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# Functional Neuroanatomy & Neurophysiology

*How the brain is wired for emotion, memory and arousal, and the physiology the exam tests on top of it. One complete set of notes, read circuits not spots.*

CONTENTS


- Functional neuroanatomy
- Neurophysiology
- Apply and consolidate



Wilfred D'souza · Niharika H. S.

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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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# 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.

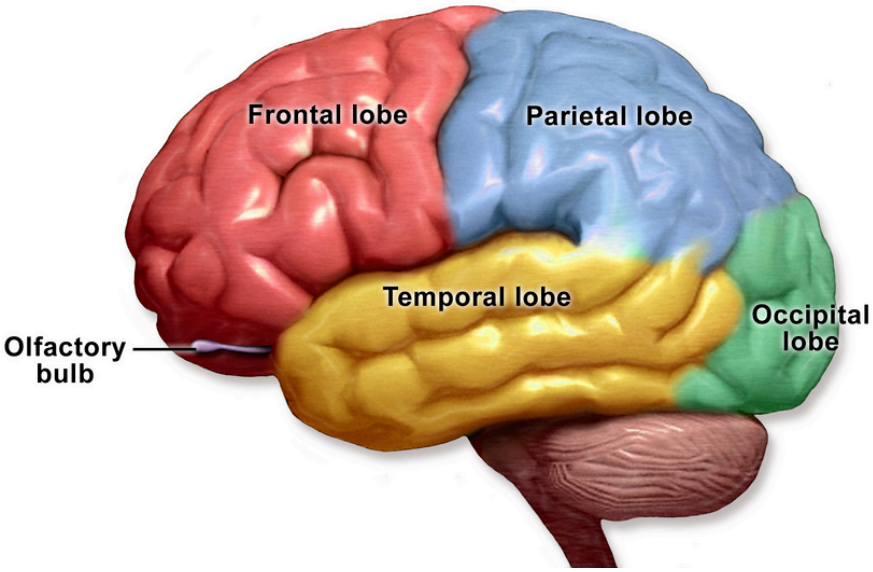



Image: Blausen.com staff (2014), CC BY 3.0, via Wikimedia Commons

**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.

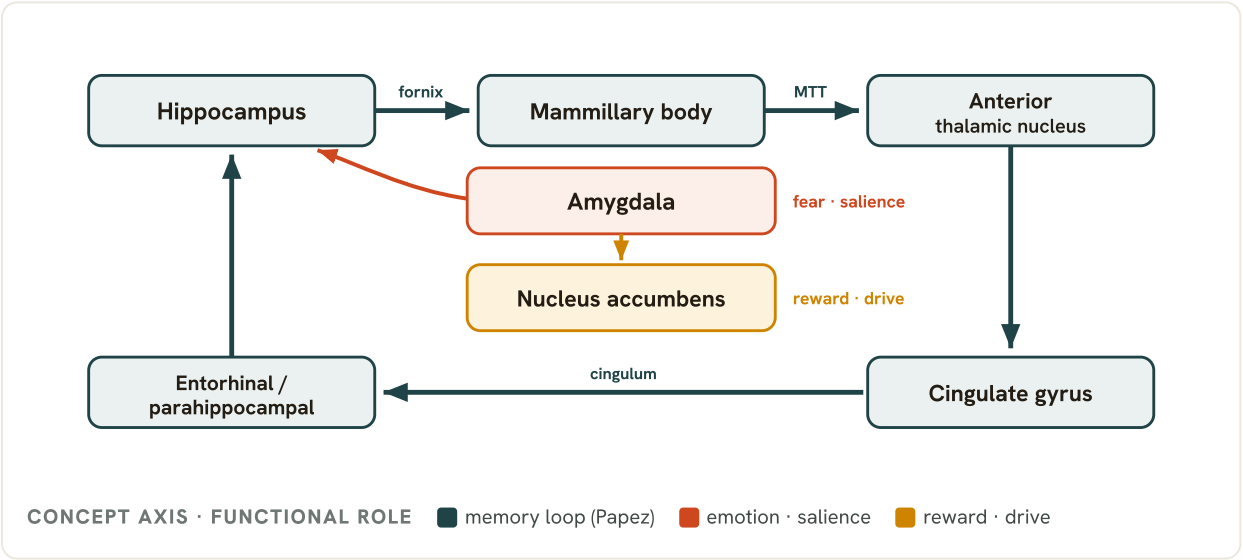



**Fig 1.2** The Papez circuit drawn as a closed ring (petrol): hippocampus to fornix to mammillary body to anterior thalamus to cingulate to entorhinal and back. The amygdala (coral) tags emotional salience onto encoding and feeds the accumbens (marigold) reward hub. MTT, mammillothalamic tract.

