WEAVE SPRINT
PAPER I · VOLUME ONE

MD and DNB psychiatry, theory revision

Foundations of Psychiatry

The Brain and Its Chemistry

How the brain is wired for emotion, memory and arousal. Then the chemistry that runs it, the hormonal axes, the imaging, and the drugs that follow.

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 of three volumes of the opening paper, and the most physical of them. It is the brain itself: how it is wired for emotion, memory and arousal, the chemistry and hormones that run it, how we look at it, and the drug actions that follow directly from that chemistry. Nothing here is a symptom list yet.

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.

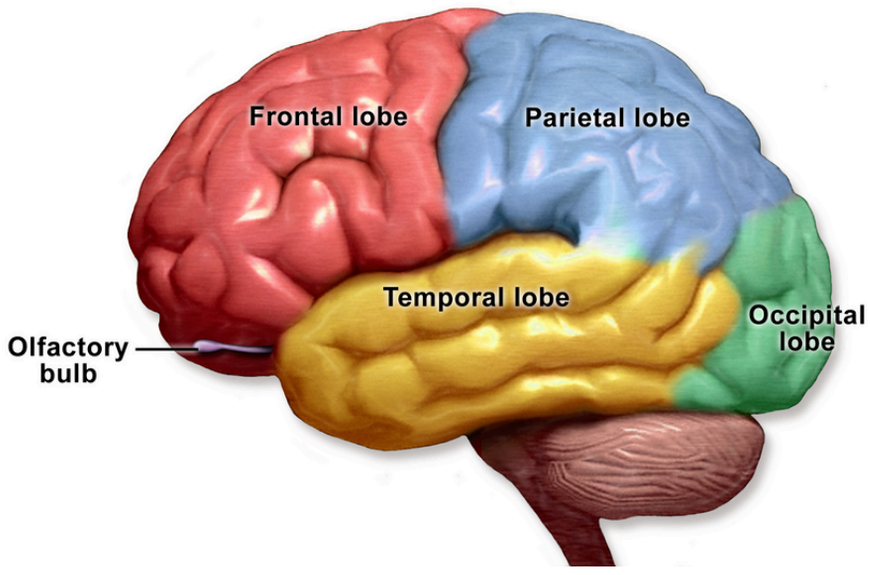


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Fig 1.1 The four cerebral lobes on the lateral surface. The central sulcus (of Rolando) separates the frontal lobe from the parietal; the lateral (Sylvian) fissure drops the temporal lobe below the frontoparietal cortex; the parieto-occipital and calcarine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

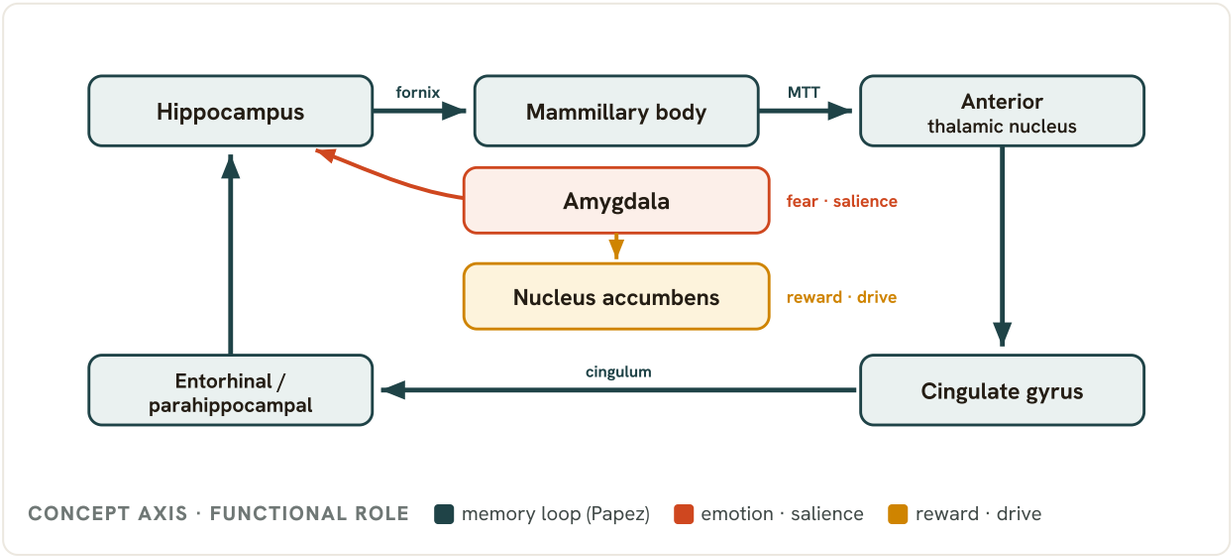


Fig 1.2 The Papez circuit drawn as a closed ring (petrol): hippocampus to fornix to mammillary body to anterior thalamus to cingulate to entorhinal and back. The amygdala (coral) tags emotional salience onto encoding and feeds the accumbens (marigold) reward hub. MTT, mammillothalamic tract.

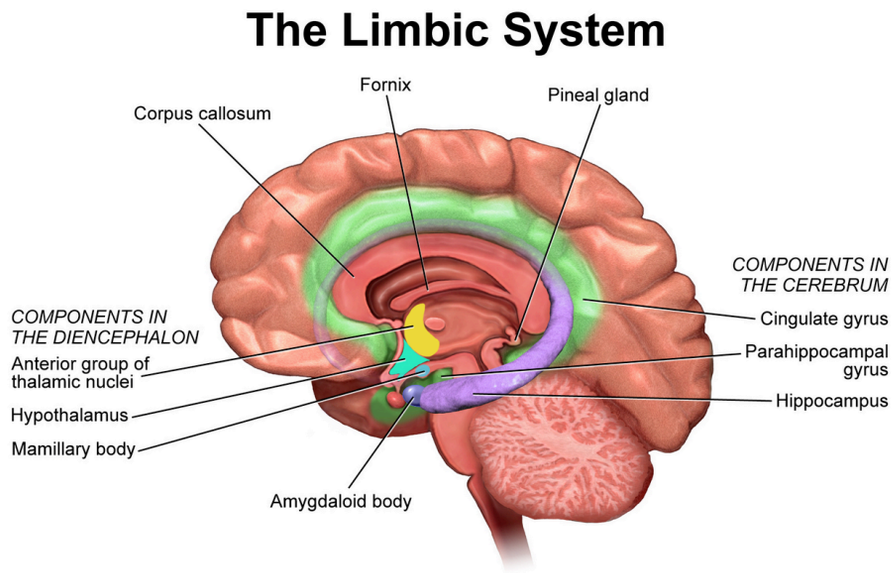


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Fig 1.3 The same structures in situ. Trace the Papez loop of Fig 1.2 across real anatomy: the cingulate gyrus and fornix carry the loop, the amygdala sits at the temporal pole tagging salience, and the hippocampus curls beneath it encoding new memory.

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. Limic 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).

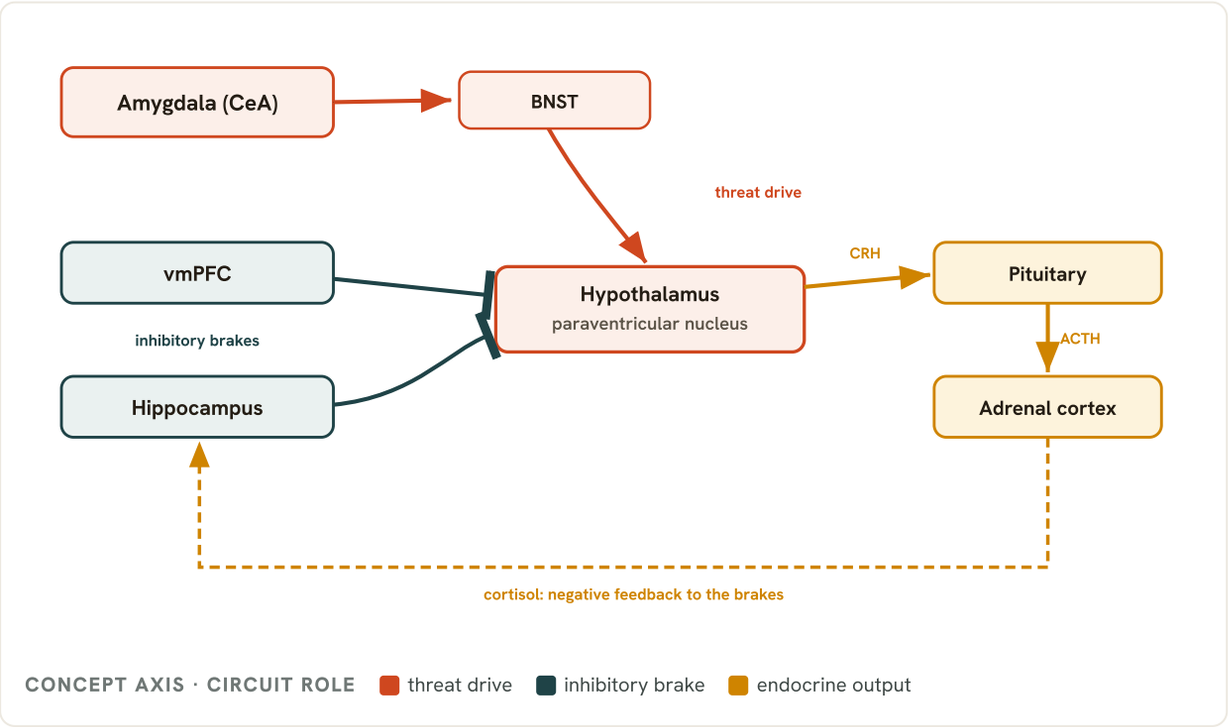


Fig 1.4 The stress loop. The amygdala (coral) drives the paraventricular nucleus, relayed through the BNST for sustained anxiety; the hippocampus and vmPFC (petrol) apply inhibitory brakes; the cortisol output limb (marigold) closes the loop by feeding back onto its own brakes, so that when chronic stress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

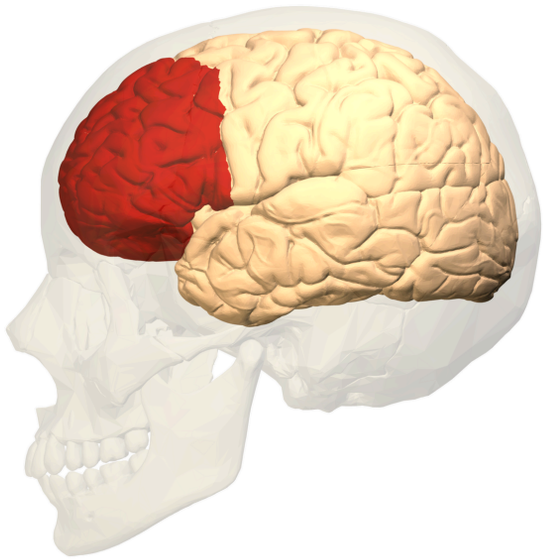


Image: Database Center for Life Science (DBCLS), CC BY-SA 2.1 Japan, via Wikimedia Commons

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.

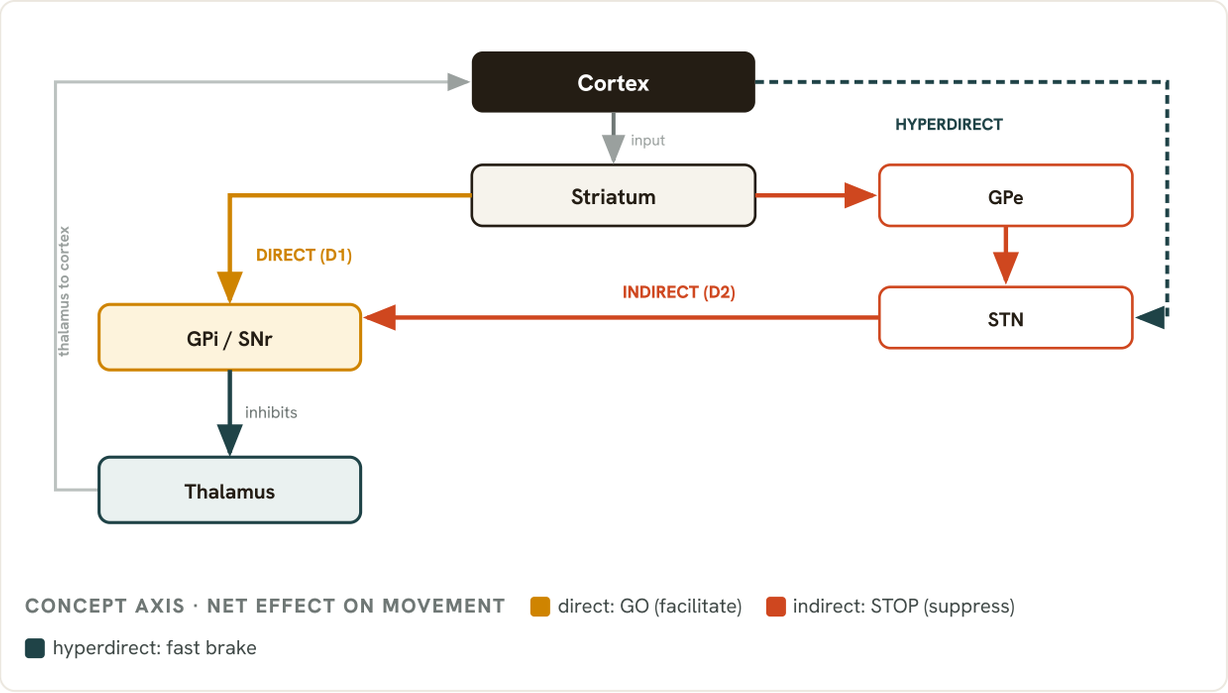


Fig 1.6 The cortico-striato-thalamo-cortical loop. The output nuclei (GPi/SNr) tonically inhibit the thalamus: the direct pathway (marigold, D1) disinhibits it to release movement, while the indirect (coral, D2) and hyperdirect (petrol) pathways raise GPi/SNr output to clamp it. Dopamine via D1 strengthens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

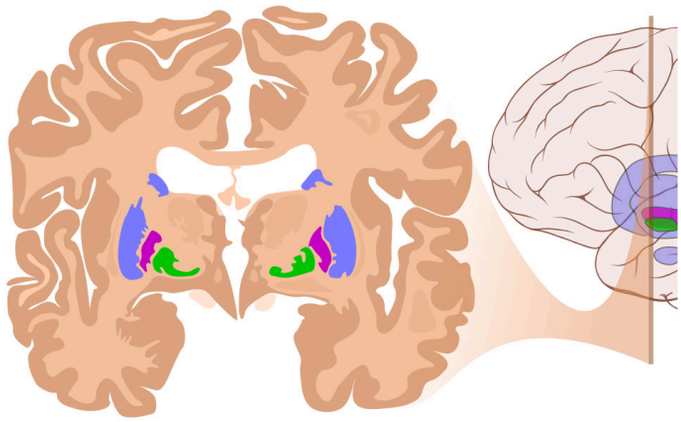


Image: Andrew Meyerson, CC BY-SA 3.0, via Wikimedia Commons

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).

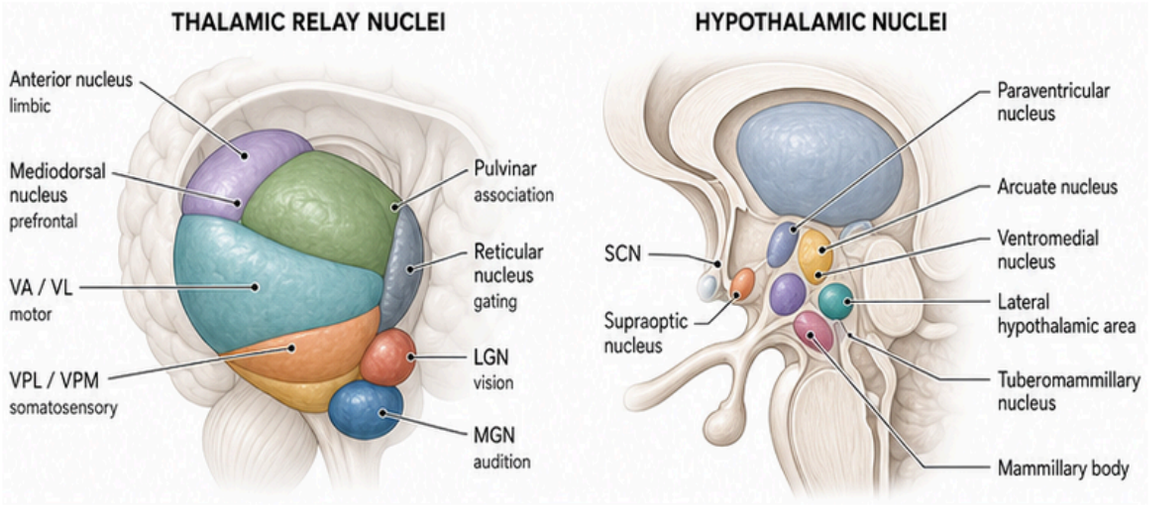


Fig 1.8 Thalamic relay nuclei and hypothalamic nuclei arranged by function: cortical relay and gating on the left, endocrine, autonomic, circadian and homeostatic control on the right.

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.

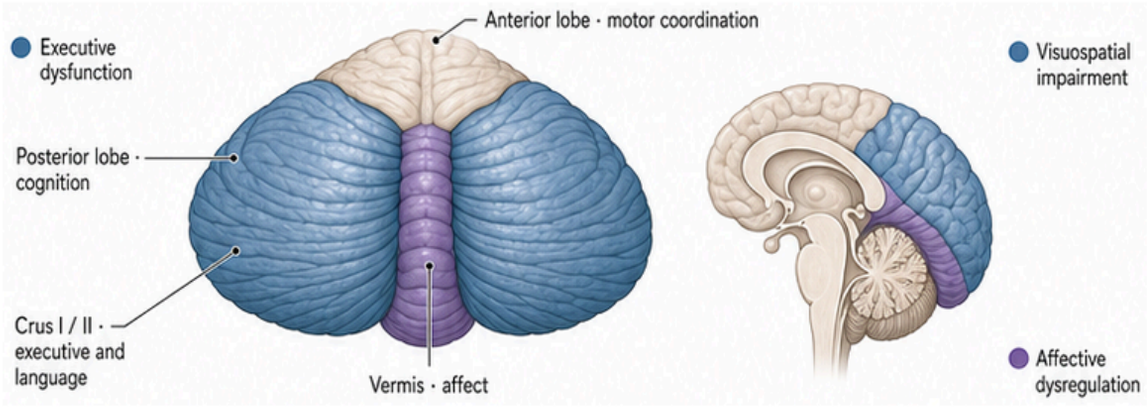


Fig 1.9 Cerebellar cognitive-affective topography. Motor coordination maps anteriorly; executive, language and visuospatial functions map posteriorly; affective regulation is concentrated in the vermis.

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.

