does it decide whether a parametric test is even permissible?
6. Two independent groups, a continuous roughly-normal outcome: name the test. Now make the two groups paired: name the test.
7. Three or more independent groups with a numerical outcome: name the parametric test and its non-parametric equivalent.
8. Which test compares paired categorical (before-after yes/no) data in a single group?
9. Define incidence and prevalence, and give the equation that links them through duration.
10. Which study design is needed to measure incidence directly, and why can a cross-sectional survey never give it?
11. Write the formula for the relative risk and the formula for the odds ratio from a 2x2 table.
12. Under what condition does the odds ratio approximate the relative risk, and in which direction does the odds ratio err when that condition fails?
13. Distinguish attributable risk from relative risk in one line: which is a difference and which is a ratio, and what question does each answer?
14. State the "THREE D's" seed and name the memory chain that unpacks each of the three bands.
15. For any abstract, what is the fixed order in which you name the design, the test, and the measure?

21.6 The synthesis map: redraw the whole note from memory

Rebuild the three branches on a blank page. The final consolidation move is to draw a synthesis map, a single branching diagram you redraw from memory with the "THREE D's" seed at the centre and three branches radiating out: the *design hierarchy* climbing case report to cross-sectional to case-control to cohort to RCT to systematic review; the *data-to-test analysis path* forking on data type, group number, pairing and normality down to the named test; and the *epidemiology measures* splitting into the two frequency counts (incidence, prevalence) and the two association ratios (relative risk, odds ratio). If you can redraw the synthesis map with every branch labelled and every leaf carrying its one fact, without the notes open, the note has consolidated; a gap on the map is exactly the topic to revisit.

GOOD TO REMEMBER

- **Design hierarchy:** ranks study designs by control of bias; use it to place any abstract and know what its rung can answer; order (base to apex) = case report -> cross-sectional -> case-control -> cohort -> RCT -> systematic review.
- **Data-to-test path:** selects the correct statistical test; use it once the data are in hand; the deciding chain = data type, number of groups, paired vs unpaired, normal vs not, then the test cell.
- **Incidence:** new cases over a period per population at risk; use it for a first-onset question; needs a cohort, and it is the numerator of the relative risk.
- **Prevalence:** existing cases at a point or over an interval; use it for burden and service planning; from a cross-sectional survey, and prevalence is roughly incidence times duration.
- **Relative risk:** how many times more likely disease is in the exposed; use it from a cohort; RR = incidence in exposed / incidence in unexposed (worked value 4.0).
- **Odds ratio:** the case-control measure when incidence cannot be measured; use it from a case-control study; OR = ad/bc (worked value 4.75), approximating RR only when the outcome is rare.

HOLD THIS

The "THREE D's" seed unpacks the whole note: name the Design on the hierarchy, choose the Data's test by type-groups-pairing-normality, then quote the Disease-frequency measure that design can legitimately give, in that order, every time.

Previously asked

Research methodology, biostatistics and epidemiology sit in the first paper's basic-sciences territory. In the theory catalogue sampled here they have not appeared as standalone long essays or short notes: the subject is examined **applied** rather than recited, folded into clinical questions (the epidemiology and risk factors of a named disorder, the interpretation of a trial in a management answer, the ethics of consent in a forensic scenario) and, above all, in the critical-appraisal and thesis-protocol components. Genuine standalone items will be added here as further question catalogues are sourced, never invented.

HOW THIS TERRITORY IS ACTUALLY TESTED

- As an **appraisal task**: given a study or a forest plot, name the design, its measure of association, its main bias, and whether the conclusion is justified.
- As an **applied number**: read a 2x2 for sensitivity and predictive value, interpret a p-value and a confidence interval, or compute a relative risk or an NNT.
- As an **Indian-data prompt**: quote the National Mental Health Survey prevalence and the treatment gap to frame a public-health answer.
- As **research ethics**: the four principles, informed consent and the ethics committee within a scenario, most often in the forensic and community papers.

Prepare this material to be used, not just remembered. The two selector tables (choosing a design, choosing a test) and the four worked appraisal cases in this note are deliberately built to that examinable skill. The disorder-specific epidemiology that recurs in clinical essays is developed in the clinical chapters of Paper II; the professional and forensic ethics that the ethics questions usually target are developed in the mental health legislation and forensic psychiatry notes; this note owns the general research toolkit, the statistics, and the national survey numbers.