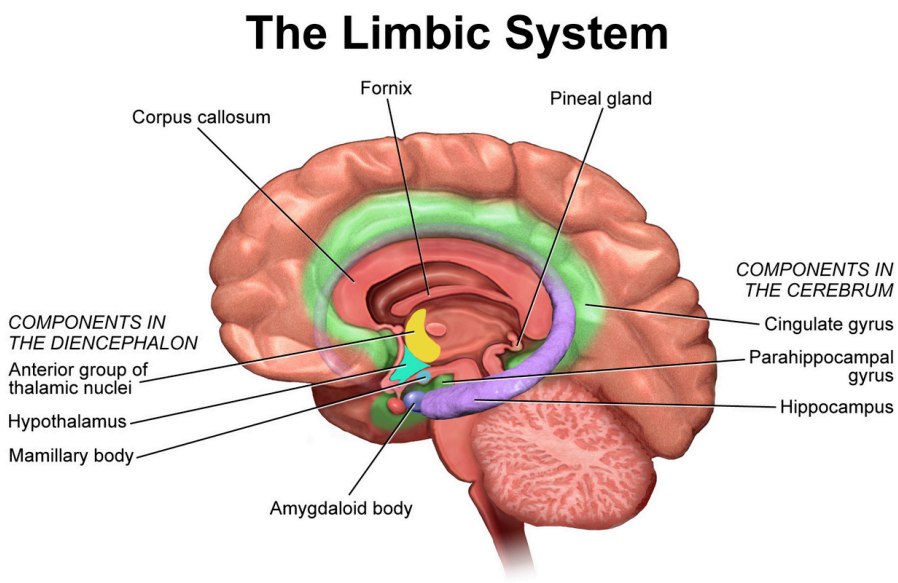



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**Fig 1.3** The same structures in situ. Trace the Papez loop of Fig 1.2 across real anatomy: the cingulate gyrus and fornix carry the loop, the amygdala sits at the temporal pole tagging salience, and the hippocampus curls beneath it encoding new 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. Limbic structures: **"The Naked Hippo Found All Memories"** (Thalamus-anterior, Nucleus accumbens, Hippocampus, Fornix, Amygdala, Mammillary bodies).

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

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

INDIA CONTEXT

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

## 3.1 Definition, boundaries and the three competing models

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

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

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

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

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

⚠ COMMON TRAP

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

### 3.2 Hippocampal formation: subfields and the trisynaptic preview

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

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

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

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

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

PEARL

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

### 3.3 Amygdala: nuclear groups and the fear circuit

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

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

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

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

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

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

♡ CLINICAL ANCHOR

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

### 3.4 Cingulate cortex: an anterior-posterior division of labour

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

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

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

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

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

♡ CLINICAL ANCHOR

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

HOLD THIS

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

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

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

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

### 3.7 Connections in and out, and a functional synthesis

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

#### Functions in one frame

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

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

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

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

CLINICAL ANCHOR

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

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

MNEMONIC

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

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

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

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

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

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

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

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

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

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

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

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

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

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

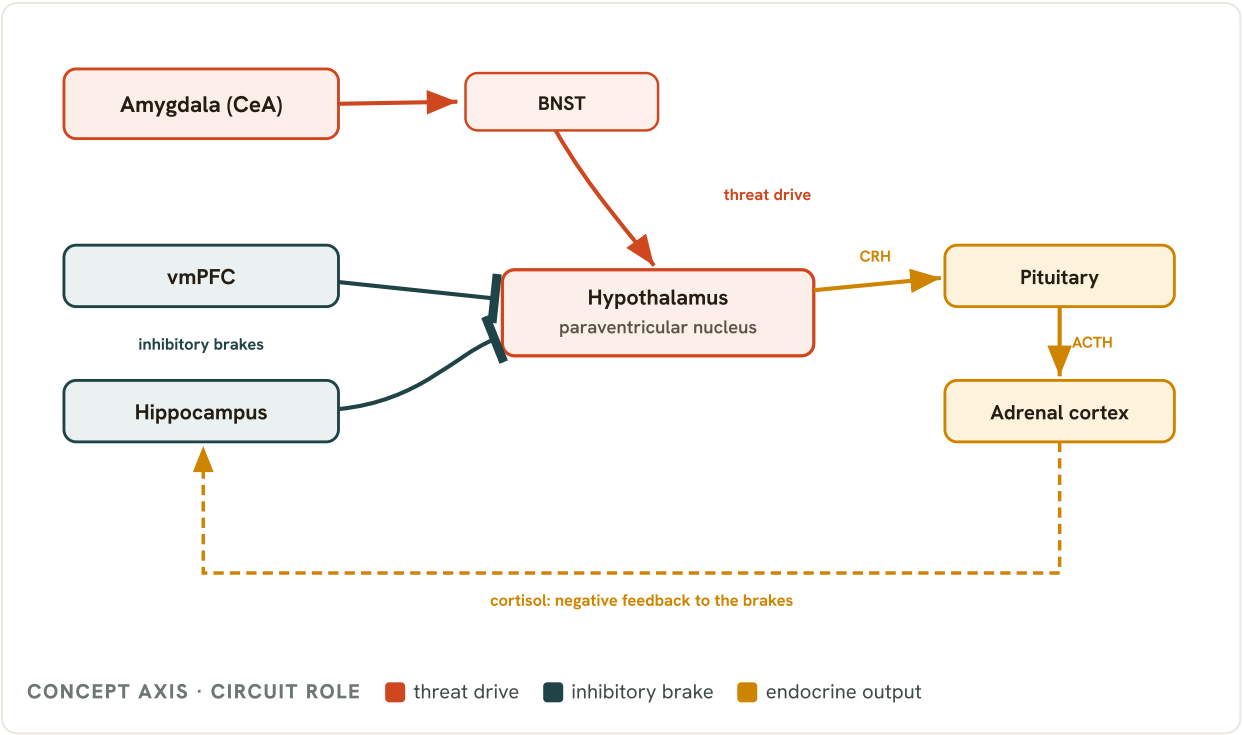



**Fig 1.4** The stress loop. The amygdala (coral) drives the paraventricular nucleus, relayed through the BNST for sustained anxiety; the hippocampus and vmPFC (petrol) apply inhibitory brakes; the cortisol output limb (marigold) closes the loop by feeding back onto its own brakes, so that when chronic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