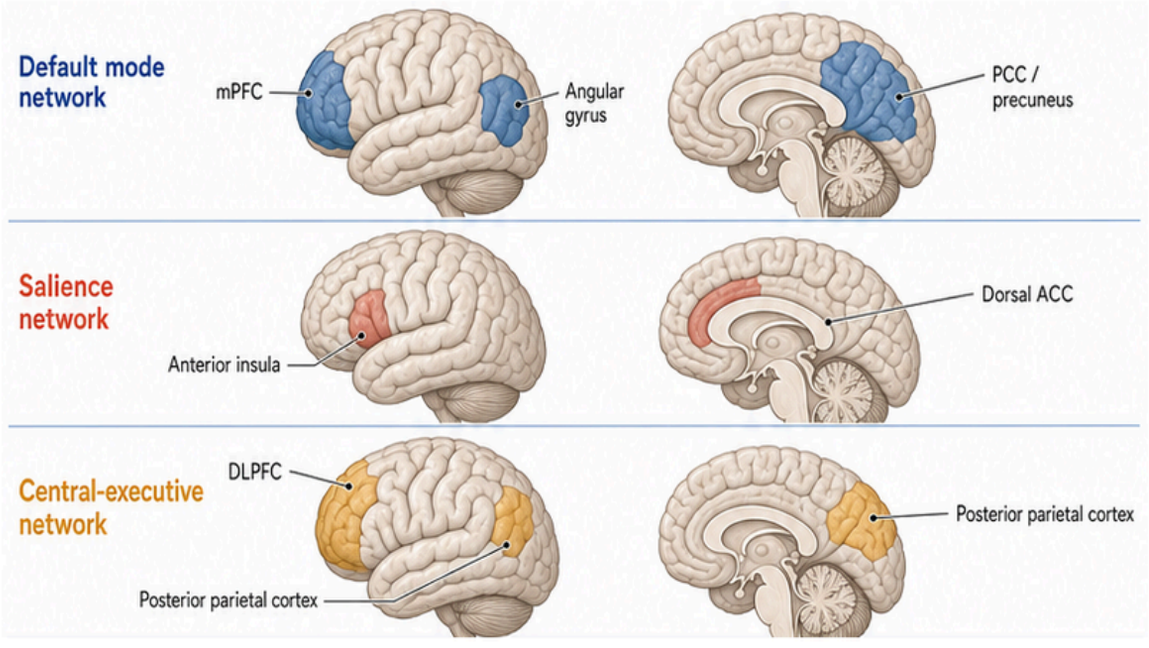


Fig 1.10 The principal anatomical nodes of the default-mode, salience and central-executive networks, shown on matched lateral and medial views.

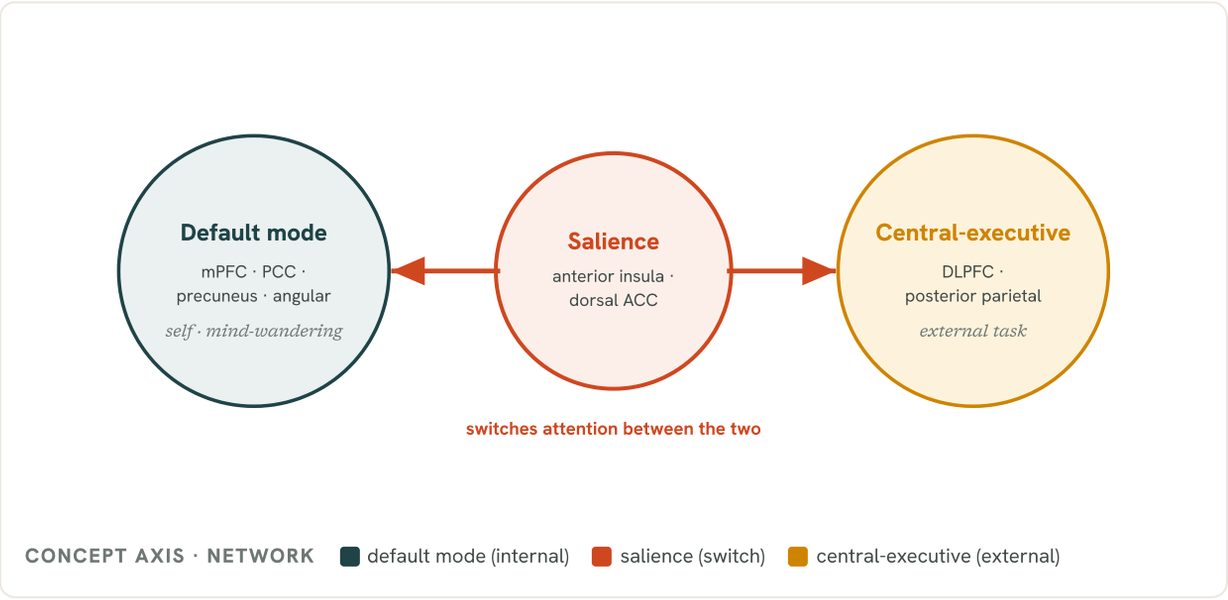


Fig 1.11 The triple network. The salience network (anterior insula, dorsal ACC) detects what matters and toggles the brain between inward self-referential processing (DMN) and outward task control (CEN).

- **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.

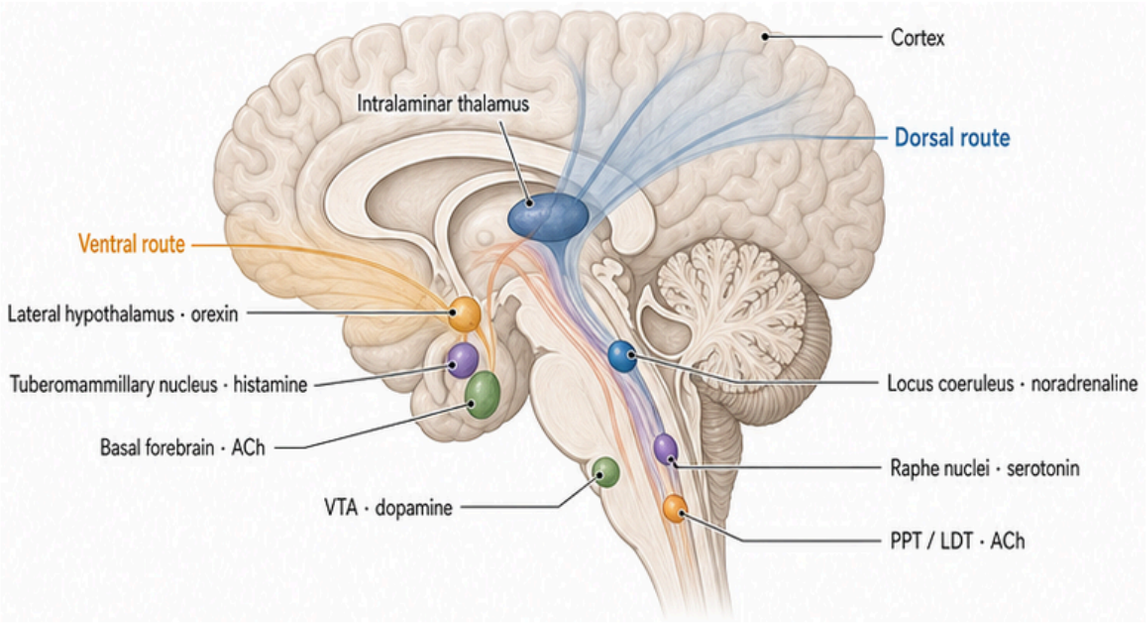


Fig 1.12 The ascending arousal and modulatory systems. Dorsal and ventral routes carry diffuse cholinergic and monoaminergic projections from compact brainstem and hypothalamic nuclei to thalamus, basal forebrain and cortex.

- **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.

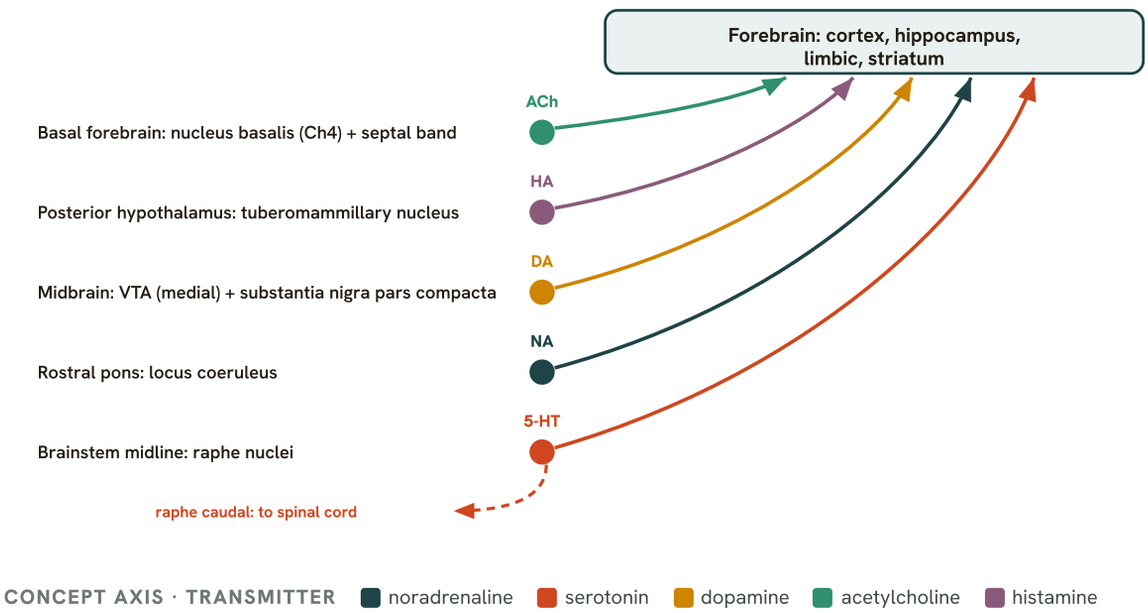


Fig 1.13 The nuclei of origin, plotted rostral to caudal. Each discrete nucleus (colour = transmitter) fans a diffuse ascending projection over the whole forebrain: one nucleus, one transmitter, one gain-setting job. The raphe alone splits its output, rostral to the forebrain and caudal to the cord. 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).

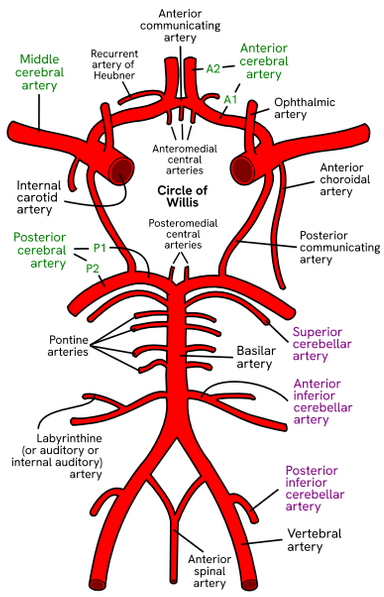


Image: Rhcastilhos, public domain, via Wikimedia Commons

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.

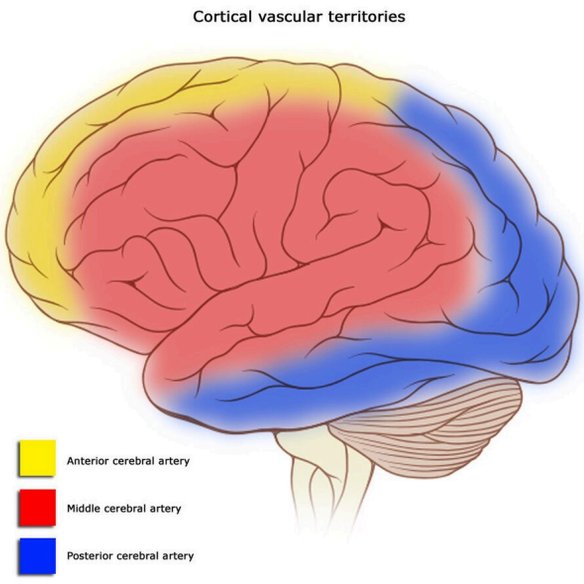


Image: Frank Gaillard, derivative of Patrick J. Lynch, CC BY 2.5, via Wikimedia Commons

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.

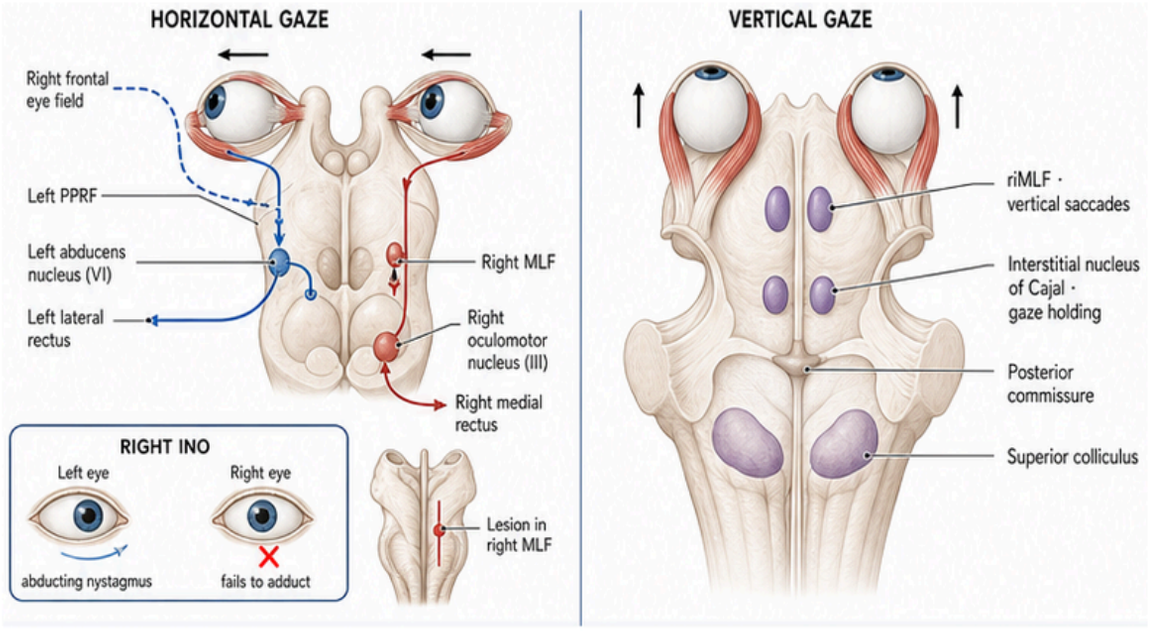


Fig 1.16 Horizontal and vertical conjugate gaze systems. The horizontal pathway links frontal eye field, contralateral PPRF, abducens nucleus and the opposite oculomotor nucleus through the medial longitudinal fasciculus.

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.

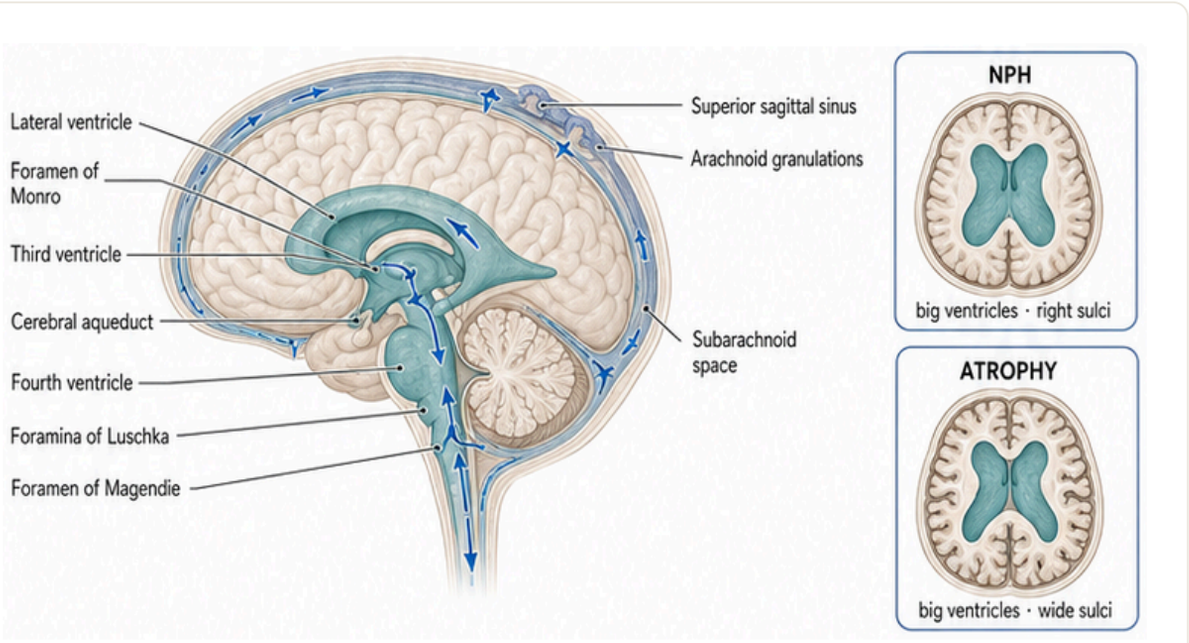


Fig 1.17 Ventricular anatomy and CSF circulation from the lateral ventricles to arachnoid granulations, with the ventricular patterns of normal-pressure hydrocephalus and cerebral atrophy contrasted at right.

- **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.

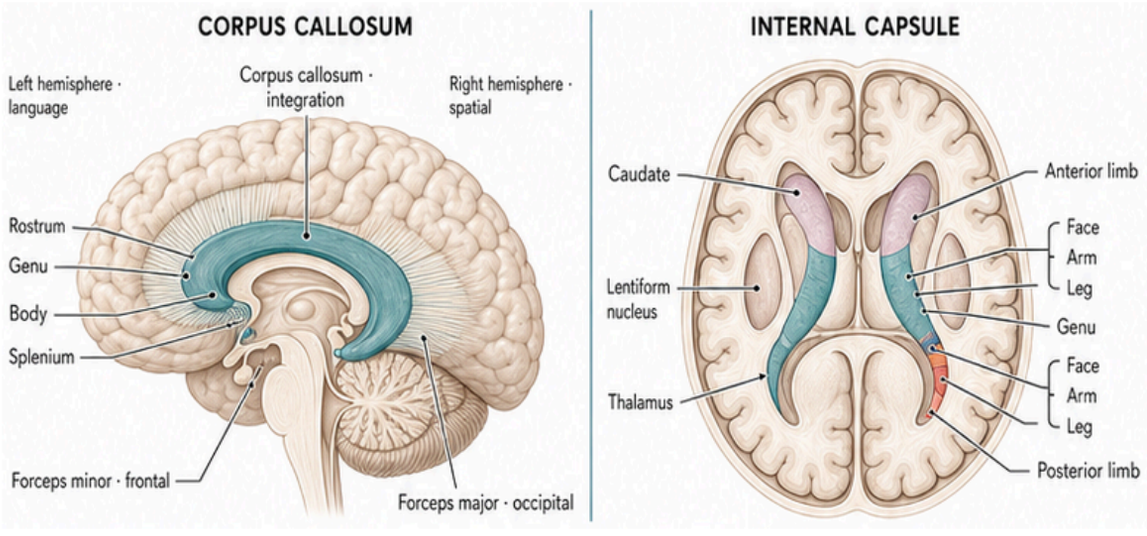


Fig 1.18 The corpus callosum and internal capsule. Callosal sectors connect homologous cortical regions; fibres in the internal capsule are ordered through the anterior limb, genu and posterior limb.

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.