Quick review

The whole subject in one table	
EVIDENCE-BASED MEDICINE	The five steps (Ask, Acquire, Appraise, Apply, Assess); the focused question via PICO; the null and alternative hypotheses. The evidence pyramid ranks designs by control of bias: case report, cross-sectional, case-control, cohort, randomised controlled trial, then systematic review and meta-analysis at the apex.
OBSERVATIONAL DESIGNS	Cross-sectional is a snapshot giving prevalence. Case-control traces outcome back to exposure, gives the odds ratio, and is efficient for rare outcomes. Cohort follows exposure forward to outcome, gives incidence and the relative risk, and suits rare exposures. Ecological studies compare populations (mind the ecological fallacy).
THE RANDOMISED CONTROLLED TRIAL	Randomisation balances known and unknown confounders; allocation concealment hides the next assignment; blinding hides the treatment; intention-to-treat analyses everyone as randomised. Parallel, crossover, factorial and cluster designs. Drug-trial phases I (safety) to IV (post-marketing).
VALIDITY, BIAS, CONFOUNDING	Internal validity (true here) versus external validity (generalisable). Bias is systematic error: selection and information (including recall) bias. Confounding is a third variable on neither causal path, controlled at design (randomisation, restriction, matching) or analysis (stratification, regression). Distinct from psychometric reliability and validity.
SAMPLING	Probability sampling (simple random, systematic, stratified, cluster, multistage) permits generalisation; non-probability sampling (convenience, purposive, snowball) does not. Stratify to guarantee a small subgroup; clustering adds a design effect.
QUALITATIVE METHODS	Grounded theory, thematic analysis, phenomenology, ethnography; the focus group and the in-depth interview. Rigour through saturation, triangulation, reflexivity and an audit trail. For meaning and hypothesis generation, not statistical generalisation.
SYSTEMATIC REVIEW AND META-ANALYSIS	The reproducible protocol-driven review versus the statistical pooling that may sit inside it. Read the forest plot (point estimates, confidence intervals, the null line, the pooled diamond). Heterogeneity via I-squared; publication bias via the funnel plot; certainty via GRADE.
REPORTING GUIDELINES AND ETHICS	CONSORT for trials, PRISMA for reviews, STROBE for observational studies, GRADE for certainty. The four principles (autonomy, beneficence, non-maleficence, justice), Helsinki and Nuremberg, informed consent, the ethics committee, and the ICMR 2017 guidelines in India.
DATA TYPES AND SCALES	Nominal, ordinal, interval and ratio; categorical versus continuous (discrete or continuous). The measurement scale decides the legal summary

The whole subject in one table	
	statistic and the legal test, so it is the first thing to settle.
DESCRIBING DATA AND THE NORMAL CURVE	Central tendency (mean, median, mode) and dispersion (range, interquartile range, variance, standard deviation). The normal distribution: mean equals median equals mode, and the empirical rule that 68, 95 and 99.7 percent lie within one, two and three SDs. Skew and kurtosis; the z-score.
TESTS OF SIGNIFICANCE	Parametric tests for normal interval data: the t-test (one-sample, independent, paired), ANOVA with post-hoc for three or more groups. Non-parametric twins for ordinal or non-normal data: Mann-Whitney, Wilcoxon, Kruskal-Wallis; chi-square (Fisher exact for small cells) for categorical data.
CORRELATION, REGRESSION, FACTOR ANALYSIS	Pearson for linear association of continuous normal variables, Spearman for ranks. Linear regression predicts a continuous outcome (r-squared as variance explained); logistic regression predicts a binary one (adjusted odds ratios). Factor analysis reduces items to latent factors (exploratory versus confirmatory, eigenvalues, loadings, PCA).
DIAGNOSTIC TEST STATISTICS	From the 2x2: sensitivity and specificity are intrinsic (SnNOUT, SpPIN); the positive and negative predictive values are what the clinician wants but move with prevalence; the likelihood ratio shifts pre-test to post-test odds. At low prevalence a positive screening test is often a false alarm.
STATISTICAL INFERENCE	The p-value is the probability of the data (or more extreme) under the null; alpha is set at 0.05. The confidence interval gives the plausible range (crossing 0 for a difference, or 1 for a ratio, means non-significant). Type I error is a false positive (alpha), type II a false negative (beta); power is 1 minus beta, aim 80 percent. Sample size and effect size drive it.
SURVIVAL, NNT AND ROC	Kaplan-Meier plots event-free probability over time with censoring; the log-rank test compares curves and the hazard ratio quantifies the difference. NNT is one over the absolute risk reduction. The ROC curve plots sensitivity against one minus specificity, and the AUC grades discrimination (0.5 chance, 1.0 perfect).
DISEASE FREQUENCY AND ASSOCIATION	Incidence (new cases) versus prevalence (existing cases, point or period; roughly incidence times duration). Relative risk from a cohort, the odds ratio from a case-control (it approximates the RR when the outcome is rare), and the attributable risk as the excess in the exposed.
THE INDIAN PICTURE (NMHS)	The National Mental Health Survey 2015-16 gives India's current and lifetime prevalence and, its policy headline, the large treatment gap that varies by disorder. Read it beside the world mental health frame; it is an applied cross-sectional multistage survey. Every quoted number is verified against the source.

The whole subject in one table	
SCREENING	The Wilson and Jungner criteria (the condition, the test, the treatment, the programme). Lead-time bias (earlier diagnosis, not longer life), length bias (indolent disease over-sampled) and overdiagnosis. Screen with a sensitive test and confirm with a specific one; low prevalence lowers the predictive value.
DISCRIMINATE	Two selectors: the study-design chooser takes a question to a design (prevalence to cross-sectional, rare outcome to case-control, rare exposure or incidence to cohort, efficacy to RCT, totality to systematic review). The statistical-test chooser takes the data type, the number of groups and pairing to the correct parametric or non-parametric test.
APPLY AND CONSOLIDATE	Four worked appraisals: read a forest plot, choose the test for a dataset, compute sensitivity and PPV from a 2x2, and interpret a p-value with its confidence interval. Then the master mnemonic (design to data to disease frequency), answer-free retrieval prompts, and the three-branch synthesis map to redraw from memory.