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

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

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

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

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

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

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

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

PEARL

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

HOLD THIS

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

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

### 4.4 Allostasis, allostatic load and early-life programming

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

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

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

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

### 4.5 The circuit in disorders: depression, PTSD and anxiety

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

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

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

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

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

## 5 · Prefrontal cortex: subdivisions and syndromes

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

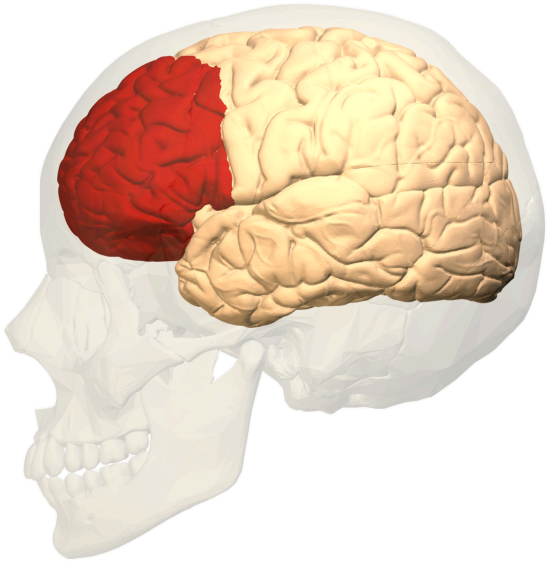


Image: Database Center for Life Science (DBCLS), CC BY-SA 2.1 Japan, via Wikimedia Commons

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

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

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

HOLD THIS

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

♡ CLINICAL ANCHOR

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

## 5.1 Cytoarchitecture and the Brodmann map

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

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

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

### Ventrolateral (BA 44, 45, 47)

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

### Orbitofrontal (BA 11, 12, 47/12)

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

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

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

MNEMONIC

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

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

## 5.2 DLPFC and working memory: the Baddeley link

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

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

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

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

### 5.3 OFC, VMPFC and the somatic marker hypothesis

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

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

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

### 5.4 Anterior cingulate cortex: dorsal versus rostral

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

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

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

### 5.5 Frontopolar cortex (BA 10) and connections

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

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

### 5.6 The three frontal syndromes, in full

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

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

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

### 5.7 Phineas Gage: the founding case

**Harlow, on Phineas Gage (1848)** LANDMARK

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

### 5.8 Frontal release signs and primitive reflexes

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

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

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

### 5.9 Clinical correlations across disorders

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

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

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

♡ CLINICAL ANCHOR

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

### 5.10 rTMS to the DLPFC: the therapeutic target

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

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

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

**INDIA CONTEXT**

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

## 6 · Basal ganglia circuits

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

### Nuclei

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

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

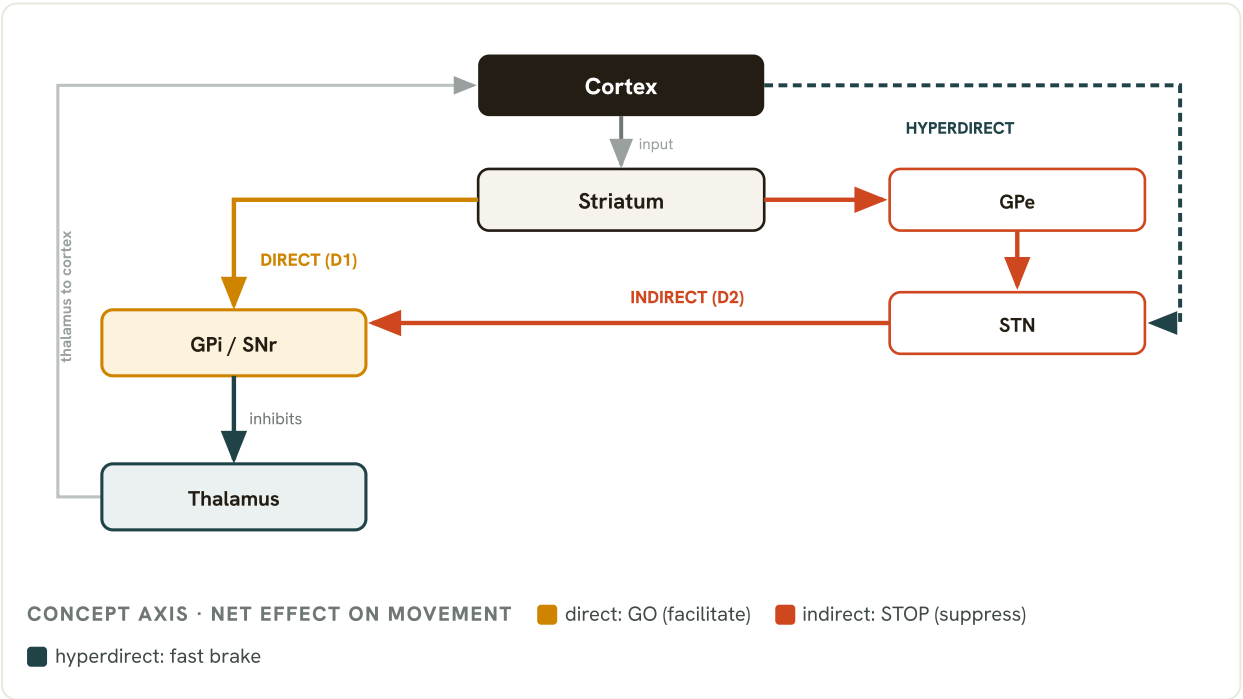



**Fig 1.6** The cortico-striato-thalamo-cortical loop. The output nuclei (GPi/SNr) tonically inhibit the thalamus: the direct pathway (marigold, D1) disinhibits it to release movement, while the indirect (coral, D2) and hyperdirect (petrol) pathways raise GPi/SNr output to clamp it. Dopamine via D1 strengthens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