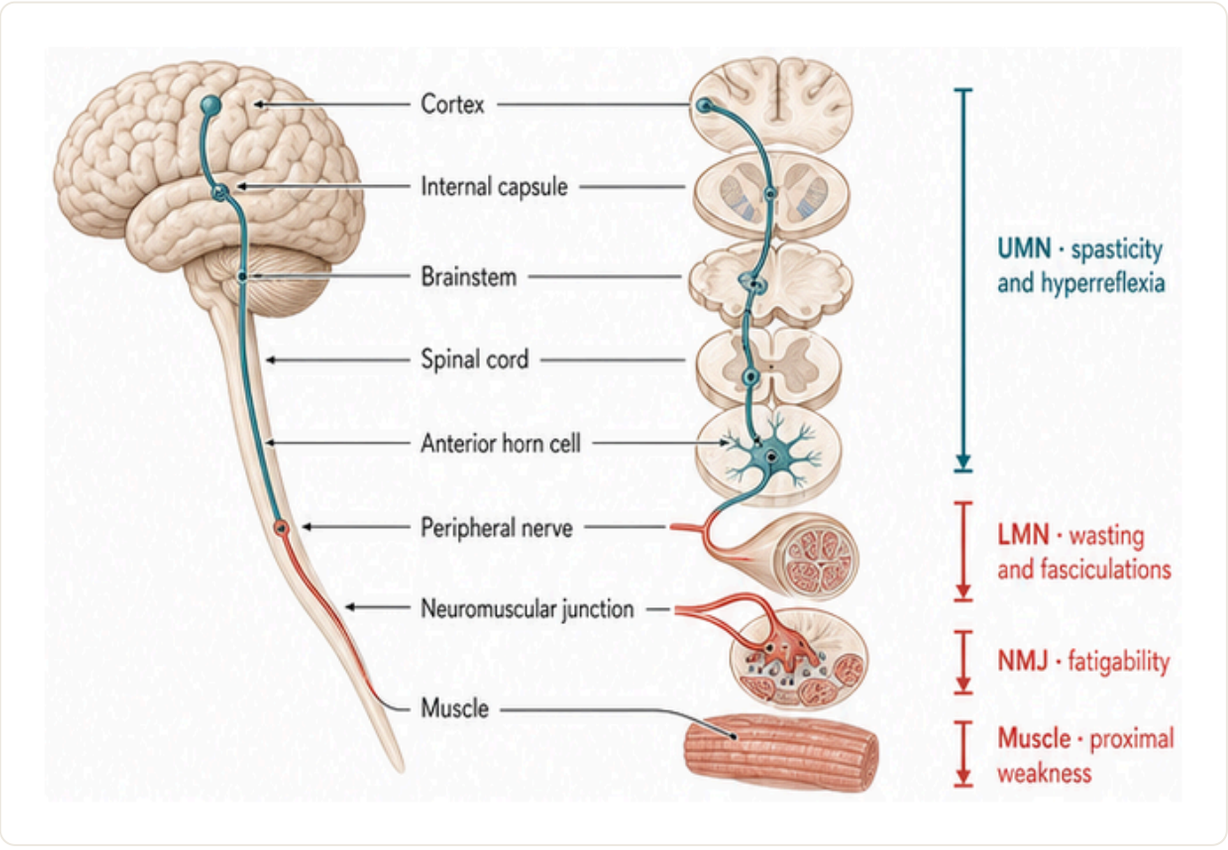


Fig 1.19 Localising a motor lesion along the neuraxis: upper-motor-neuron signs arise above the anterior horn cell, lower-motor-neuron signs below it, with neuromuscular-junction and muscle patterns completing the sequence.

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.

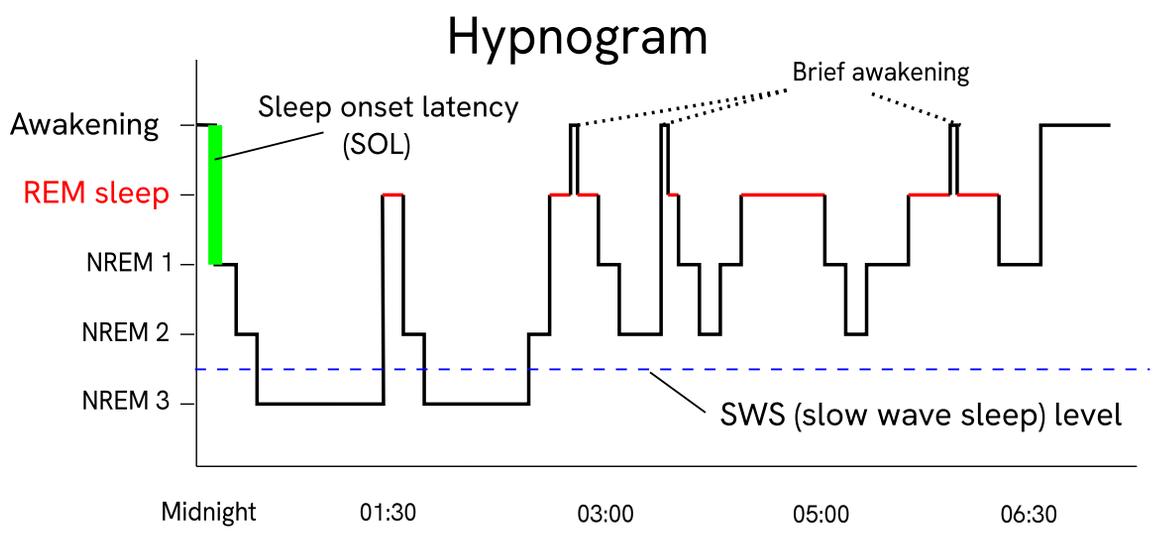


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Fig 1.20 A normal hypnogram. Slow-wave sleep (deep NREM) dominates the first cycles; REM periods lengthen toward morning. The older Rechtschaffen-Kales staging shown (1 to 4) maps to current AASM staging as N1, N2 and N3 (stages 3 and 4 combined). 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.

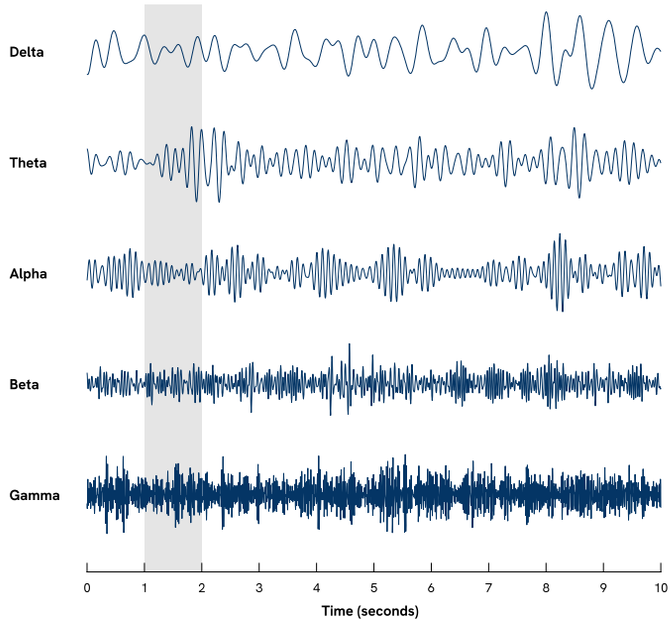


Image: Laurens R. Krol, CC0 / public domain, via Wikimedia Commons

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.

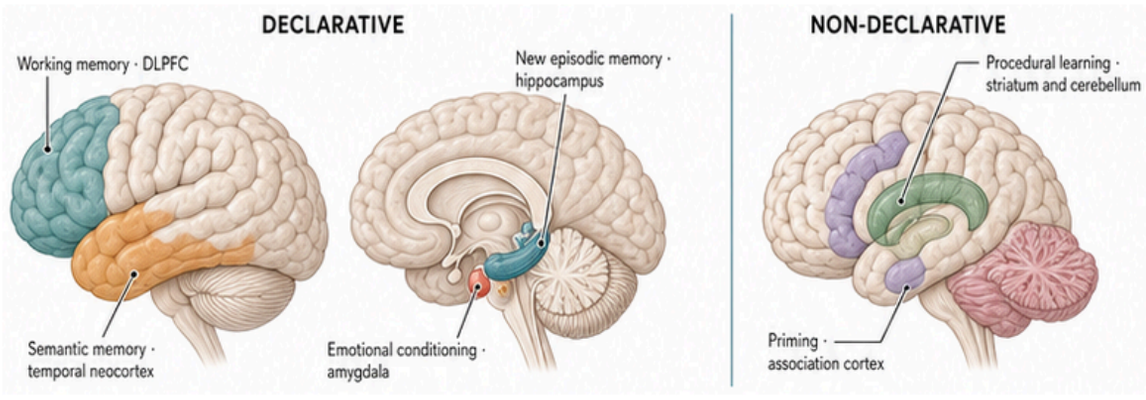


Fig 1.22 Memory systems and their principal neural substrates. Declarative memory depends on medial temporal and association cortex; non-declarative learning recruits striatum, cerebellum, amygdala and priming networks.

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.

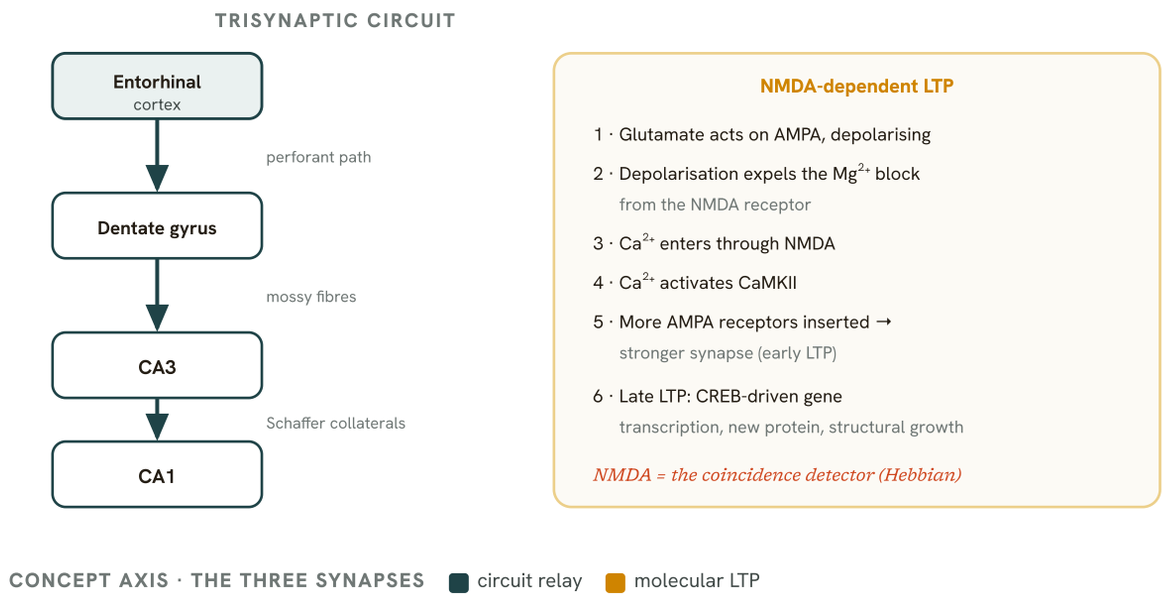


Fig 1.23 The hippocampal trisynaptic circuit (entorhinal to dentate to CA3 to CA1) and the NMDA-dependent mechanism of LTP, the synaptic basis of declarative memory.

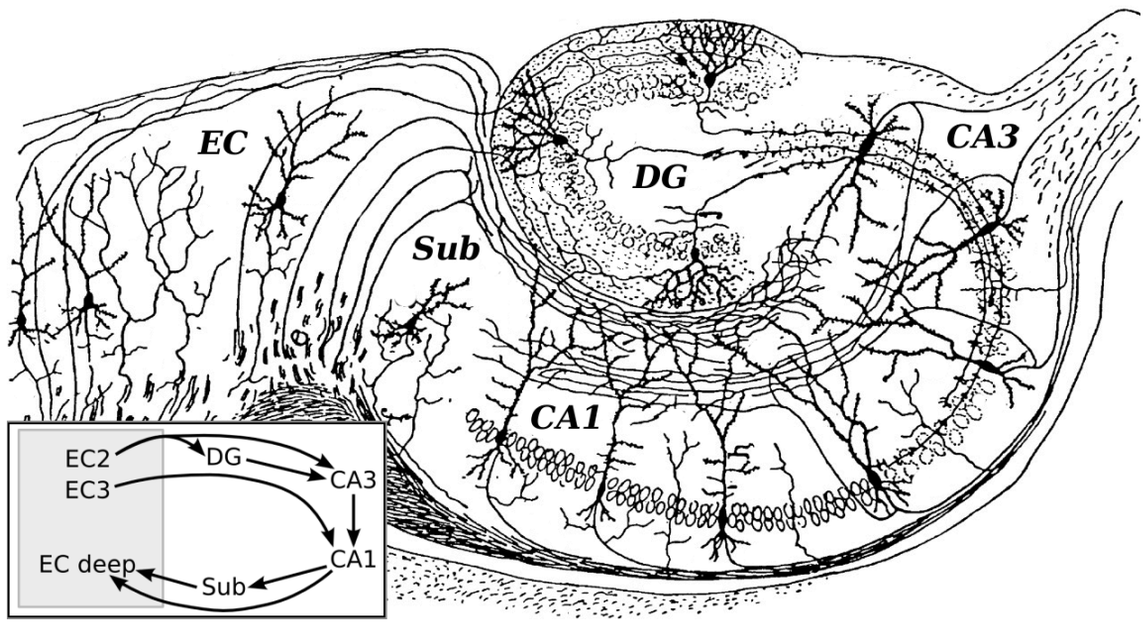


Image: Santiago Ramon y Cajal (1911), public domain, via Wikimedia Commons

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.

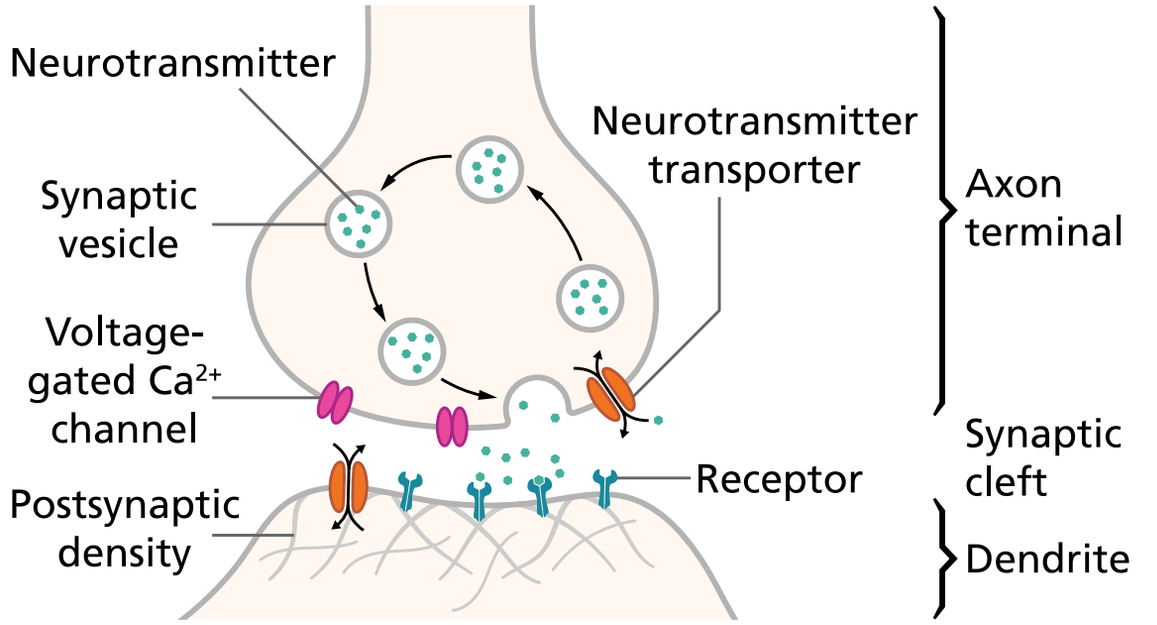


Image: Thomas Splettstoesser (scistyle.com), CC BY-SA 4.0, via Wikimedia Commons

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.

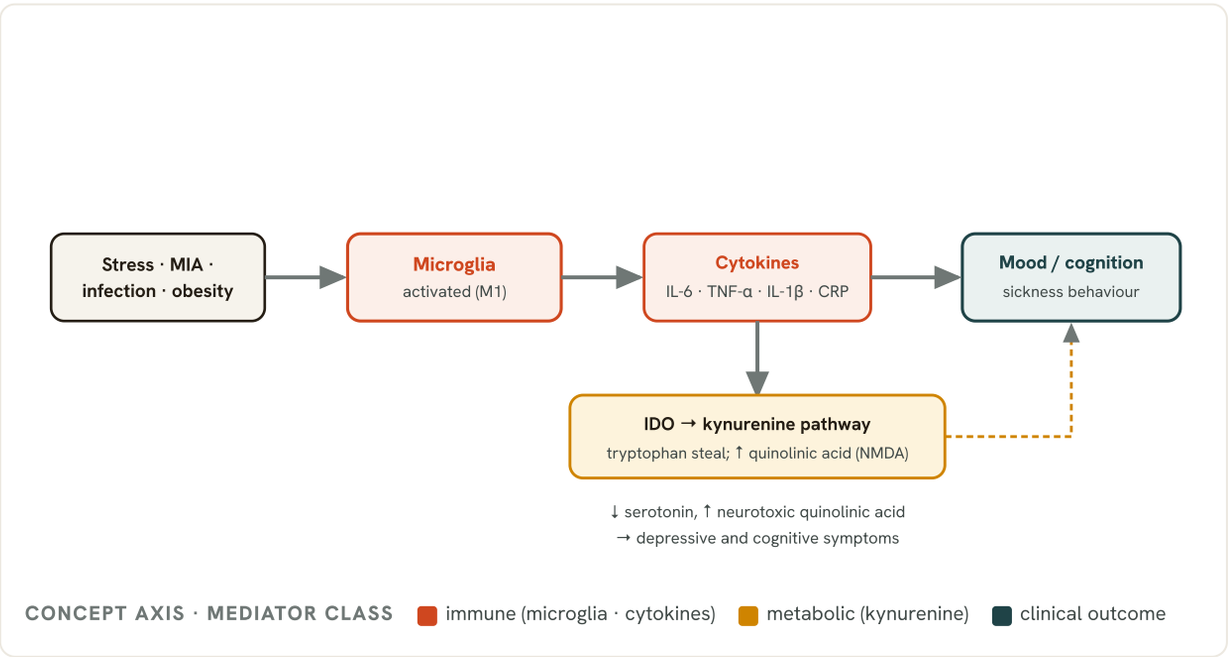


Fig 1.26 The inflammatory route to mood symptoms: peripheral and central immune activation drives cytokine release, which shunts tryptophan down the kynurenine pathway (less serotonin, more neurotoxic quinolinic acid) and produces sickness behaviour.

- **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.