References

The material is grounded in the standard texts (the source hierarchy below); statistical formulae and definitions are drawn from the medical-statistics references, and each landmark, contested or numeric claim carries a PubMed-verified journal citation. Every PMID here was checked against PubMed this build, and any citation whose identifier did not resolve to the cited paper was corrected or dropped. The National Mental Health Survey figures are taken from the primary results paper, not from a textbook summary.

SOURCE HIERARCHY (TEXTBOOKS AND STATISTICS REFERENCES)

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About the authors

Dr. Wilfred D'souza

MD Psychiatry (Resident) · Certified Gestalt Therapist · Weave, Centre for Integrative Psychiatry

Works in integrative psychiatry with Schema Therapy as the primary lens, alongside CBT, DBT, motivational interviewing and emotion-focused therapy, and is a certified Gestalt therapist. His clinical interests run through neurodivergence, ADHD, bipolar disorder, personality disorders, addiction and developmental psychiatry: work grounded in lived experience of attention difficulties long labelled as laziness, which made psychiatry personal before it became professional. He has been developing the Toroidal Model of Psychosis and Affect (TMoP), his computational model of mind, and TMoP thinking shaped the Claude Code AI system he builds with: clinical software, teaching tools and much of this series' production pipeline among its work, bringing psychiatry into the AI era in his own way. Lead author of the Weave Sprint series.

Dr. Niharika Reddy

Consultant Psychiatrist · Weave, Centre for Integrative Psychiatry

Consultant Psychiatrist at Weave, Mumbai, seeing people online through weave.clinic. Her work centres on relationships and family dynamics, family therapy and women's mental health, with a particular focus on neurodivergence in women and on adolescent mental health. Practises integrative, person-centred psychiatry. Co-author of this volume.

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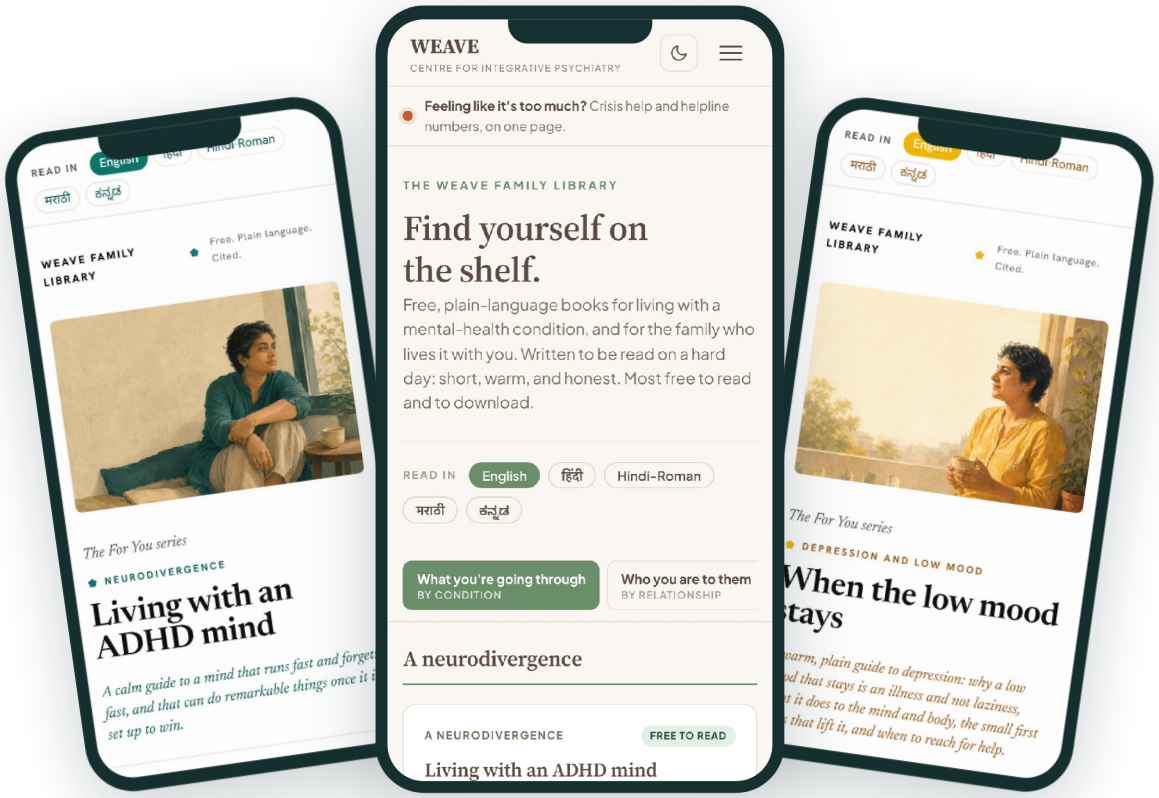
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