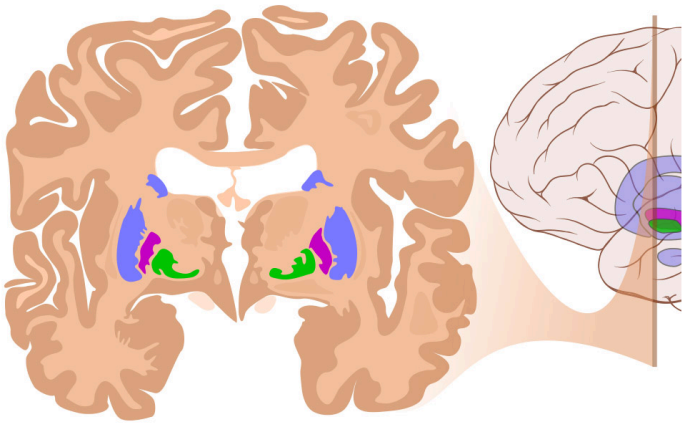


Image: Andrew Meyerson, CC BY-SA 3.0, via Wikimedia Commons

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

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

HOLD THIS

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

## 6.1 Components and subdivisions: how the nuclei are named

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

### Neostriatum (dorsal striatum)

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

### Paleostriatum (pallidum)

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

### Ventral striatum

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

### Associated nuclei

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

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

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

⚠ COMMON TRAP

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

## 6.2 The projection neuron and its co-transmitters

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

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

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

MNEMONIC

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

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

### 6.3 Direct pathway: the GO circuit in full synaptic detail

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

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

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

### 6.4 Indirect pathway: the STOP circuit through GPe and STN

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

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

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

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

### 6.5 Hyperdirect pathway: the fast cortico-subthalamic brake

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

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

### 6.6 Parallel cortico-striato-thalamo-cortical loops

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

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

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

## 6.7 Neurotransmitters and modulation at a glance

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

### Nigrostriatal dopamine

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

### Thalamostriatal fibres

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

### Dopamine-acetylcholine balance

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

## 6.8 Functions: action selection, habit and reward

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

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

of dopaminergic addiction.

### 6.9 Clinical correlation: hypokinetic and hyperkinetic disorders

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

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

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

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

### 6.10 Antipsychotic motor adverse effects: the psychiatry-facing payoff

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

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

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

HOLD THIS

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

**INDIA CONTEXT**

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

**CLINICAL ANCHOR**

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

## 7 · Thalamus: nuclei and relay functions

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

| 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 |

| NUCLEUS | KEY AFFERENT (INPUT) | CORTICAL TARGET | LESION SIGNATURE |
|---|---|---|---|
| **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"**

**F**eeding (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** |

| NUCLEUS | ZONE | REGION | CORE FUNCTION (AND LESION SIGNATURE) |
|---|---|---|---|
| **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.

**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)

**F**astigial, **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.

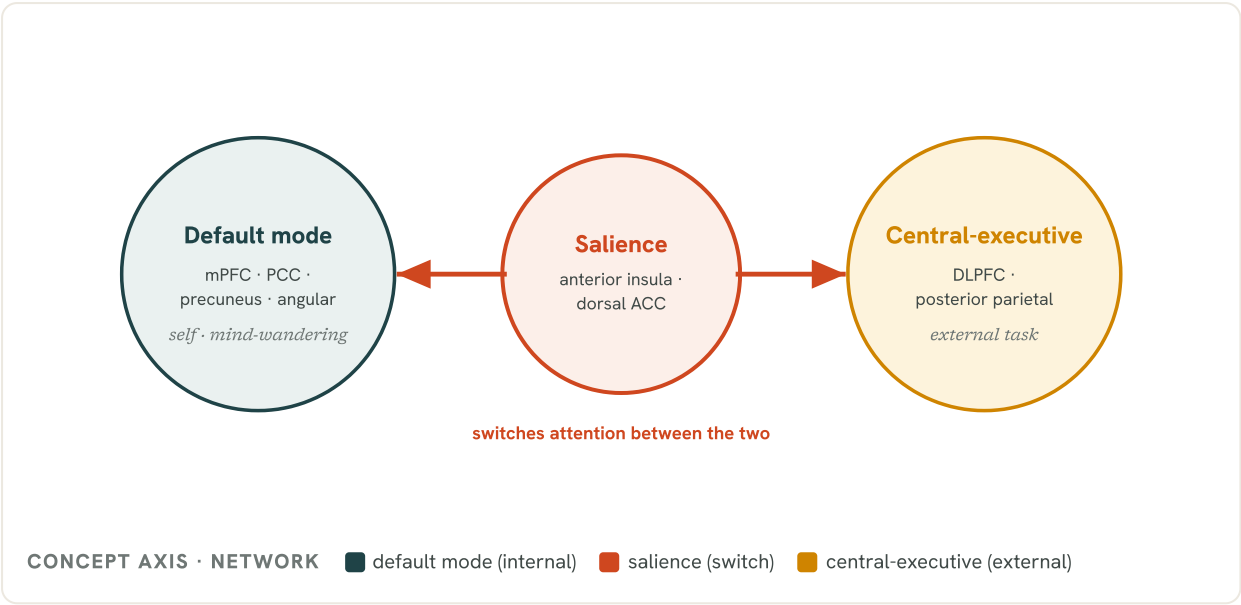



**Fig 1.8** The triple network. The salience network (anterior insula, dorsal ACC) detects what matters and toggles the brain between inward self-referential processing (DMN) and outward task control (CEN).

- **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"**

**A**nterior **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 1.8).

### 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.

- **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. |
| **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. |

| NUCLEUS | TRANSMITTER | LOCATION | FIRING ACROSS STATES | FUNCTIONAL ROLE / CLINICAL HOOK |
|---|---|---|---|---|
| **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.