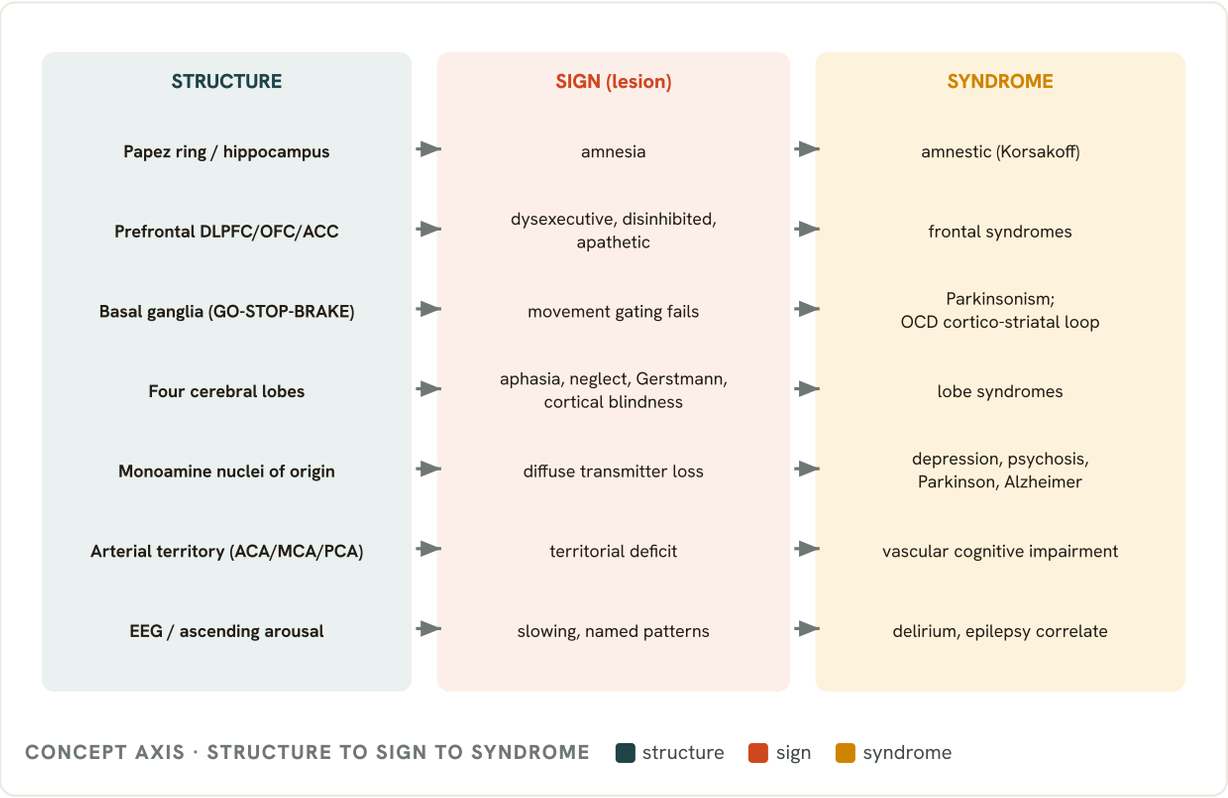


Fig 1.27 The whole-chapter synthesis map. Every system reduces to one line: a structure, the sign its lesion produces, and the named syndrome. Cover the right two columns and rebuild them from the structure alone; the rows you cannot complete are the topics to reopen.

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.

REFERENCES (PUBMED-VERIFIED)

1. Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 10th ed. Philadelphia: Wolters Kluwer; 2017. [Neuroanatomy, neurophysiology, sleep backbone]
2. Stahl SM. Stahl's Essential Psychopharmacology. 5th ed. Cambridge: Cambridge University Press; 2021. [Neurotransmission, plasticity]
3. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain. 1998;121(Pt 4):561-579. PMID 9577385.
4. Papez JW. A proposed mechanism of emotion. Arch Neurol Psychiatry. 1937;38(4):725-743. (Reprinted: J Neuropsychiatry Clin Neurosci. 1995;7(1):103-112. PMID 7711480.)
5. Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry. 1957;20(1):11-21. PMID 13406589.
6. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15(10):483-506. PMID 21908230.
7. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA. 2001;98(2):676-682. PMID 11209064.
8. Borbély AA. A two process model of sleep regulation. Hum Neurobiol. 1982;1(3):195-204. PMID 7185792.
9. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. Biol Psychiatry. 2010;67(5):446-457. PMID 20015486.
10. Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. Biol Psychiatry. 2008;64(6):527-532. PMID 18571629.
11. Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. Neuron. 2010;68(6):1023-1042. PMID 21172606.
12. Köhler-Forsberg O, Lydholm CN, Hjorthøj C, et al. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. Acta Psychiatr Scand. 2019;139(5):404-419. PMID 30834514.
13. Bliss TVP, Lømo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol. 1973;232(2):331-356. PMID 4727084.
14. Wilson S, Anderson K, Baldwin D, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: an update (2019). J Psychopharmacol. 2019;33(8):923-947. PMID 31271339.
15. Gururaj G, Varghese M, Benegal V, et al. National Mental Health Survey of India, 2015-16: Prevalence, patterns and outcomes. Bengaluru: NIMHANS; 2016.

REFERENCES (LOBES, VASCULAR, STRESS, LOCALISATION AND CONSOLIDATION TOPICS; PUBMED-VERIFIED)

1. Javed K, Reddy V, Lui F. Neuroanatomy, Cerebral Cortex. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. [lobar functional anatomy]
2. El-Baba RM, Schury MP. Neuroanatomy, Frontal Cortex. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. PMID 32119370.
3. Altabakhi IW, Liang JW. Gerstmann Syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. PMID 30137813.
4. Rehman A, Al Khalili Y. Neuroanatomy, Occipital Lobe. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. PMID 31335040.
5. Das JM, Naqvi IA. Anton Syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. PMID 30844182.
6. Chayer C, Freedman M. Frontal lobe functions. Curr Neurol Neurosci Rep. 2001;1(6):547-552. PMID 11898568.
7. Lanska DJ. The Kluver-Bucy Syndrome. Front Neurol Neurosci. 2018;41:77-89. PMID 29145186.
8. Konan LM, Reddy V, Mesfin FB. Neuroanatomy, Cerebral Blood Supply. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. [circle of Willis, arterial territories]
9. Benjamin R, Tadi P, Singh J. Posterior Cerebral Artery Stroke. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2026. PMID 30335329.
10. Kayalvizhi I, et al. Neurological Localization (NBK493159). In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023. [UMN/LMN, crossed signs, sensory level, false localisers]
11. Virgo JD, Plant GT. Internuclear ophthalmoplegia. Pract Neurol. 2017;17(2):149-153. PMID 27927777.
12. Pastora-Salvador N, Peralta-Calvo J. Foster Kennedy syndrome. CMAJ. 2011;183(18):2135. PMID 21948724.

13. Ulrich-Lai YM, Herman JP. Neural regulation of endocrine and autonomic stress responses. Nat Rev Neurosci. 2009;10(6):397-409. PMID 19469025.
14. LeDoux J. Rethinking the emotional brain. Neuron. 2012;73(4):653-676. PMID 22365542.
15. Reul JM, de Kloet ER. Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. Endocrinology. 1985;117(6):2505-2511. PMID 2998738.
16. Diamond DM, Bennett MC, Fleshner M, Rose GM. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. Hippocampus. 1992;2(4):421-430. PMID 1308198.
17. Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. J Neurosci. 2002;22(15):6810-6818. PMID 12151561.
18. Sapolsky RM, Krey LC, McEwen BS. The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. Endocr Rev. 1986;7(3):284-301. PMID 3527687.
19. Lupien SJ, de Leon M, de Santi S, et al. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nat Neurosci. 1998;1(1):69-73. PMID 10195112.
20. Starkman MN, Gebarski SS, Berent S, Schteingart DE. Hippocampal formation volume, memory dysfunction, and cortisol levels in patients with Cushing's syndrome. Biol Psychiatry. 1992;32(9):756-765. PMID 1450290.
21. Yehuda R, McFarlane AC, Shalev AY. Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. Biol Psychiatry. 1998;44(12):1305-1313. PMID 9861473.
22. Santini E, Quirk GJ, Porter JT. Fear conditioning and extinction differentially modify the intrinsic excitability of infralimbic neurons. J Neurosci. 2008;28(15):4028-4036. PMID 18400902.
23. Choi DC, Furay AR, Evanson NK, et al. Bed nucleus of the stria terminalis subregions differentially regulate hypothalamic-pituitary-adrenal axis activity. J Neurosci. 2007;27(8):2025-2034. PMID 17314298.
24. McEwen BS, Stellar E. Stress and the individual: mechanisms leading to disease. Arch Intern Med. 1993;153(18):2093-2101. PMID 8379800.
25. Drevets WC, Raichle ME. Neuroanatomical circuits in depression: implications for treatment mechanisms. Psychopharmacol Bull. 1992;28(3):261-274. PMID 1480730.
26. Dafny N, Claussen C, Frazier E, Liu Y. Differential roles of key brain regions: ventral tegmental area, locus coeruleus, dorsal raphe and others in regulating response to methylphenidate. Int J Mol Sci. 2024;25(11):5938. PMID 38892125.
27. Berlin HA, Rolls ET, Kischka U. Impulsivity, time perception, emotion and reinforcement sensitivity in patients with orbitofrontal cortex lesions. Brain. 2004;127(Pt 5):1108-1126. PMID 14985269.
28. Parton A, Malhotra P, Husain M. Hemispatial neglect. J Neurol Neurosurg Psychiatry. 2004;75(1):13-21. PMID 14707298.
29. Aldrich MS, Alessi AG, Beck RW, Gilman S. Cortical blindness: etiology, diagnosis, and prognosis. Ann Neurol. 1987;21(2):149-158. PMID 3827223.
30. Roediger HL 3rd, Karpicke JD. Test-enhanced learning: taking memory tests improves long-term retention. Psychol Sci. 2006;17(3):249-255. PMID 16507066.
31. Cannon WB. Bodily Changes in Pain, Hunger, Fear and Rage. New York: Appleton; 1915. [fight-or-flight, historical]
32. Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. In: Fisher S, Reason J, eds. Handbook of Life Stress, Cognition and Health. New York: Wiley; 1988. [allostasis, book chapter]

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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.

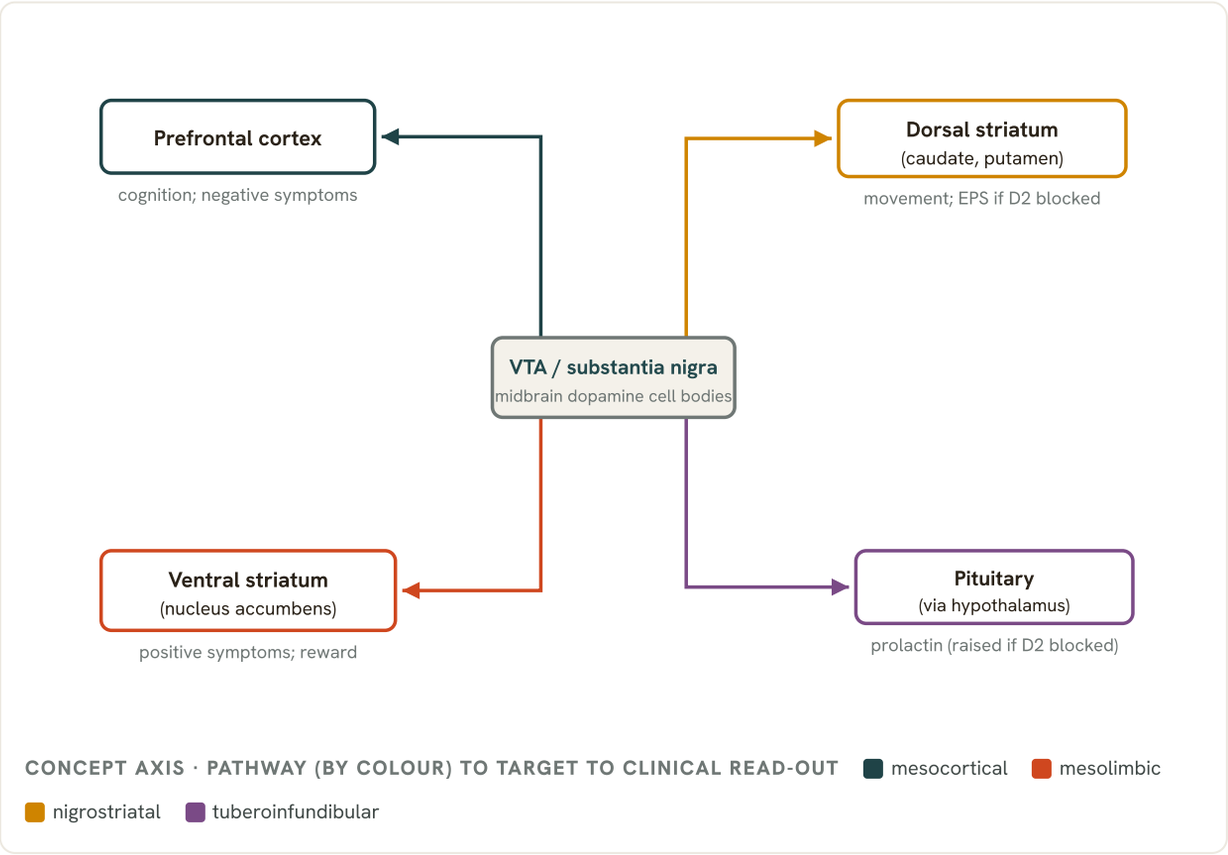


Fig 2.1 The four dopamine pathways from the midbrain nuclei (VTA and substantia nigra), each ending at its target with the clinical read-out a D2 blocker produces there. Mesocortical (petrol) runs to prefrontal cortex, mesolimbic (coral) to ventral striatum, nigrostriatal (marigold) to dorsal striatum, 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*.

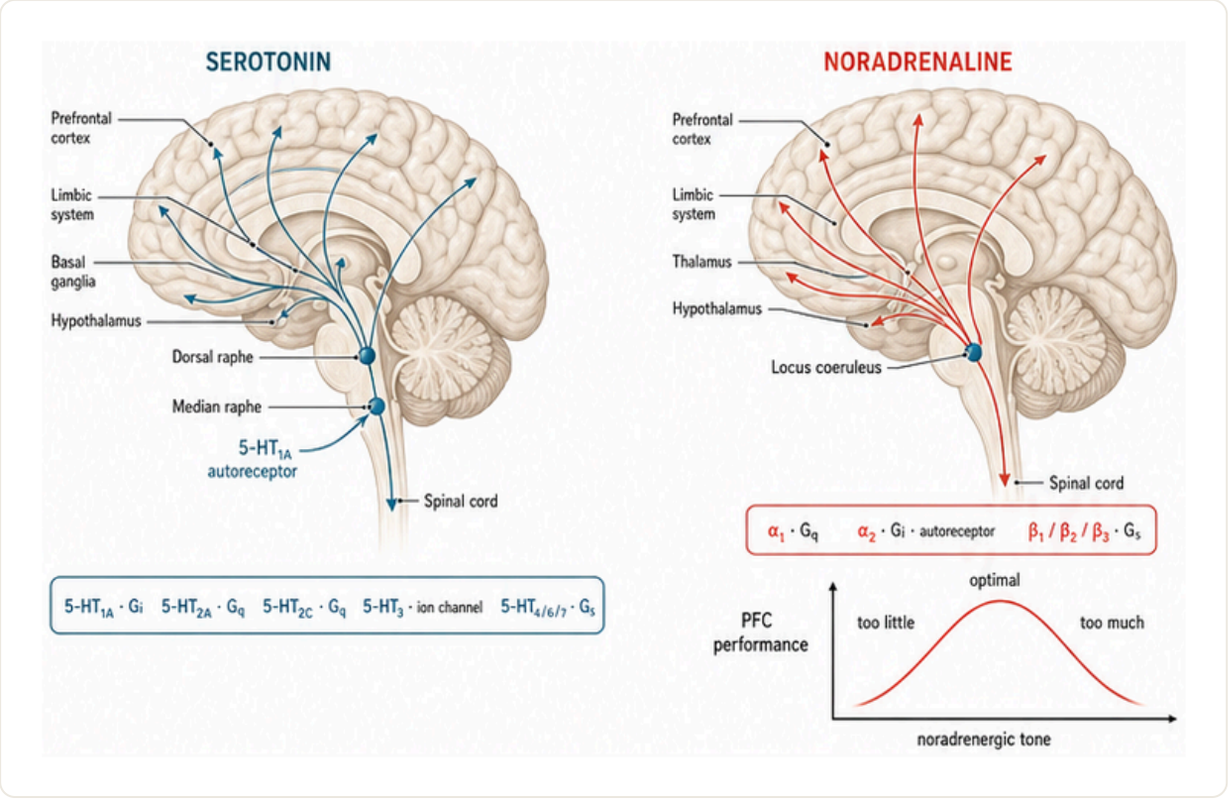


Fig 2.2 Serotonin and noradrenaline systems.

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.

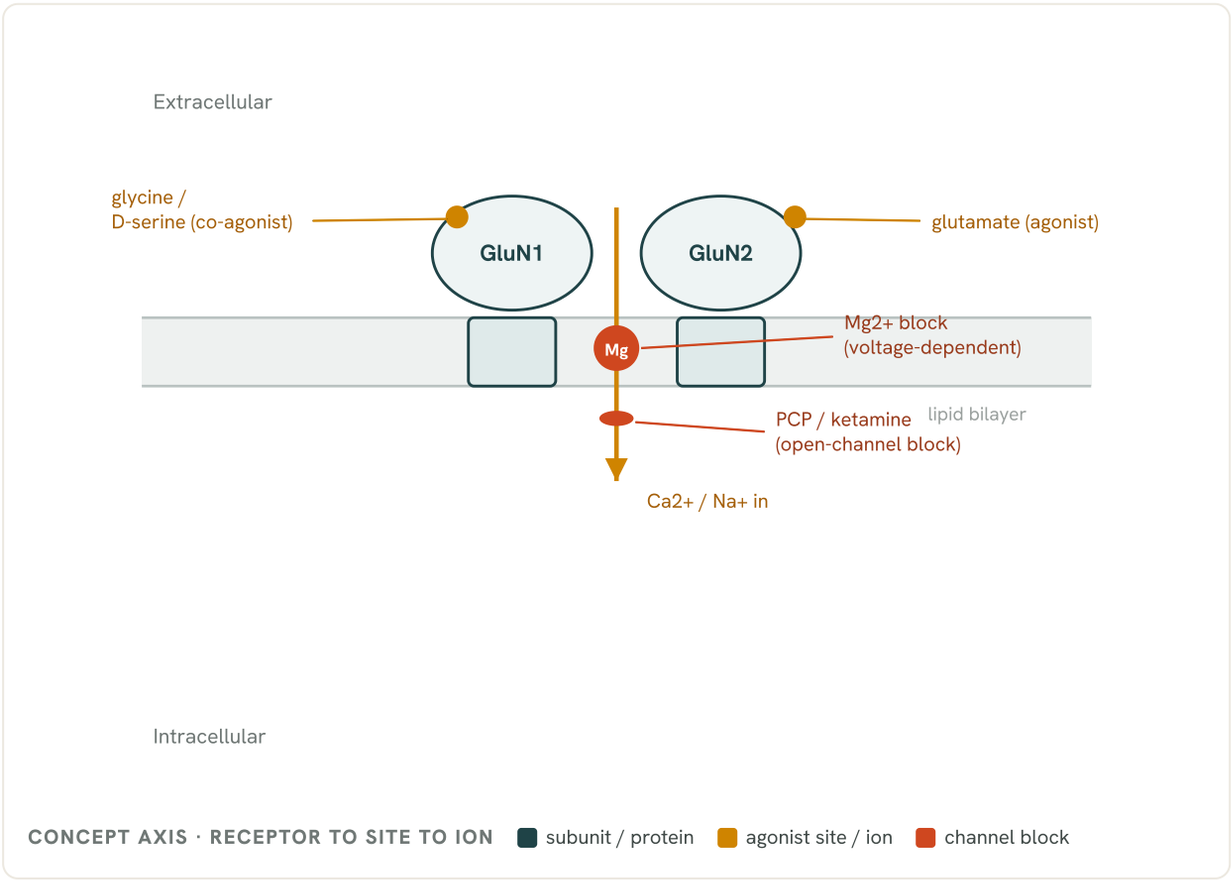


Fig 2.3 The NMDA receptor as a coincidence detector. Opening needs two things at once: the agonist glutamate at GluN2 and the co-agonist glycine or D-serine at GluN1, plus depolarisation to expel the voltage-dependent Mg2+ block from the pore. Only then do Ca2+ and Na+ flow in. Ketamine and PCP are open-channel 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).