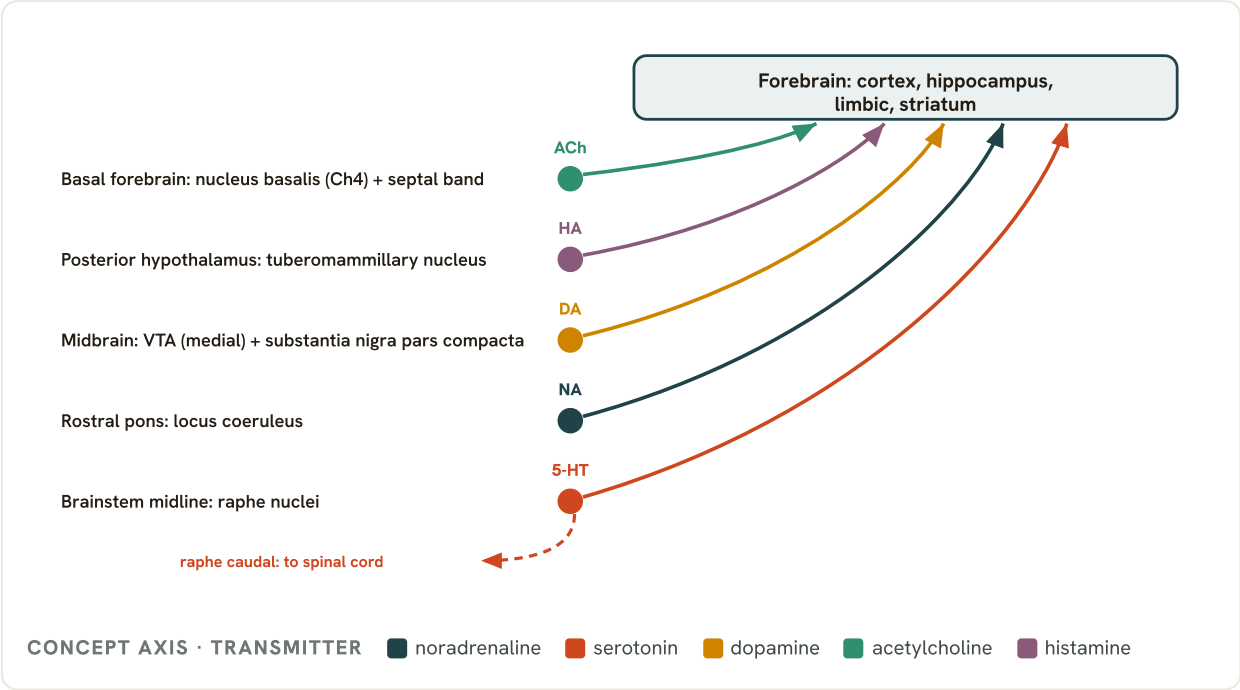



**Fig 1.9** The nuclei of origin, plotted rostral to caudal. Each discrete nucleus (colour = transmitter) fans a diffuse ascending projection over the whole forebrain: one nucleus, one transmitter, one gain-setting job. The raphe alone splits its output, rostral to the forebrain and caudal to the cord. 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).

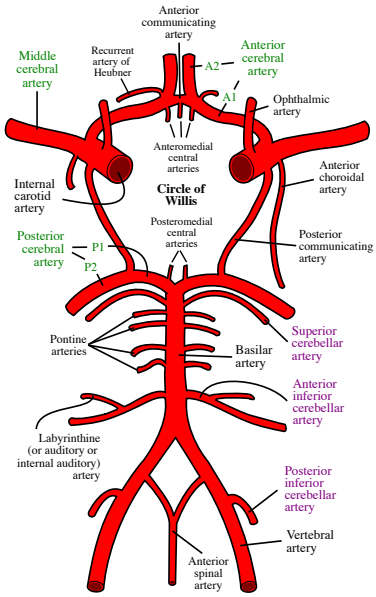



Image: Rhcastilhos, public domain, via Wikimedia Commons

**Fig 1.10** 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.

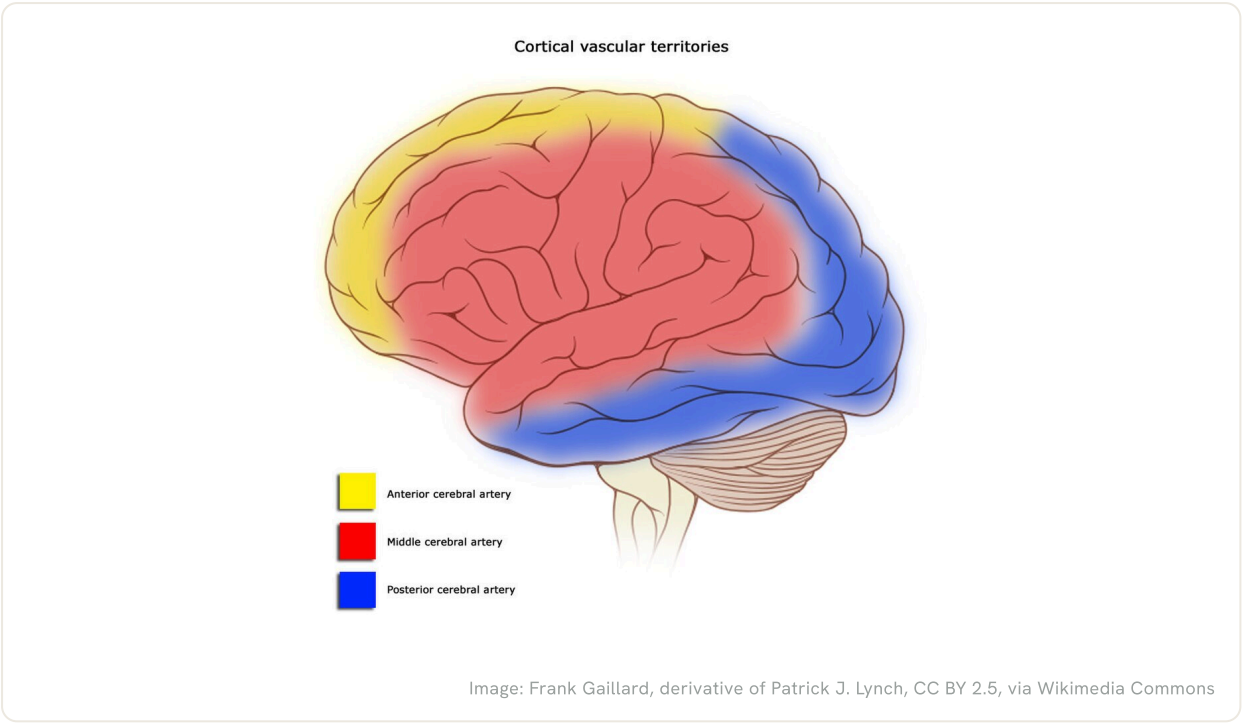



Image: Frank Gaillard, derivative of Patrick J. Lynch, CC BY 2.5, via Wikimedia Commons

**Fig 1.11** 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.

#### 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.

- **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.

**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.

**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** |

| SIGN | LOCALISES TO | DISCRIMINATING LOGIC |
|---|---|---|
| **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.

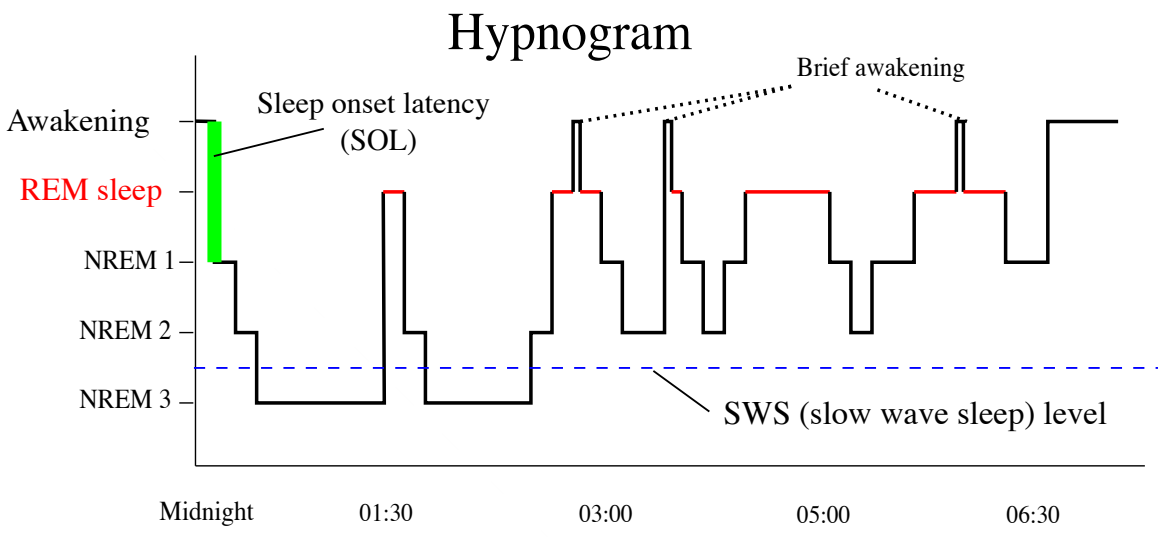



Image: RazerM, CC BY-SA 3.0, via Wikimedia Commons

**Fig 1.12** 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.<br>MID TERM Cognitive behavioural therapy for insomnia (CBT-I) as the definitive first-line treatment; taper hypnotics.<br>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 1.12, 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 1.12 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.