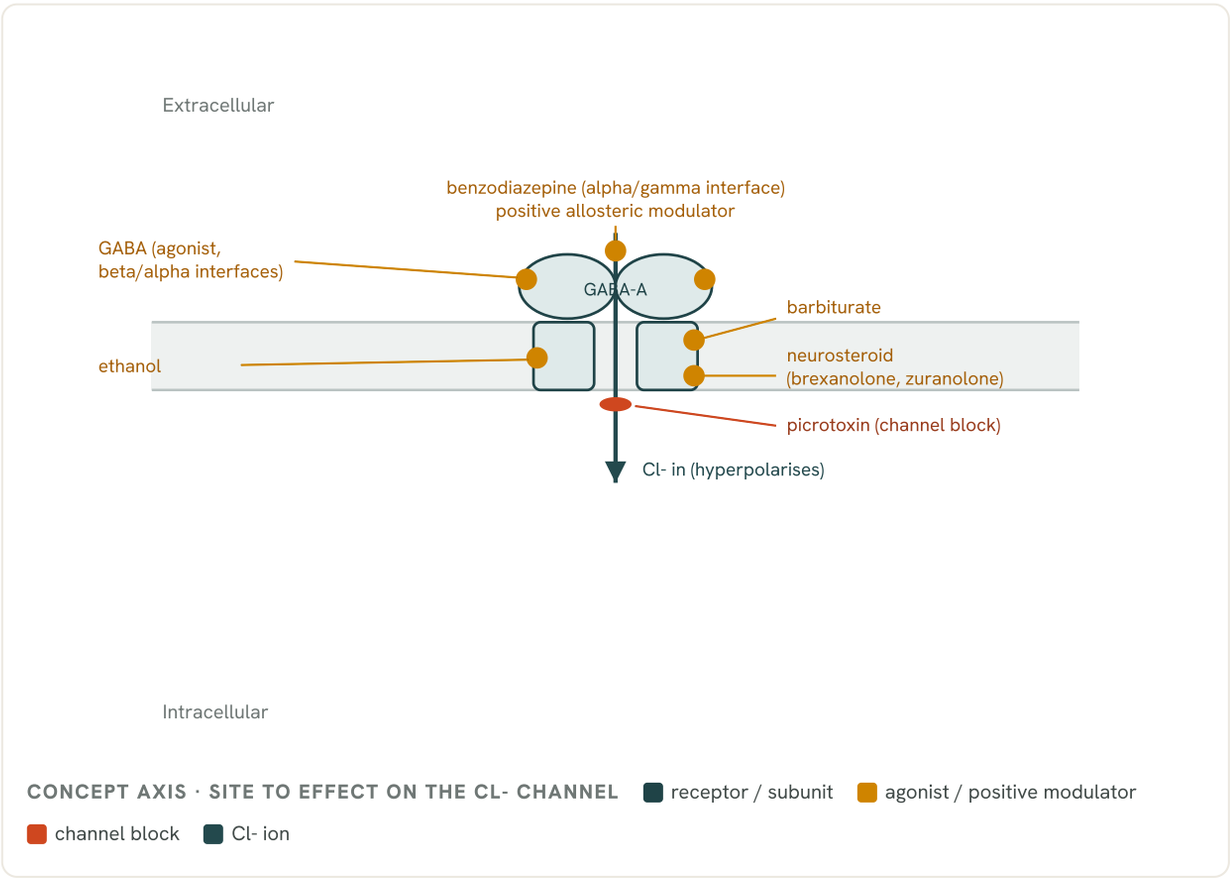


Fig 2.4 The GABA-A receptor is one chloride channel with many doors. GABA itself opens it at the beta/alpha subunit interfaces; benzodiazepines bind the separate alpha/gamma site and increase the frequency of opening (flumazenil blocks this site); barbiturates increase the duration of opening; neurosteroids (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).

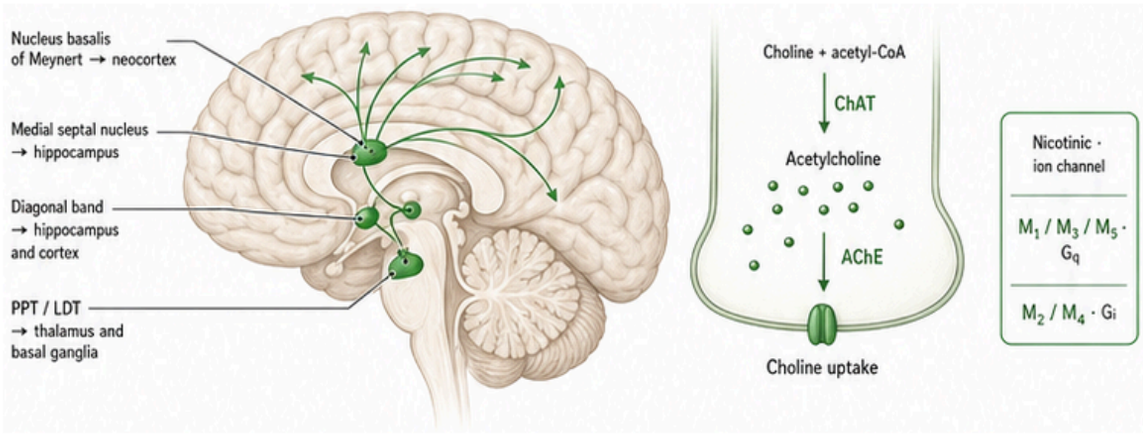


Fig 2.5 Central cholinergic systems.

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.

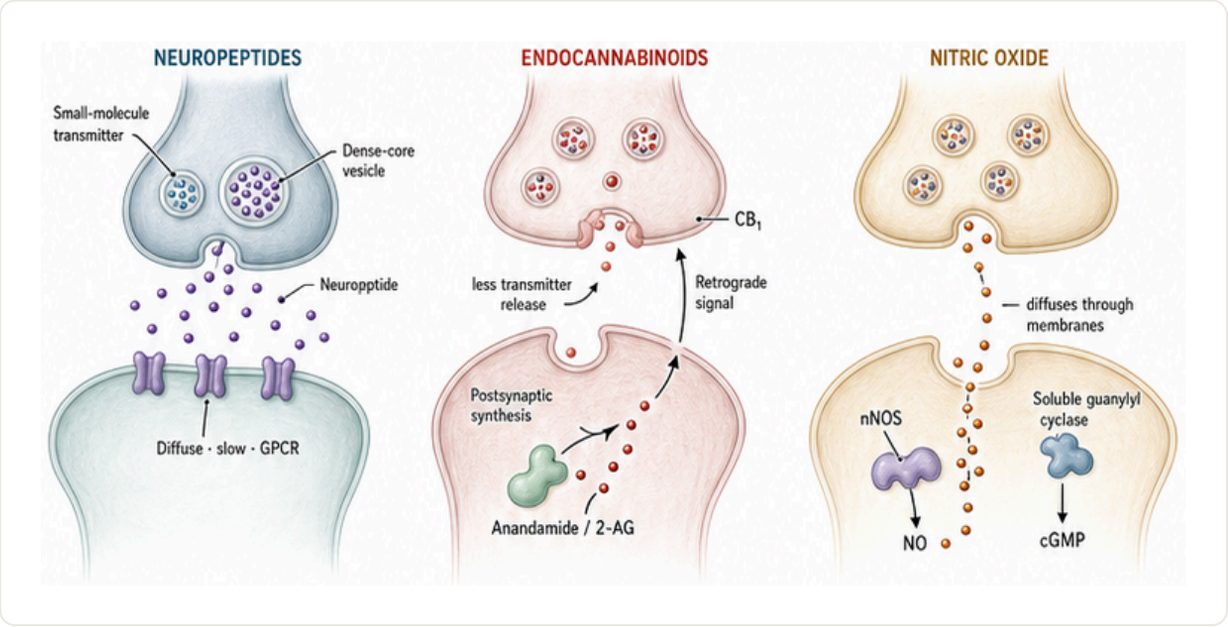


Fig 2.6 Unconventional neurotransmission.

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.

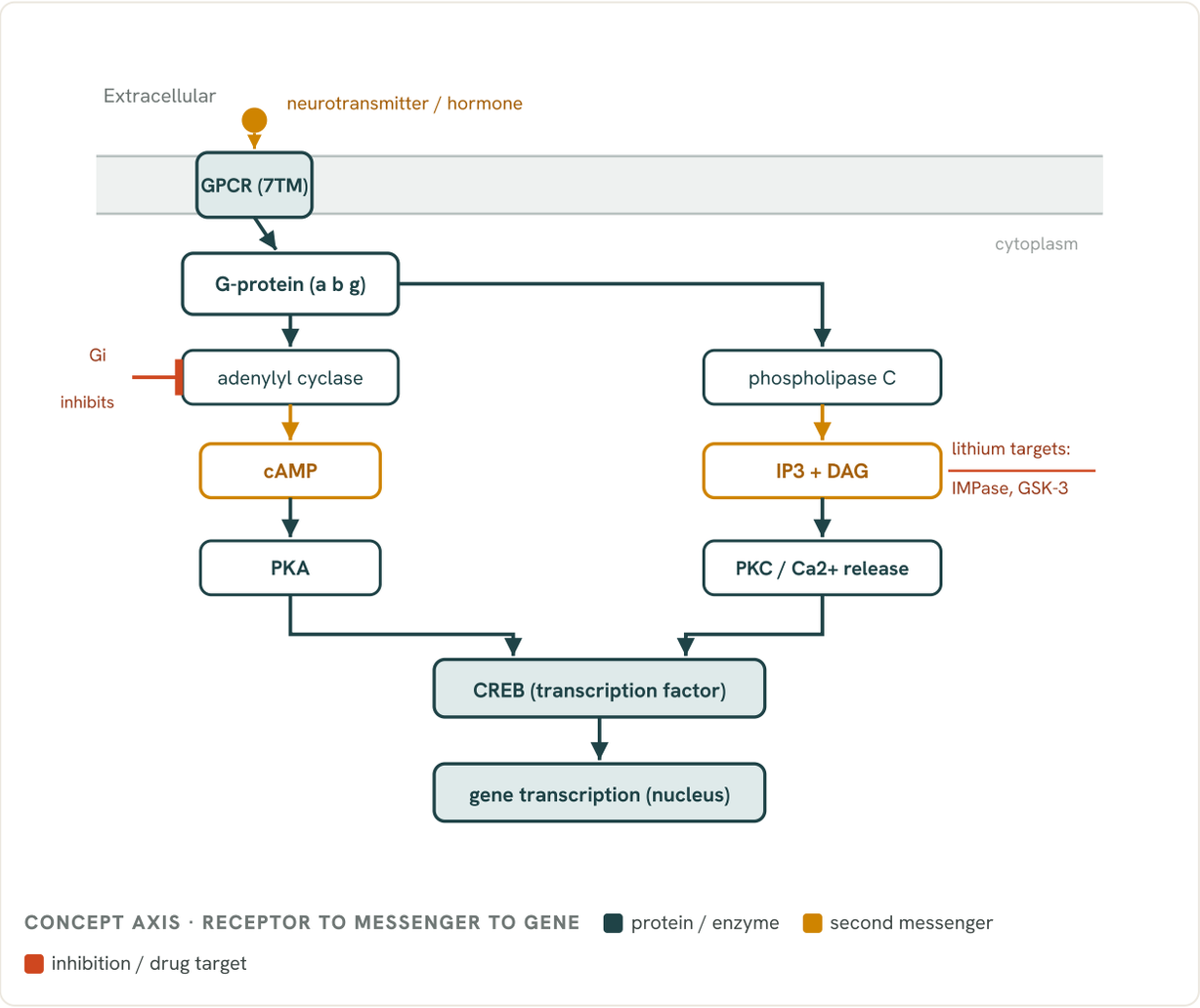


Fig 2.7 The two main G-protein-coupled cascades. Gs drives adenylyl cyclase to cAMP to PKA; Gq drives phospholipase C to IP3 and DAG, raising intracellular Ca2+ and activating PKC; Gi inhibits adenylyl cyclase. Both converge on CREB and gene transcription, the slow, plasticity-relevant layer that explains 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"

G**q** 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).

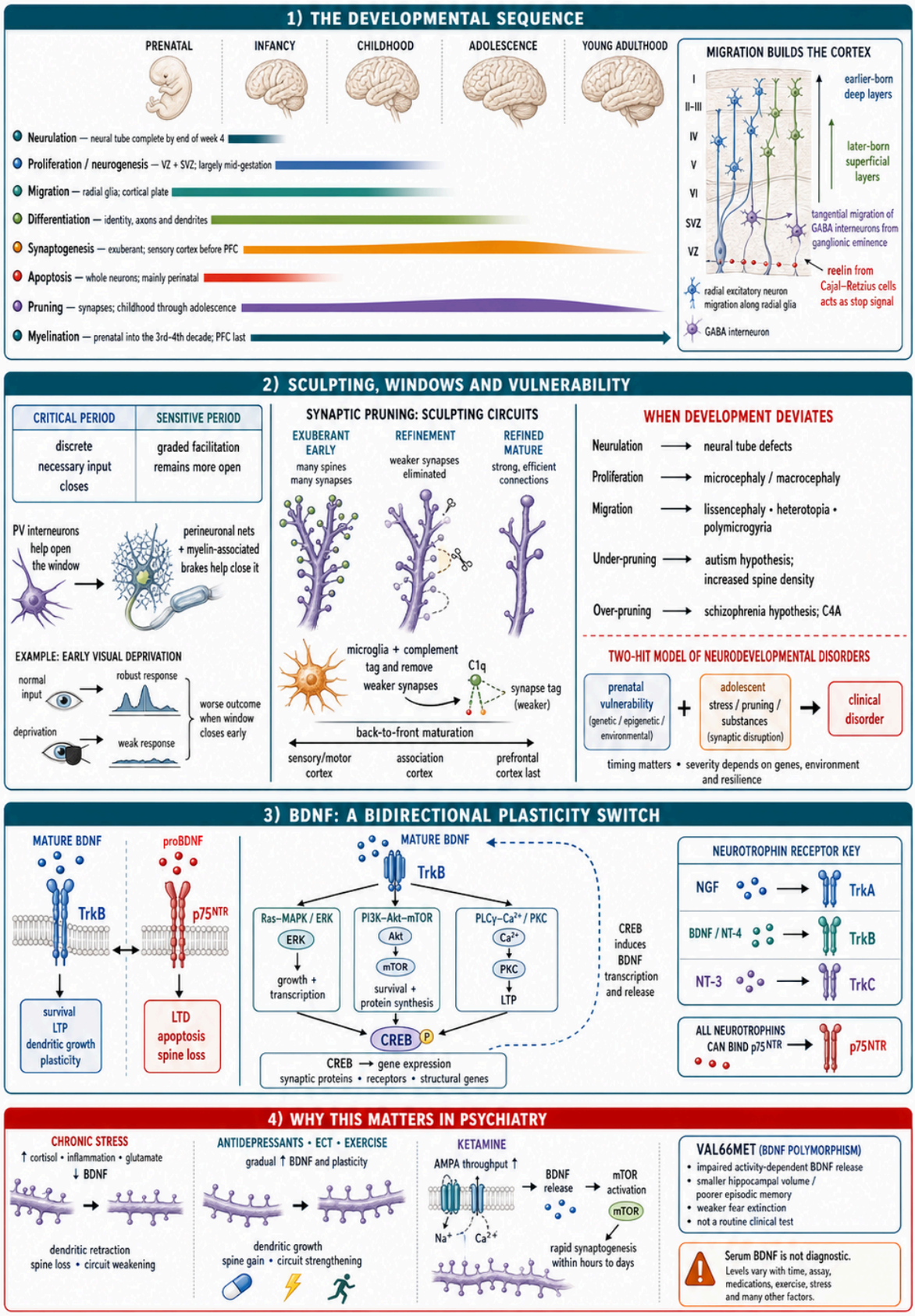


Fig 2.8 Neurodevelopment and BDNF: build, sculpt, rebuild.

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

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.

> **CLINICAL ANCHOR**
>
> 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.

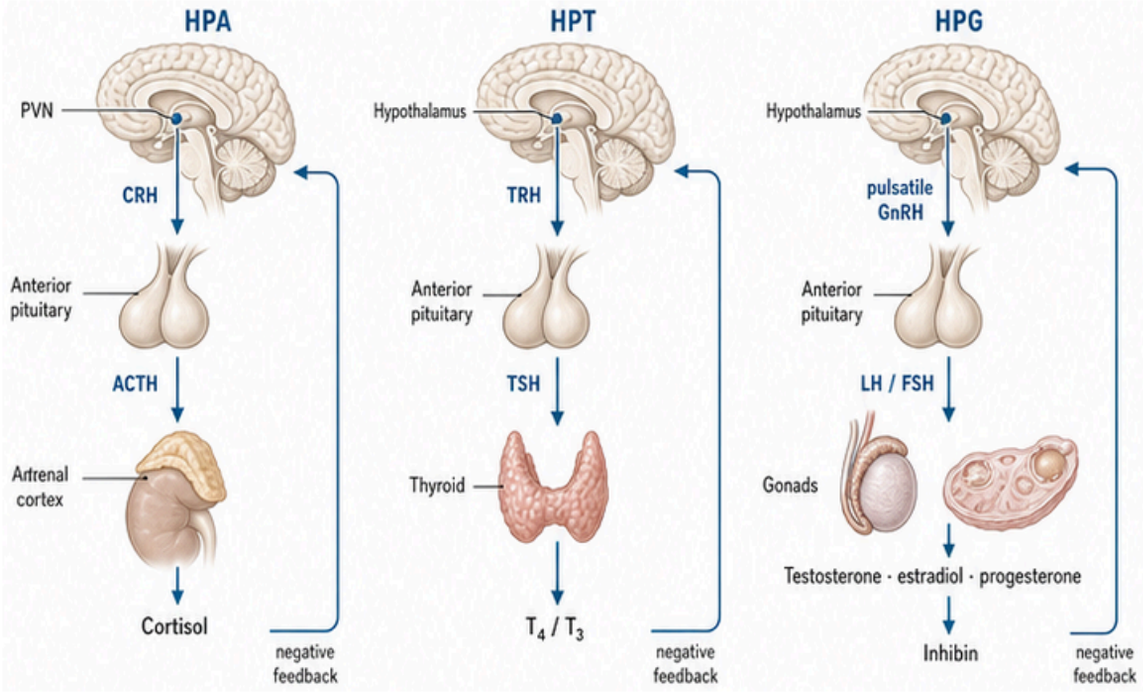


Fig 2.9 The three neuroendocrine axes.

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.