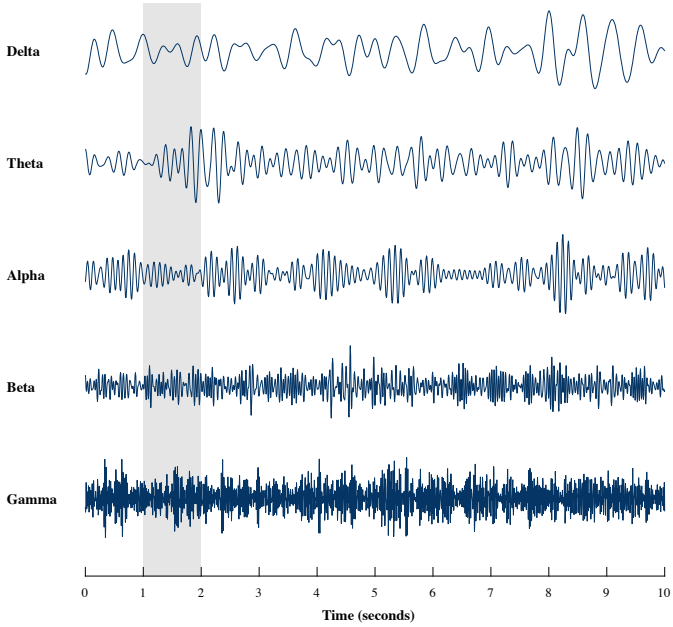



Image: Laurens R. Krol, CC0 / public domain, via Wikimedia Commons

**Fig 1.13** 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.

**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.

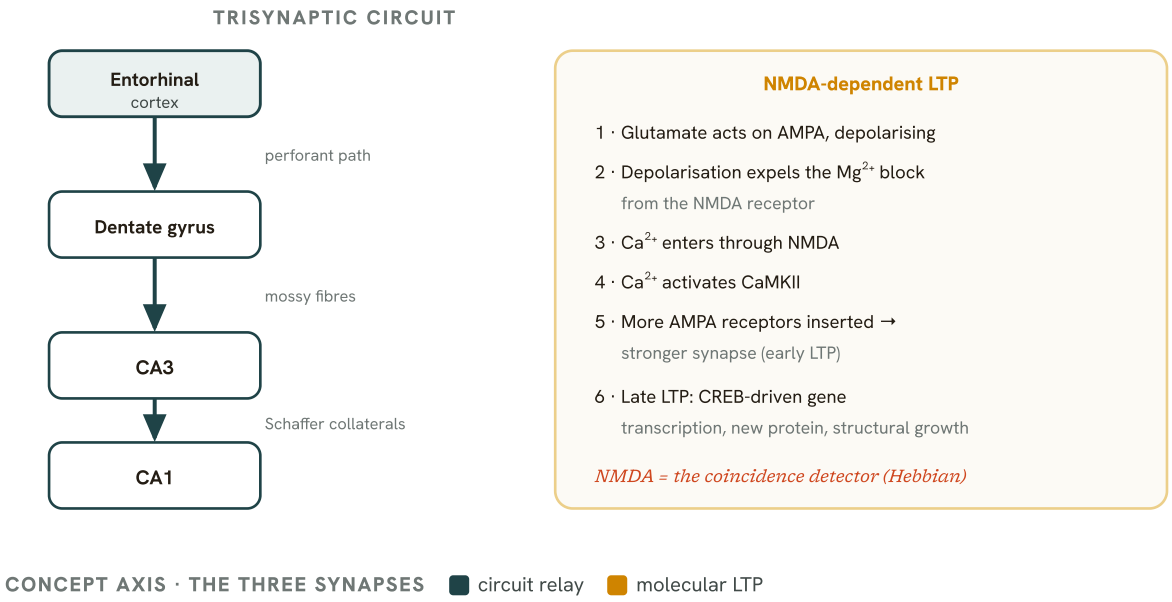



**Fig 1.14** The hippocampal trisynaptic circuit (entorhinal to dentate to CA3 to CA1) and the NMDA-dependent mechanism of LTP, the synaptic basis of declarative memory.

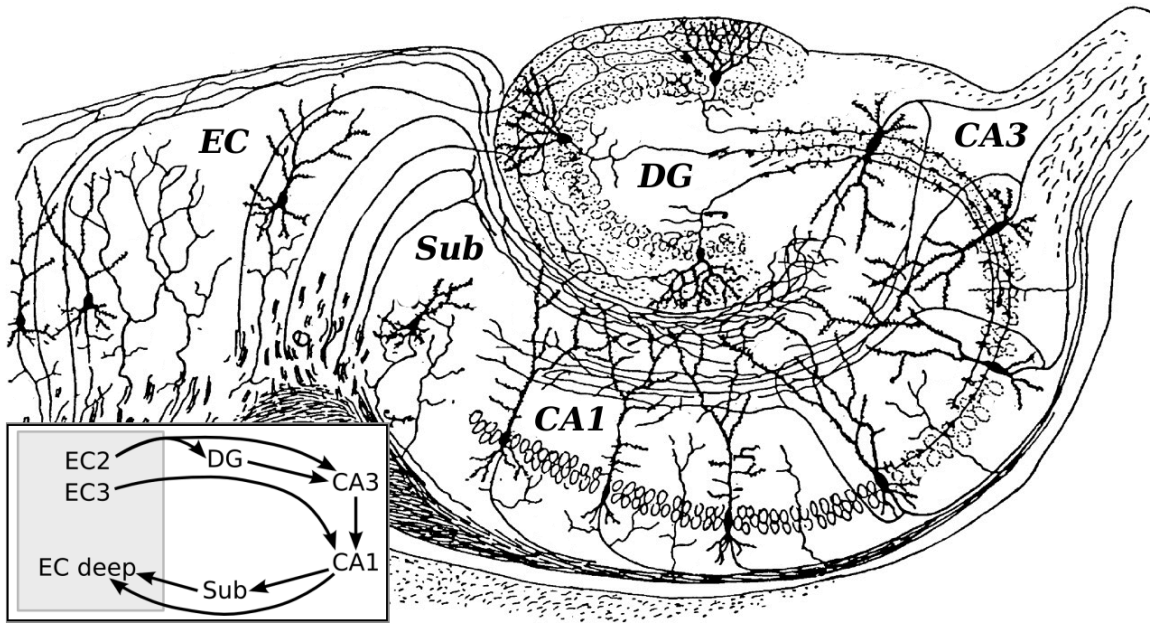



Image: Santiago Ramon y Cajal (1911), public domain, via Wikimedia Commons

**Fig 1.15** Cajal's own Golgi-stain drawing of the hippocampus. The dentate gyrus, CA3 and CA1 fields of the schematic in Fig 1.14, 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"**

**P**riming, **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 1.14 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 |
| **Transient global amnesia** | Transient hippocampal (CA1) dysfunction, often diffusion-restricting | Abrupt, isolated, self-limited (under 24 h) anterograde amnesia with repetitive questioning, full recovery |

| CONDITION | LESION / MECHANISM | MEMORY SIGNATURE |
|---|---|---|
| **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.