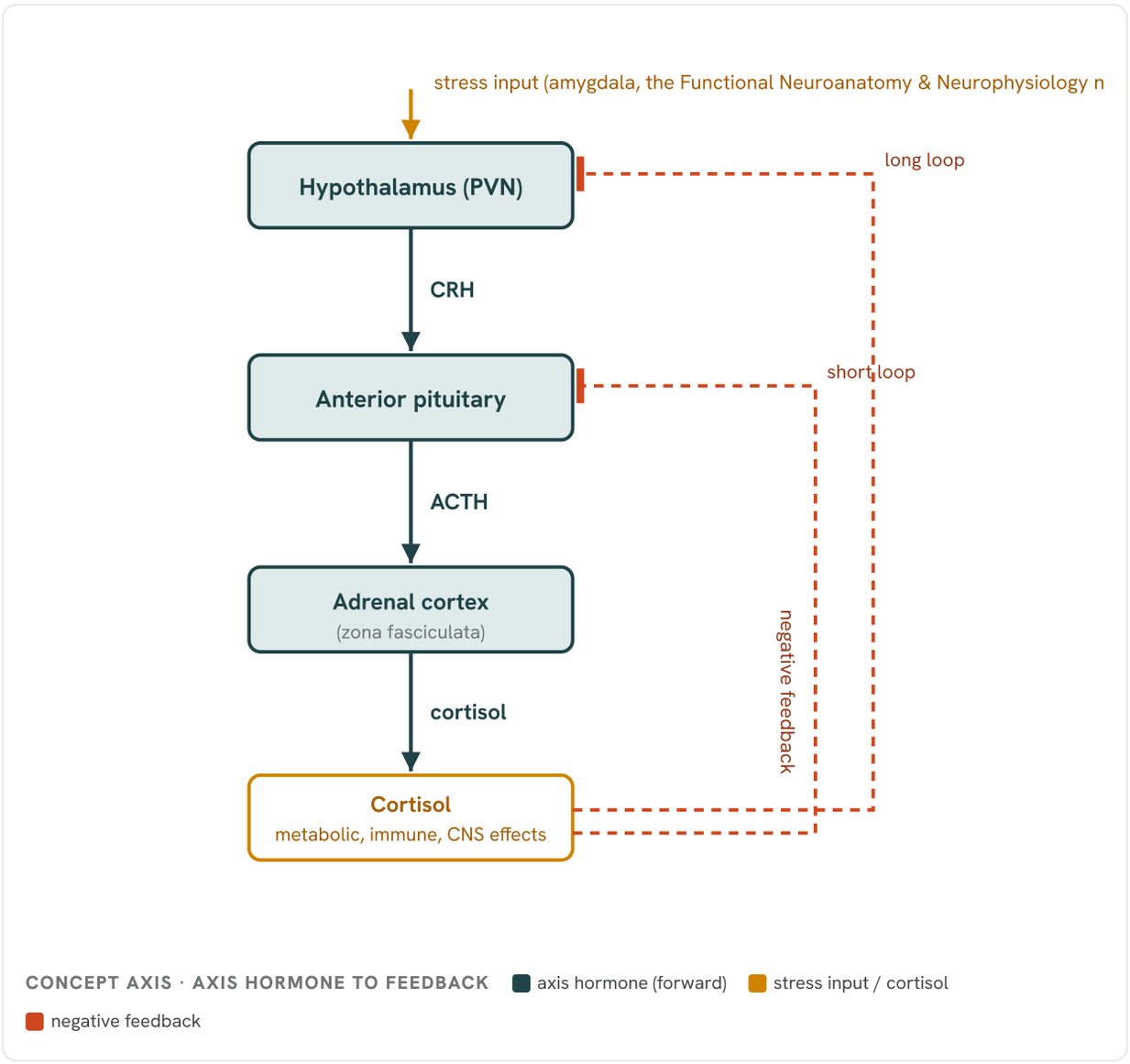


Fig 2.10 The HPA axis. A limbic stress signal (from the Functional Neuroanatomy & Neurophysiology circuit) drives the hypothalamic paraventricular nucleus to release CRH, which drives pituitary ACTH, which drives adrenal cortisol. Cortisol then closes two negative-feedback loops, a short loop onto the 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.

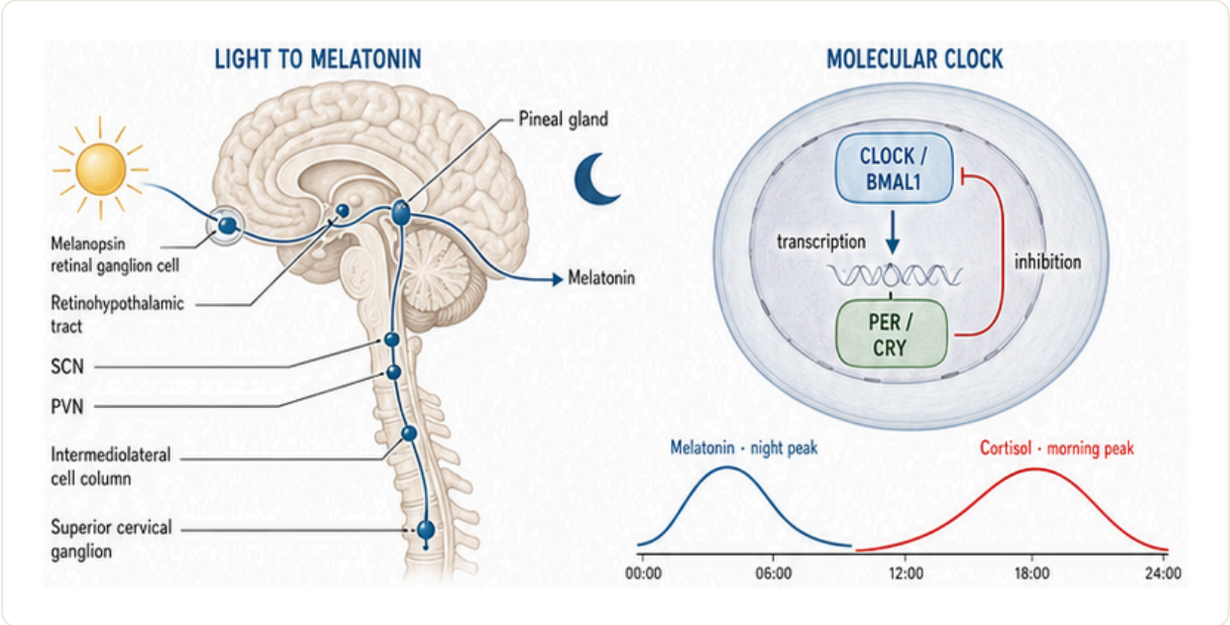


Fig 2.11 The circadian clock.

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.

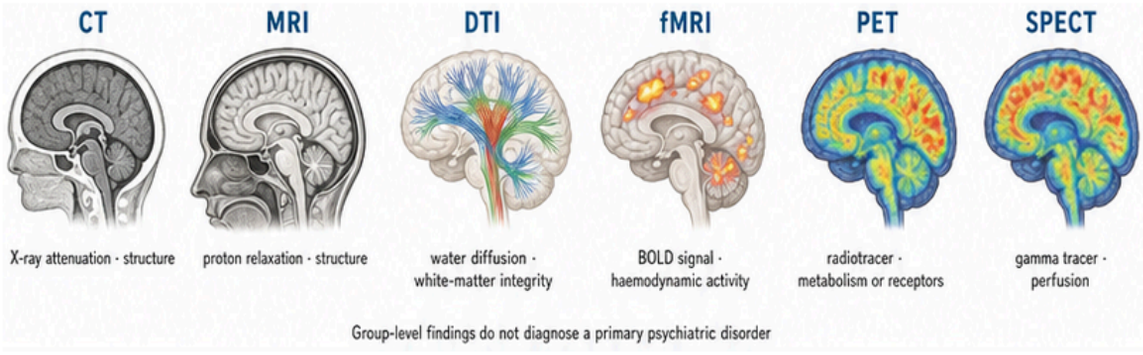
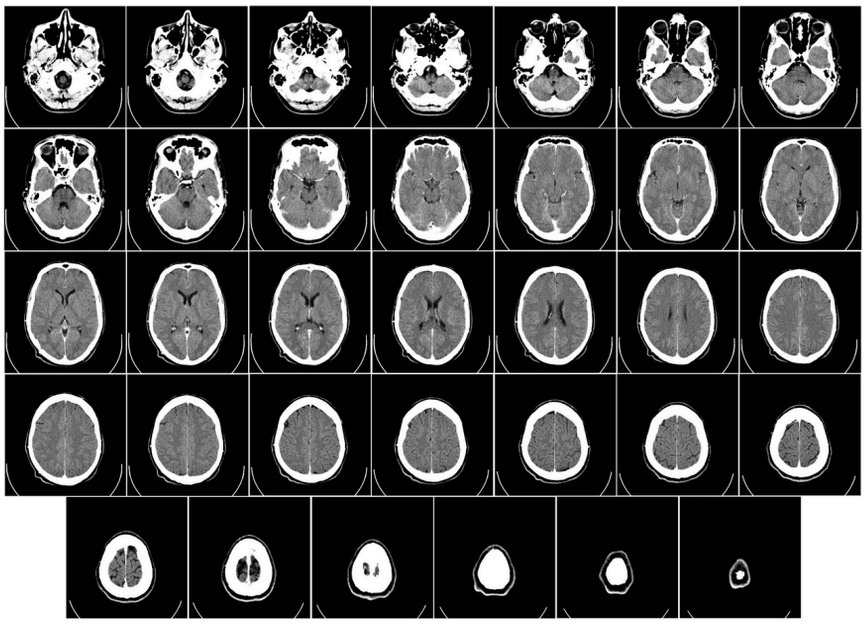
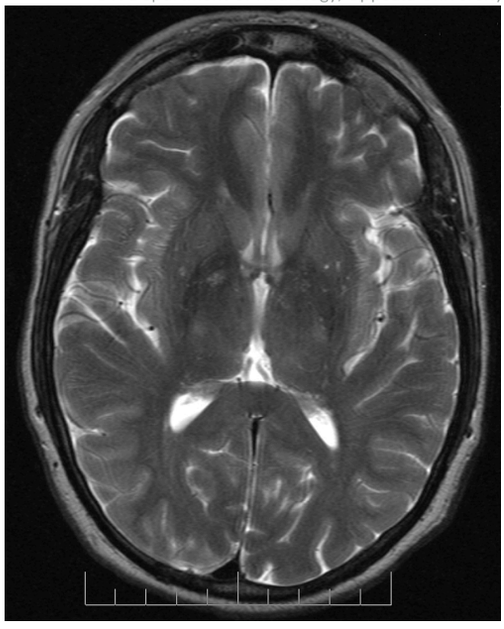


Fig 2.12 What each imaging modality measures.

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.

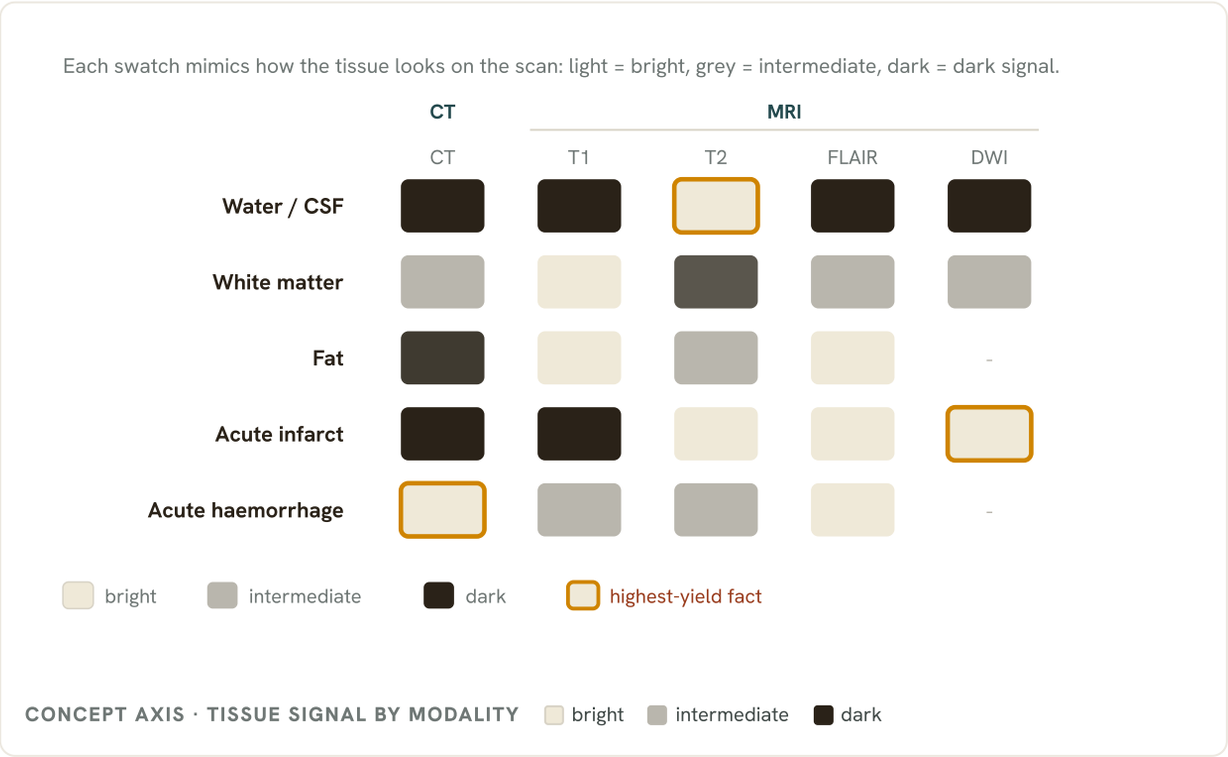


Fig 2.14 How to read the sequences at a glance. Anchor on water: CSF is bright only on T2, and FLAIR is a T2 with the CSF signal suppressed (so a periventricular lesion stands out). Fat is bright on T1. Acute haemorrhage is bright (hyperdense) on CT, which is why CT is the emergency scan; an acute infarct 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

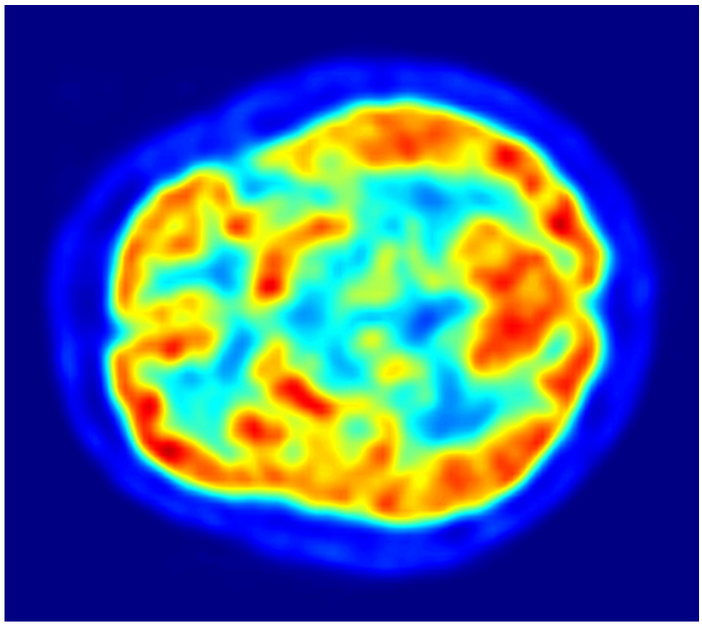
"Ventricles up, hippocampus down, white matter bright, atrophy where the syndrome lives"

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

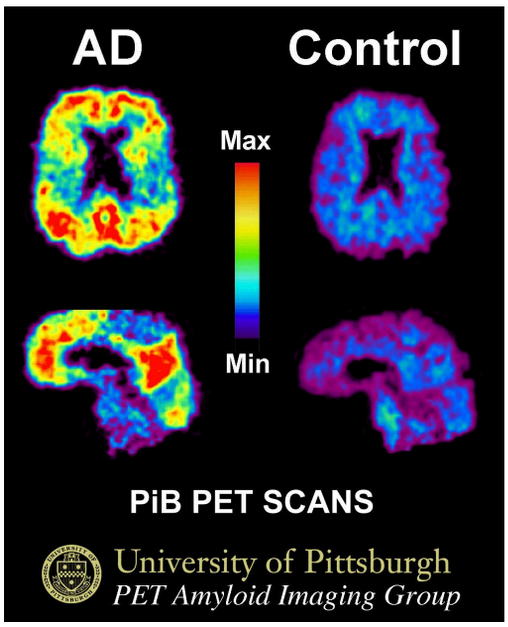
Functional imaging is where the molecular material of this paper meets the phenomenology of the clinical papers, and examiners exploit that junction relentlessly. Structural imaging shows what the brain *is*; functional imaging shows what the brain *is doing*, either through a haemodynamic surrogate 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.

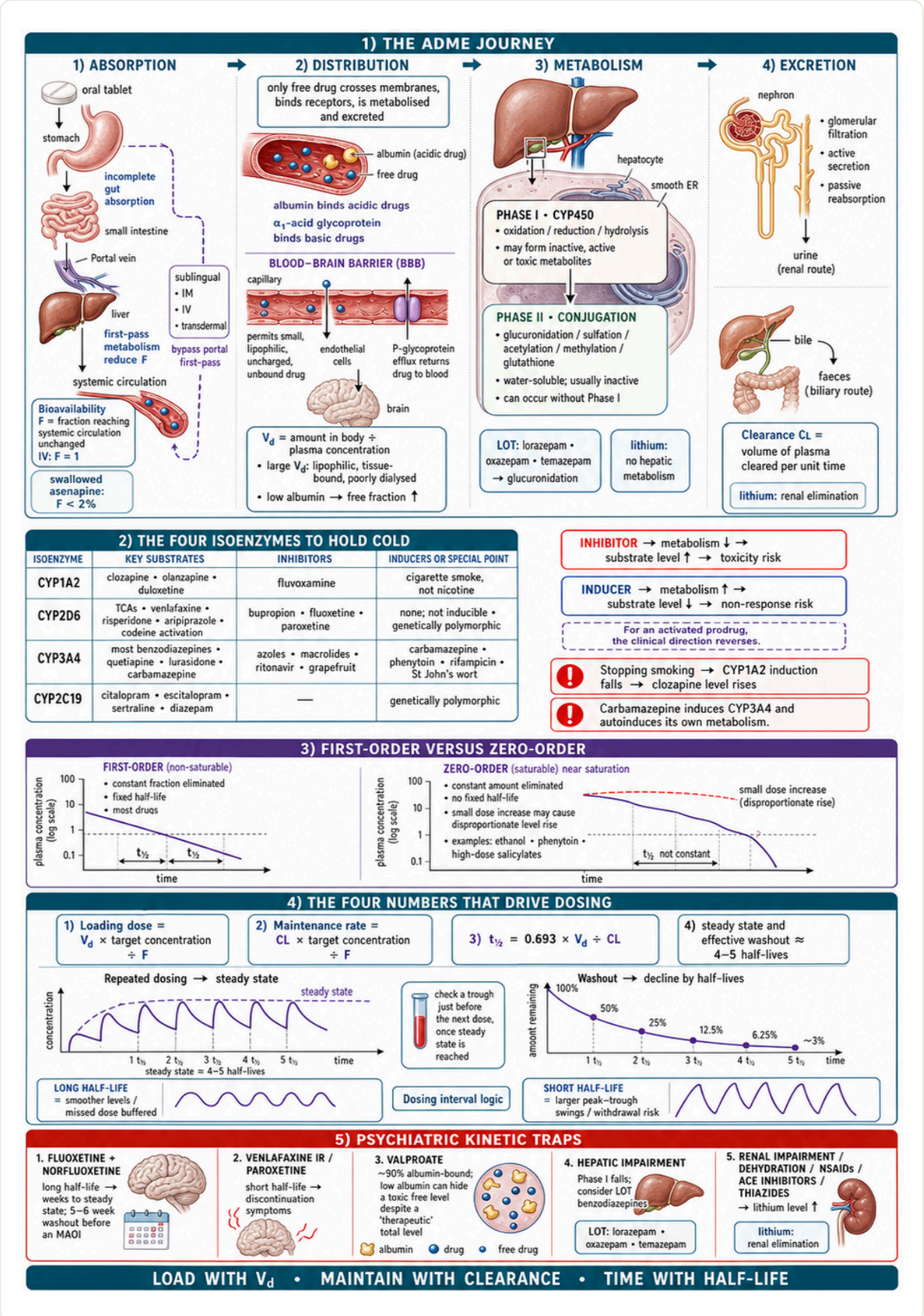


Fig 2.17 ADME and CYP450: the journey of a psychotropic.

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.

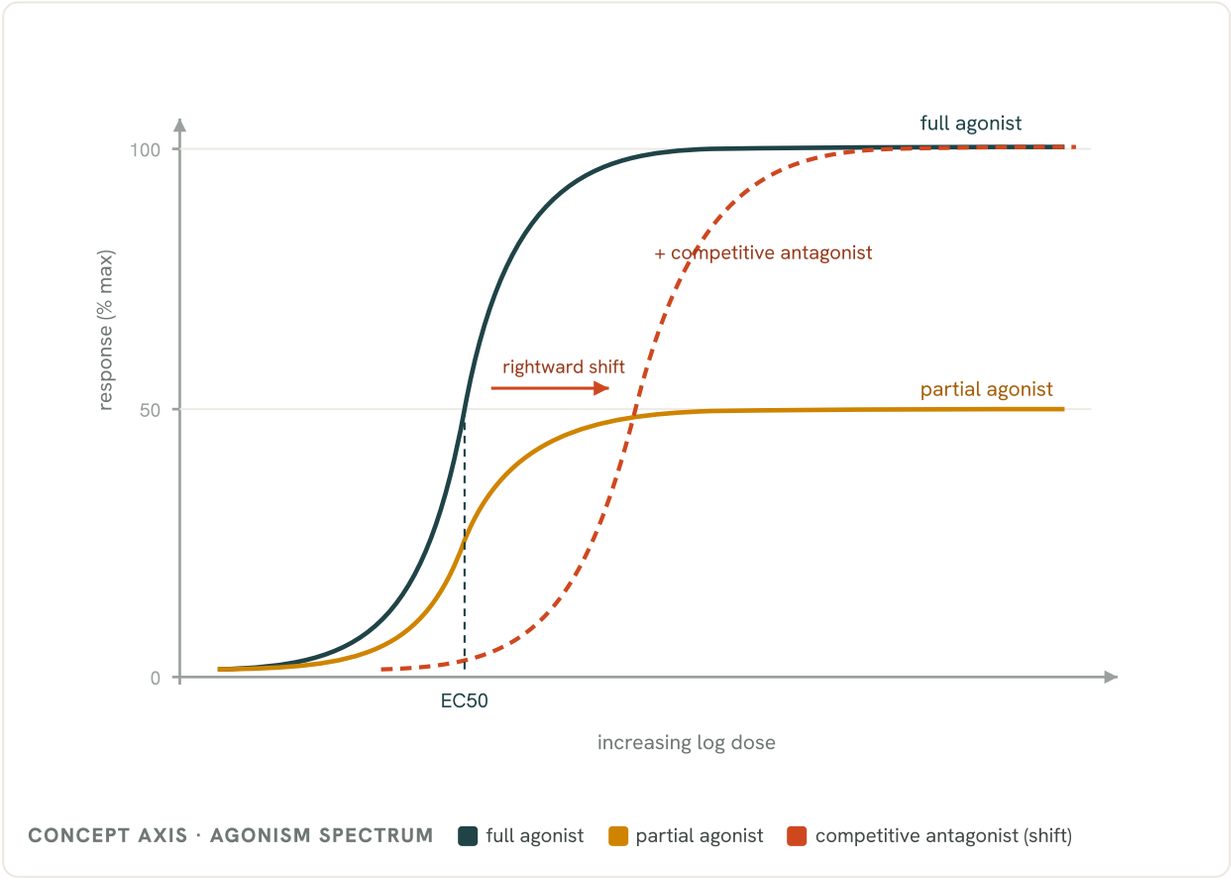


Fig 2.18 The log dose-response curve and the agonism spectrum. A full agonist reaches the maximal response; a partial agonist has lower intrinsic activity and plateaus below maximum (aripiprazole at D2, buprenorphine at mu); a competitive antagonist shifts the agonist curve rightward without lowering 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.

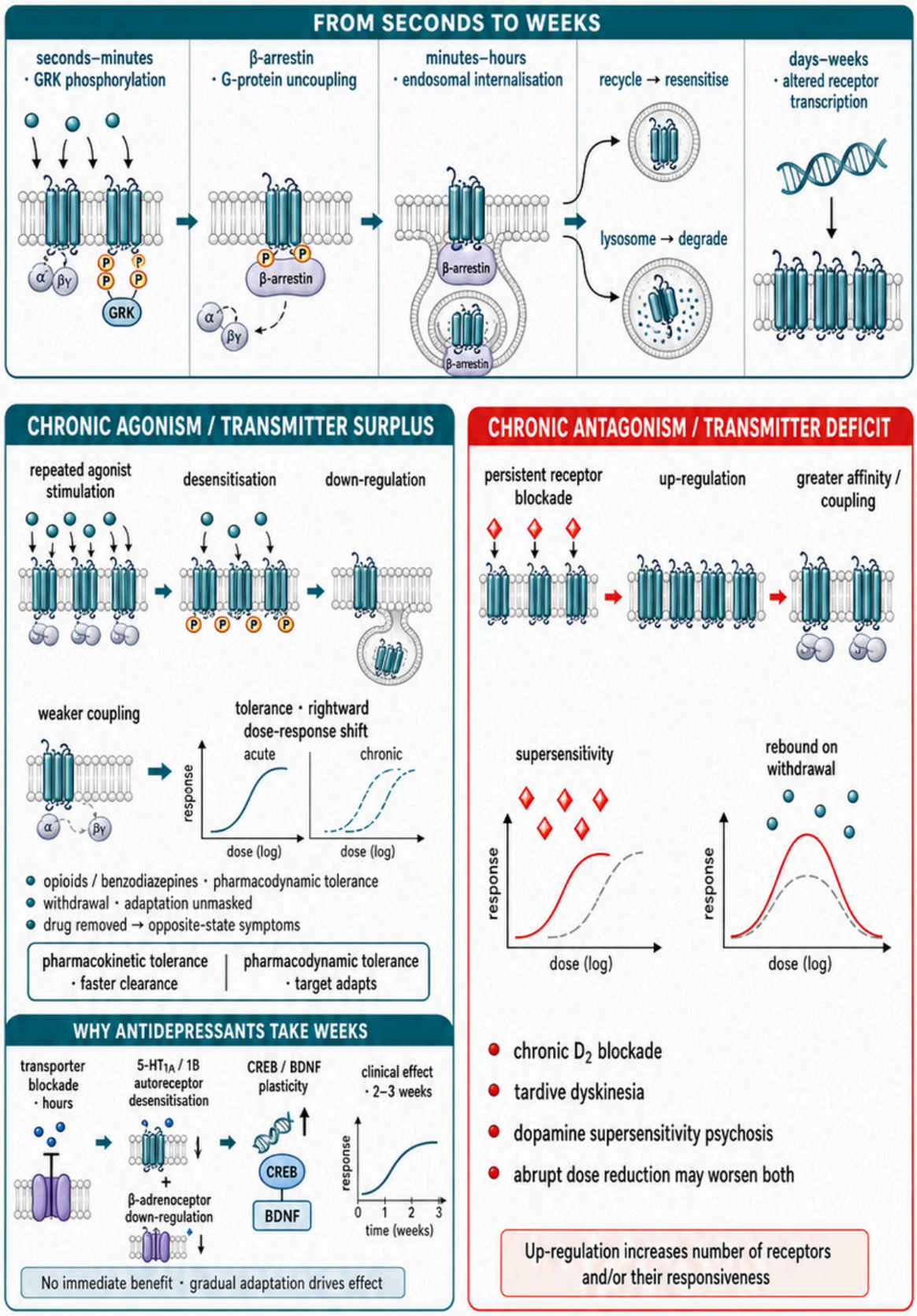


Fig 2.19 Receptor adaptation over time: regulation, trafficking and chronic exposure.

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.

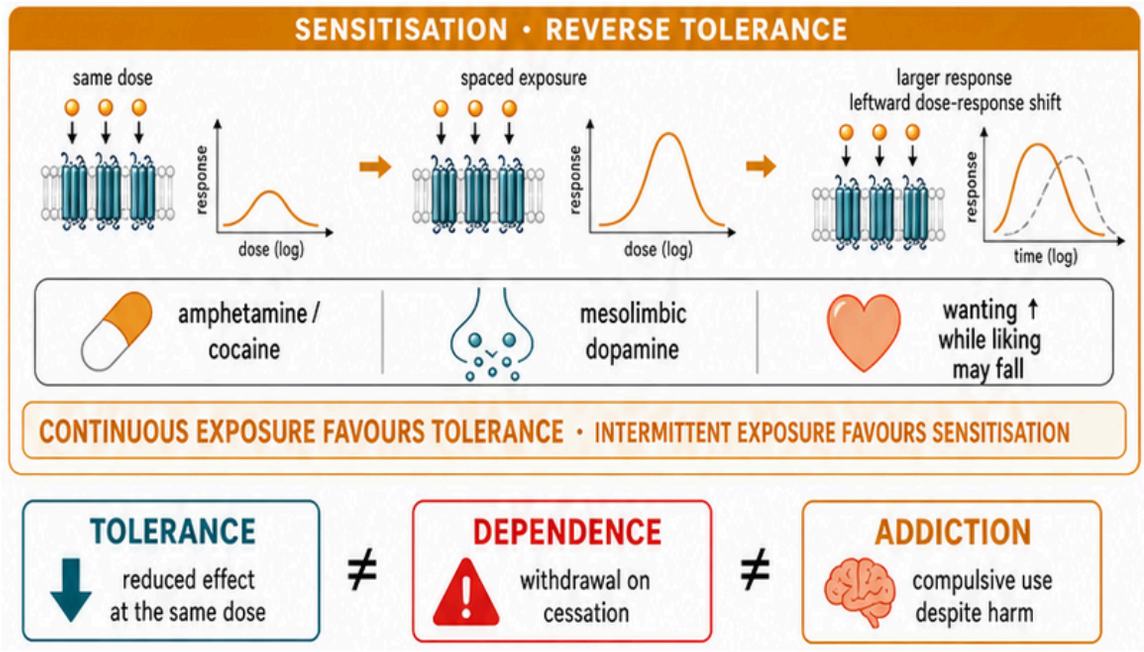


Fig 2.20 Sensitisation, reverse tolerance, dependence and addiction.

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.

References

This chapter is grounded in the standard texts (the source hierarchy below); landmark and contested claims carry a PubMed-verified journal citation. Every PMID here was checked against PubMed this build.

SOURCE HIERARCHY (TEXTBOOKS)

1. Boland R, Verduin ML. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 11th ed. Philadelphia: Wolters Kluwer; 2024. [neurochemistry, neuroendocrinology, neuroimaging backbone]
2. Stahl SM. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 5th ed. Cambridge: Cambridge University Press; 2021. [receptor pharmacology, transmitter systems]
3. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 14th ed. Oxford: Wiley Blackwell; 2021. [drug monitoring, pharmacokinetics]
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-5-TR). Washington, DC: APA; 2022.
5. World Health Organization. ICD-11 Clinical Descriptions and Diagnostic Requirements for Mental, Behavioural and Neurodevelopmental Disorders. Geneva: WHO; 2024.
6. Sharp T. Neurotransmitters and signalling. In: New Oxford Textbook of Psychiatry. 3rd ed. Oxford University Press. Chapter 14. No PMID (textbook chapter).
7. Tasman A, et al. (eds). Tasman's Psychiatry. 5th ed. Springer/Wiley; 2024. (serotonin receptor subtypes as pathophysiological and drug targets; 5-HT1A/2A density findings in schizophrenia; mCPP provocation in OCD)
8. Johnstone EC, Owens DGC, Lawrie SM, McIntosh AM, Sharpe M, eds. Companion to Psychiatric Studies. 8th ed. Churchill Livingstone/Elsevier; 2010. (Nicotinic vs muscarinic receptor classes, septohippocampal cholinergic projection, ChAT reduction and nucleus basalis in AD) - no PMID (textbook)
9. Tasman A, Kay J, Lieberman JA, First MB, Riba MB, eds. Psychiatry. 4th ed. Wiley-Blackwell; 2015. (Correlation of amnesia depth with nucleus basalis of Meynert damage; anticholinergic delirium in geriatric patients) - no

PMID (textbook)

10. Swales MA (ed). The Oxford Handbook of Dialectical Behaviour Therapy. Oxford University Press; 2018. (endogenous opioid system three classes: beta-endorphin, enkephalin, dynorphin; mu/delta/kappa; NSSI)
11. Tasman A, Kay J, Lieberman JA, First MB, Riba M (eds). Psychiatry. 4th ed. Wiley-Blackwell; 2013. (neuropeptide co-localisation; substance P; CRF receptor knockout)
12. Brunton LL, Knollmann BC (eds). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th ed. McGraw-Hill, 2022. Purinergic (P1 adenosine A1/A2A/A2B/A3, P2X, P2Y) receptor pharmacology. No PMID (textbook).
13. Johnstone EC, et al (eds). Companion to Psychiatric Studies. 8th ed. Churchill Livingstone/Elsevier; 2010. (Lithium and signal transduction: IP3/DAG/PKC; inositol monophosphatase inhibition and inositol depletion hypothesis; GSK-3 inhibition and substrates Wnt/beta-catenin/tau/AP-1/CREB)
14. Geddes JR, Andreasen NC, Goodwin GM (eds). New Oxford Textbook of Psychiatry. 3rd ed. Oxford University Press; 2020. (Reelin and inside-out cortical layering; Cajal-Retzius cells; LIS1/DCX; tangential interneuron migration from ganglionic eminences)
15. Tasman A, Riba MB, Alarcón RD, et al. (eds). Tasman's Psychiatry. 5th ed. Springer; 2024. (Neurodevelopmental model of schizophrenia; two epochs; absence of gliosis; fetal migration abnormalities)
16. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th ed. (Goodman & Gilman 2018) - MR vs GR affinity, 11-beta-HSD2 protection of MR, glucocorticoid pharmacology.
17. Semple D, Smyth R. Oxford Handbook of Psychiatry (structural brain imaging in schizophrenia, mood disorders; Johnstone 1976 CT landmark; Haijma et al. 2013 meta-analysis of >18,000 subjects: ventricular volume +30%, brain volume -2.6%, ICV -2%). Also drawn from Cowen P, Harrison P, Burns T. Shorter Oxford Textbook of Psychiatry, 7th ed, OUP 2018 (schizophrenia Box 11.13; depression WMH and hippocampal volume; bipolar lithium reversal). No single PMID (textbook).
18. Johnstone EC, Owens DC, Lawrie SM, et al. Companion to Psychiatric Studies. 8th ed. Churchill Livingstone/Elsevier; 2010. (hypofrontality of dorsolateral prefrontal cortex in schizophrenia; frontostriatal circuitry)
19. Tasman A, Kay J, Lieberman JA, First MB, Riba MB (eds). Psychiatry. 4th ed. Wiley-Blackwell; 2015. (P-glycoprotein, first-pass metabolism, poor-metaboliser toxicity risk with narrow-index drugs)
20. Johnstone EC, Owens DGC, Lawrie SM, et al (eds). Companion to Psychiatric Studies, 8th ed. Churchill Livingstone/Elsevier; 2010. (receptor sensitivity, desensitisation/down-regulation mechanisms, opioid dependence/withdrawal, ECT and receptor sensitivity)

JOURNAL REFERENCES (PUBMED-VERIFIED)

1. Aizenstein HJ, et al. Vascular depression consensus / white-matter hyperintensity substrate of late-life depression (as cited in Shorter Oxford). Representative: Aizenstein HJ et al. Vascular depression consensus report. Mol Psychiatry. 2016;21(11):1600.
2. Arana GW, Baldessarini RJ, Ornsteen M. The dexamethasone suppression test for diagnosis and prognosis in psychiatry. Arch Gen Psychiatry. 1985;42:1193-1204. PMID: 3000317 - pooled DST performance/prognosis meta-analysis.
3. Arnsten AFT, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion. J Am Acad Child Adolesc Psychiatry. 2012;51(4):356-367. PMID: 22449642.
4. Bamalan OA, Moore MJ, Al Khalili Y. Physiology, Serotonin. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; updated 2023 Jul 30. (pre-cached source: NCBI Bookshelf NBK545168)
5. Barde YA, Edgar D, Thoenen H. Purification of a new neurotrophic factor from mammalian brain. EMBO J. 1982;1(5):549-553. PMID:7188352.
6. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry. 2000;47(4):351-354. PMID: 10686270 - first controlled human study, single IV ketamine 0.5 mg/kg
7. Berridge KC, Robinson TE. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res Rev. 1998;28(3):309-369. PMID: 9858756.
8. Berridge MJ, Downes CP, Hanley MR. Lithium amplifies agonist-dependent phosphatidylinositol responses in brain and salivary glands. Biochem J. 1982;206(3):587-595. PMID 7150264 (inositol depletion hypothesis)
9. Bertilsson L, Dahl ML, Dalen P, Al-Shurbaji A. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. Br J Clin Pharmacol. 2002;53(2):111-122. PMID: 11851634
10. Bunney BG, Li JZ, Walsh DM, et al. Circadian dysregulation of clock genes: clues to rapid treatments in major depressive disorder. Mol Psychiatry. 2015;20(1):48-55. PMID: 25349171.

11. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther. 2002;302(1):381-389. PMID: 12065741.
12. Cahill CM, Walwyn W, Taylor AMW, et al. Allostatic Mechanisms of Opioid Tolerance Beyond Desensitization and Downregulation. Trends Pharmacol Sci. 2016;37(11):963-976. PMID: 27670390. (opponent process, allostasis, cAMP superactivation, pass-forward allostasis)
13. Carroll BJ. A specific laboratory test for the diagnosis of melancholia: standardization, validation, and clinical utility. Arch Gen Psychiatry. 1981;38:15-22. PMID: 7458567 - original DST validation for melancholia.
14. Castren E, Monteggia LM. Brain-derived neurotrophic factor signaling in depression and antidepressant action. Biol Psychiatry. 2021;90(2):128-136.
15. Chen ZY, Jing D, Bath KG, et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science. 2006;314(5796):140-143. PMID:17023662.
16. Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. Am J Psychiatry. 1980;137(1):16-21. PMID: 6101522.
17. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet. 2007;370(9600):1706-1713. PMID 18022033.
18. Contreras F, et al. Contributions of cortisol suppression tests to understanding of psychiatric disorders: a narrative review of literature. Endocrinol Nutr (English ed). 2013 - 1 mg DST 67% sensitivity / 96% specificity for melancholia, 44% sensitivity in general MDD, PTSD low-cortisol paradox, increased lymphocyte GR density/sensitivity, 0.5 mg DST hypersuppression, atypical depression hypocortisolism.
19. Costa T, Herz A. Antagonists with negative intrinsic activity at delta opioid receptors coupled to GTP-binding proteins. Proc Natl Acad Sci USA. 1989;86(19):7321-7325. PMID: 2552439.
20. Currie GM. Pharmacology, Part 2: Introduction to Pharmacokinetics. J Nucl Med Technol. 2018;46(3):221-230. PMID 29599397 (half-life, clearance, steady-state fundamentals corroborating Pharmaceutical Press 2023 summary).
21. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. Arch Gen Psychiatry. 1997;54(7):597-606. PMID:9236543.
22. Edwards Z, Preuss CV. GABA Receptor Positive Allosteric Modulators. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Feb 28. Bookshelf ID: NBK554443. PMID: 32119330.
23. Faust TE, Gunner G, Schafer DP. Mechanisms governing activity-dependent synaptic pruning in the developing mammalian CNS. Nat Rev Neurosci. 2021;22(11):657-673. PMID: 34545240; PMCID: PMC8541743.
24. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res. 1982-1983;17(4):319-334. PMID: 7187776.
25. Felmingham KL, Dobson-Stone C, Schofield PR, Quirk GJ, Bryant RA. The BDNF Val66Met polymorphism predicts response to exposure therapy in posttraumatic stress disorder. Biol Psychiatry. 2013;73(11):1059-1063. PMID:23312562.
26. Gaedigk A, Sangkuhl K, Whirl-Carrillo M, Klein T, Leeder JS. Prediction of CYP2D6 phenotype from genotype across world populations. Genet Med. 2017;19(1):69-76. PMID: 27388693
27. Gopaldas JA, Padyana M, Rai PP. Practice Patterns in the Diagnosis and Management of Alcohol Withdrawal Syndrome in Indian Intensive Care Units. Indian J Crit Care Med. 2023 Nov;27(11):816-820. PMID: 37936810.
28. Griebel G, Holmes A. 50 years of hurdles and hope in anxiolytic drug discovery. Nat Rev Drug Discov. 2013;12(9):667-687. PMID: 23989795 (V1b antagonist SSR149415 discontinuation; peptide translational failures)
29. Grogan S, Preuss CV. Pharmacokinetics. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; updated 2023. Bookshelf ID NBK557744; PMID 32491676.
30. Haijma SV, Van Haren N, Cahn W, et al. Brain volumes in schizophrenia: a meta-analysis in over 18,000 subjects. Schizophr Bull. 2013;39(5):1129-1138. PMID: 23042112.
31. Hallahan B, et al. Structural MRI in bipolar disorder: an international collaborative mega-analysis (hippocampal volume, lithium effect). Biol Psychiatry. 2011;69(4):326-335. PMID: 21030008.
32. Hensch TK. Critical period plasticity in local cortical circuits. Nat Rev Neurosci. 2005;6(11):877-888. PMID: 16261181.
33. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III - the final common pathway. Schizophr Bull. 2009;35(3):549-562. PMID: 19325164. doi:10.1093/schbul/sbp006
34. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III, the final common pathway. Schizophr Bull. 2009;35(3):549-562. PMID: 19325164. (presynaptic striatal dopamine synthesis capacity on

FDOPA-PET)

35. Hussain LS, Reddy V, Maani CV. Physiology, Noradrenergic Synapse. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. (synthesis cascade, DNB/VNB projections, adrenoceptor second messengers, NE degradation to VMA)
36. Johnstone EC, Crow TJ, Frith CD, et al. Cerebral ventricular size and cognitive impairment in chronic schizophrenia (landmark CT study). Lancet. 1976;2(7992):924-926. PMID: 62160.
37. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D2 occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry. 2000;157(4):514-520. PMID: 10739409. (65-80% striatal D2 occupancy window)
38. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry. 2003;160(1):13-23. PMID: 12505794.
39. Kenakin T, Christopoulos A. Signalling bias in new drug discovery: detection, quantification and therapeutic impact. Nat Rev Drug Discov. 2013;12(3):205-216. PMID: 23411724. (affinity/efficacy, spare receptors, allosteric modulation, functional selectivity).
40. Knudsen EI. Sensitive periods in the development of the brain and behavior. J Cogn Neurosci. 2004;16(8):1412-1425. PMID: 15509387.
41. Koob GF, Volkow ND. Neurocircuitry of addiction. Neuropsychopharmacology. 2010;35(1):217-238. PMID: 19710631. doi:10.1038/npp.2009.110
42. Kormos V, Gaszner B. Role of neuropeptides in anxiety, stress, and depression: from animals to humans. Neuropeptides. 2013;47(6):401-419. PMID: 24210138 (co-transmission, translational review)
43. Kramer MS, Cutler N, Feighner J, et al. Distinct mechanism for antidepressant activity by blockade of central substance P receptors. Science. 1998;281(5383):1640-1645. PMID: 9733503 (MK-869 / aprepitant depression trial)
44. Le J. Drug Distribution to Tissues / Blood-brain barrier. In: Ernstmeyer K, Christman E (eds). Nursing Pharmacology, 2nd ed. Chippewa Valley Technical College, 2023. Bookshelf ID NBK595006 (no PMID).
45. Liu CY, Zhu J, Zheng XY, Ma C, Wang X. Anti-N-Methyl-D-aspartate Receptor Encephalitis: A Severe, Potentially Reversible Autoimmune Encephalitis. Mediators Inflamm. 2017;2017:6361479. PMID: 28698711; PMCID: PMC5494059
46. Matuszewska A, Kowalski K, Jawien P, et al. The Hypothalamic-Pituitary-Gonadal Axis in Men with Schizophrenia. Int J Mol Sci. 2023;24(7):6492. doi:10.3390/ijms24076492. PMID: 37047464. (Oestrogen-protection hypothesis, testosterone-dopamine interaction, raloxifene/SERM adjunct, menopause incidence peak).
47. Mayberg HS, Brannan SK, Mahurin RK, et al. Cingulate function in depression: a potential predictor of treatment response. Neuroreport. 1997;8(4):1057-1061. PMID: 9141092. (subgenual anterior cingulate / BA25 hyperactivity in depression)
48. Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci. 2011;15(10):483-506. PMID: 21908230. (default mode / salience / central executive triple-network model)
49. Molero P, Ramos-Quiroga JA, Martin-Santos R, Calvo-Sanchez E, Gutierrez-Rojas L, Meana JJ. Antidepressant Efficacy and Tolerability of Ketamine and Esketamine: A Critical Review. CNS Drugs. 2018 May;32(5):411-420. PMID: 29736744
50. Paez-Pereda M, Hausch F, Holsboer F. Corticotropin releasing factor receptor antagonists for major depressive disorder. Expert Opin Investig Drugs. 2011;20(4):519-535. PMID: 21395482
51. Perucca E, Bialer M, White HS. New GABA-Targeting Therapies for the Treatment of Seizures and Epilepsy. CNS Drugs. 2023 Sep;37(9):755-779. PMID: 37603262.
52. Petanjek Z, Judaš M, Šimić G, et al. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc Natl Acad Sci U S A. 2011;108(32):13281-13286. PMID: 21788513; PMCID: PMC3156171.
53. Phillips C. Brain-Derived Neurotrophic Factor, Depression, and Physical Activity: Making the Neuroplastic Connection. Neural Plast. 2017;2017:7260130. PMID:28928987.
54. Rauch SL, Shin LM, Phelps EA. Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research, past, present, and future. Biol Psychiatry. 2006;60(4):376-382. PMID: 16919525. (amygdala hyperactivity, ventromedial prefrontal hypoactivity, hippocampal changes in PTSD)
55. Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect. 2000;108(Suppl 3):511-533. PMID: 10852851; PMCID: PMC1637807.

56. Roediger HL, Karpicke JD. Test-enhanced learning: taking memory tests improves long-term retention. Psychol Sci. 2006;17(3):249-255. PMID: 16507066.

57. Sam C, Bordoni B. Physiology, Acetylcholine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; updated 2023 Apr 10. Bookshelf ID NBK557825. (ACh synthesis via ChAT, choline transporter rate-limiting step, VAChT, SNARE release, AChE/BuChE hydrolysis, N1/N2 nicotinic subtypes, M1-M5 muscarinic coupling and locations, basal forebrain and mesopontine tegmentum sources, botulinum/black-widow toxins, scopolamine amnesia) - pre-cached source

58. Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl. 1998;(35):26-37. PMID: 9829024. (hyperactive orbitofrontal-caudate-thalamus CSTC loop, normalising with treatment)

59. Schafer DP, Lehrman EK, Kautzman AG, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron. 2012;74(4):691-705. PMID: 22632727; PMCID: PMC3528177.

60. Schwarz LA, Luo L. Organization of the locus coeruleus-norepinephrine system. Curr Biol. 2015;25(21):R1051-R1056. PMID: 26528750

61. Sekar A, Bialas AR, de Rivera H, et al. Schizophrenia risk from complex variation of complement component 4. Nature. 2016;530(7589):177-183. PMID: 26814963; PMCID: PMC4752392.

62. Shirayama Y, Chen ACH, Nakagawa S, Russell DS, Duman RS. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci. 2002;22(8):3251-3261. PMID:11943826.

63. Smith GW, Aubry JM, Dellu F, et al. Corticotropin releasing factor receptor 1-deficient mice display decreased anxiety, impaired stress response, and aberrant neuroendocrine development. Neuron. 1998;20(6):1093-1102.

64. Spina E, Trifiro G, Caraci F. Clinically significant drug interactions with newer antidepressants. CNS Drugs. 2012;26(1):39-67 (review synthesised via cached PMC4335312; inhibitor/inducer tables, olanzapine clearance +98% with smoking, lurasidone ~10x with ketoconazole, asenapine +29%/-16%, valproate-UGT-lamotrigine, carbapenem-valproate). PMID 22171584

65. Stambolic V, Ruel L, Woodgett JR. Lithium inhibits glycogen synthase kinase-3 activity and mimics wingless signalling in intact cells. Curr Biol. 1996;6(12):1664-1668. PMID: 8994831

66. StatPearls: NMDA Receptor (Bookshelf NBK519495) - memantine as uncompetitive antagonist, excitotoxicity, anti-NMDAR encephalitis with ovarian teratoma association. [Web-mined, no journal PMID]

67. StatPearls: Physiology, GABA (Bookshelf ID: NBK545230). StatPearls Publishing; 2026. (GAD/pyridoxal-phosphate synthesis, GABA-T shunt, SSADH deficiency, GABA-A/B/C receptor subtypes, subunit binding sites, developmental excitation).

68. Stevens B, Allen NJ, Vazquez LE, et al. The classical complement cascade mediates CNS synapse elimination. Cell. 2007;131(6):1164-1178. PMID: 18083105.

69. Tripathi KD. Essentials of Medical Pharmacology (KDT), 8th ed. Jaypee, 2019 (first-pass metabolism, bioavailability; textbook, no PMID).

70. Tripathi KD. Essentials of Medical Pharmacology (KDT). 8th ed. Jaypee. (Co-transmission: the one-neurone-one-transmitter model as oversimplification; fast small-molecule plus slow neuropeptide co-release). No PMID (textbook).

71. Tripathi KD. Essentials of Medical Pharmacology. 8th ed. Jaypee; 2019. (Buprenorphine partial mu agonist; competitive antagonism; flumazenil reversal).

72. Tuplin EW, Holahan MR. Aripiprazole, a drug that displays partial agonism and functional selectivity. Curr Neuropharmacol. 2017;15(8):1192-1207. PMID: 28412910.

73. US FDA. Xanomeline-trospium (KarXT / Cobenfy) approval for schizophrenia, September 2024 (M1/M4 muscarinic agonist antipsychotic, non-D2 mechanism).

74. Varghese FP, Brown ES. The Hypothalamic-Pituitary-Adrenal Axis in Major Depressive Disorder: A Brief Primer for Primary Care Physicians. Prim Care Companion J Clin Psychiatry. 2001;3(4):151-155. PMID: 15014598. doi:10.4088/pcc.v03n0401 - DST non-suppression 43% MDD / 67% psychotic depression, age-dependence 34%-64%, DEX/CRH sensitivity up to 90%, CSF CRH state marker, relapse/suicide prognostic value.

75. Volkow ND, Wang GJ, Newcorn JH, et al. Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. Mol Psychiatry. 2011;16(11):1147-1154. PMID 20856250.

76. Web-cached review (Bioengineering 2023, PMC9952193): neuropeptides in depression and anxiety - substance P, neurotensin, orexin/hypocretin, MCH amino-acid counts and receptor subtypes

77. Westacott LJ, Wilkinson LS. Complement Dependent Synaptic Reorganisation During Critical Periods of Brain Development and Risk for Psychiatric Disorder. Front Neurosci. 2022;16:840266. PMID: 35600620; PMCID: PMC9120629.

78. Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol. 1963;26:1003-1017. PMID: 14084161.
79. Yang T, Nie Z, Shu H, et al. The Role of BDNF on Neural Plasticity in Depression. Front Cell Neurosci. 2020;14:82. doi:10.3389/fncel.2020.00082. PMID:32351365.
80. Yehuda R. Risk and resilience in posttraumatic stress disorder / low-dose (0.5 mg) DST hypersuppression and enhanced GR feedback in PTSD (Yehuda 2004).
81. Yin J, Barr AM, Ramos-Miguel A, Procyshyn RM. Antipsychotic Induced Dopamine Supersensitivity Psychosis: A Comprehensive Review. Curr Neuropharmacol. 2017;15(1):174-183. PMID: 27264948.
82. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry. 2006;63(8):856-864. PMID: 16894061 - confirmed rapid antidepressant effect of IV ketamine 0.5 mg/kg in TRD
83. Zhao M, Chen L, Yang J, et al. BDNF Val66Met polymorphism, life stress and depression: a meta-analysis of gene-environment interaction. J Affect Disord. 2018;227:226-235. PMID:29102837.
84. de Bartolomeis A, Tomasetti C, Iasevoli F. Update on the mechanism of action of aripiprazole: translational insights into antipsychotic strategies beyond dopamine receptor antagonism. CNS Drugs. 2015;29(9):773-799. PMID: 26346901.

FIGURE CREDITS

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4. Figs 2.1, 2.3, 2.4, 2.7, 2.10, 2.14, 2.18 and 2.21 are original concept schematics drawn for Weave Sprint.

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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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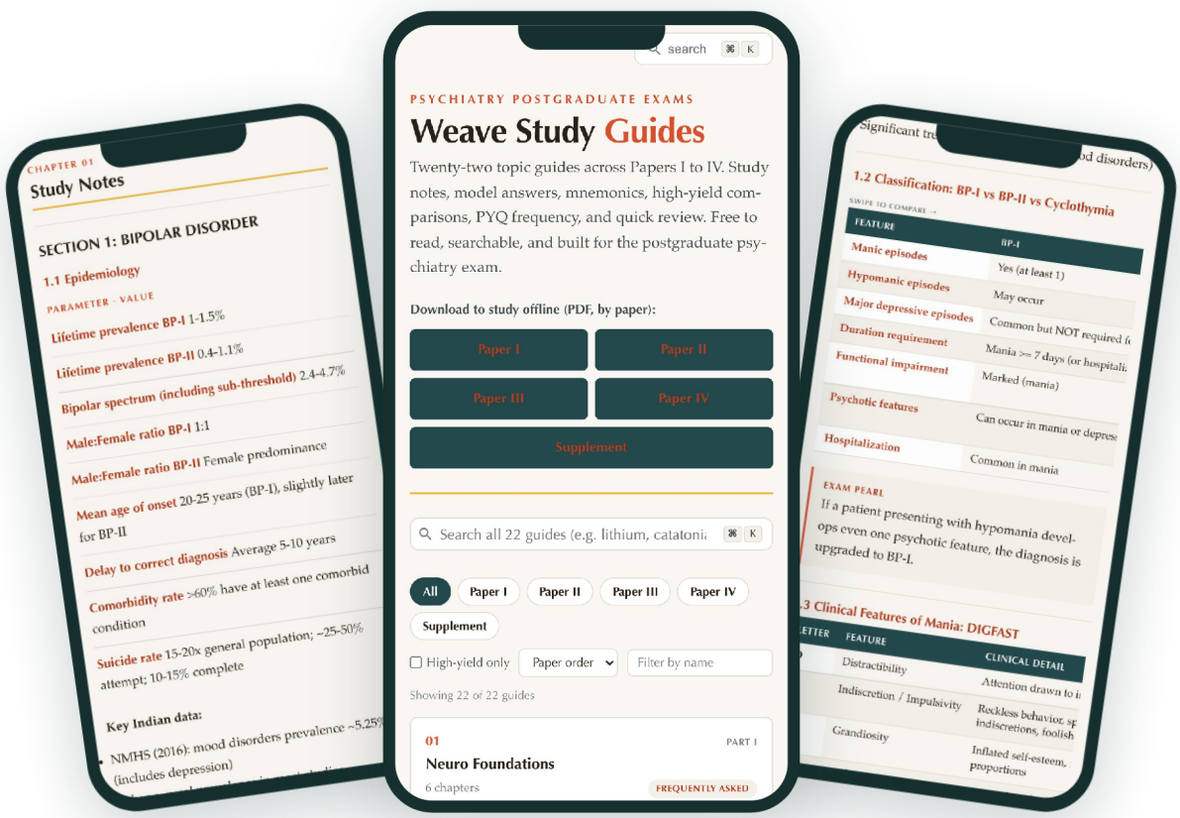
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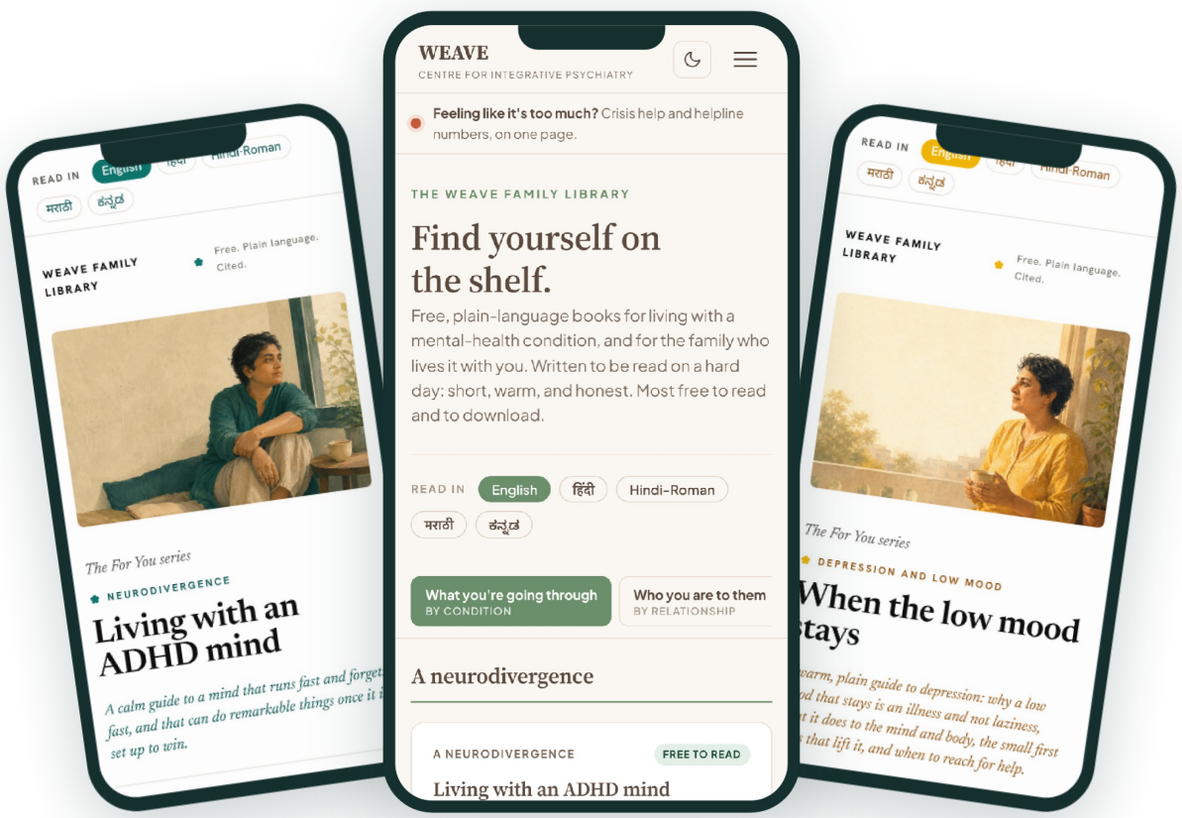
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