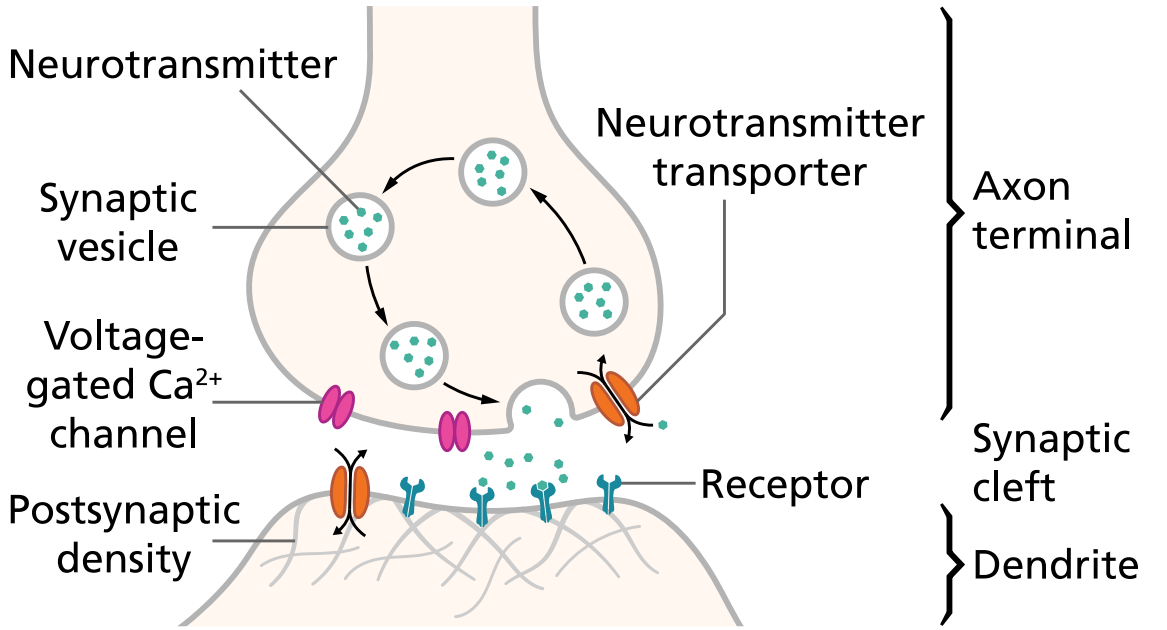



Image: Thomas Splettstoesser (scistyle.com), CC BY-SA 4.0, via Wikimedia Commons

**Fig 1.16** 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)**

**E**ighth 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.

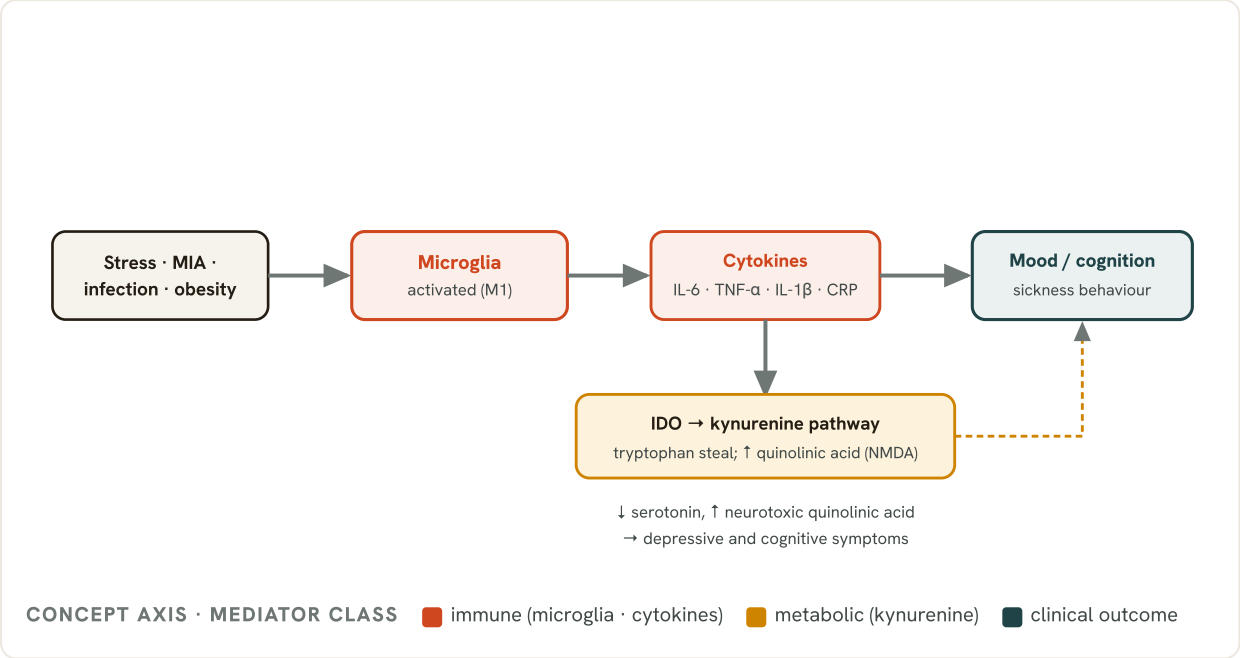



**Fig 1.17** The inflammatory route to mood symptoms: peripheral and central immune activation drives cytokine release, which shunts tryptophan down the kynurenine pathway (less serotonin, more neurotoxic quinolinic acid) and produces sickness behaviour.

- **Depression.** Meta-analysis shows consistently elevated IL-6 and TNF-$\alpha$[9] (with raised CRP); IL-1$\beta$ findings are less consistent. This grounds the "cytokine hypothesis" and the overlap of inflammation with treatment resistance. Interferon-$\alpha$ 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 1.17 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"

**A**strocytes 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.<br>MID TERM Behavioural and environmental structure; treat target symptoms (irritability, impulsivity) pharmacologically only where they drive risk.<br>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.<br>**MID TERM** Neglect-directed rehabilitation (visual scanning training, cueing to the left, prism adaptation), secondary prevention (antiplatelet, risk-factor and cardioembolic-source workup).<br>**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.<br>**MID TERM** Behavioural management of hyperorality and hypersexuality; structured routine and external memory aids for the amnesia.<br>**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.<br>**MID TERM** Secondary prevention of further ischaemia; visual and functional rehabilitation, recognising that outcome depends on cause, severity and duration.<br>**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.

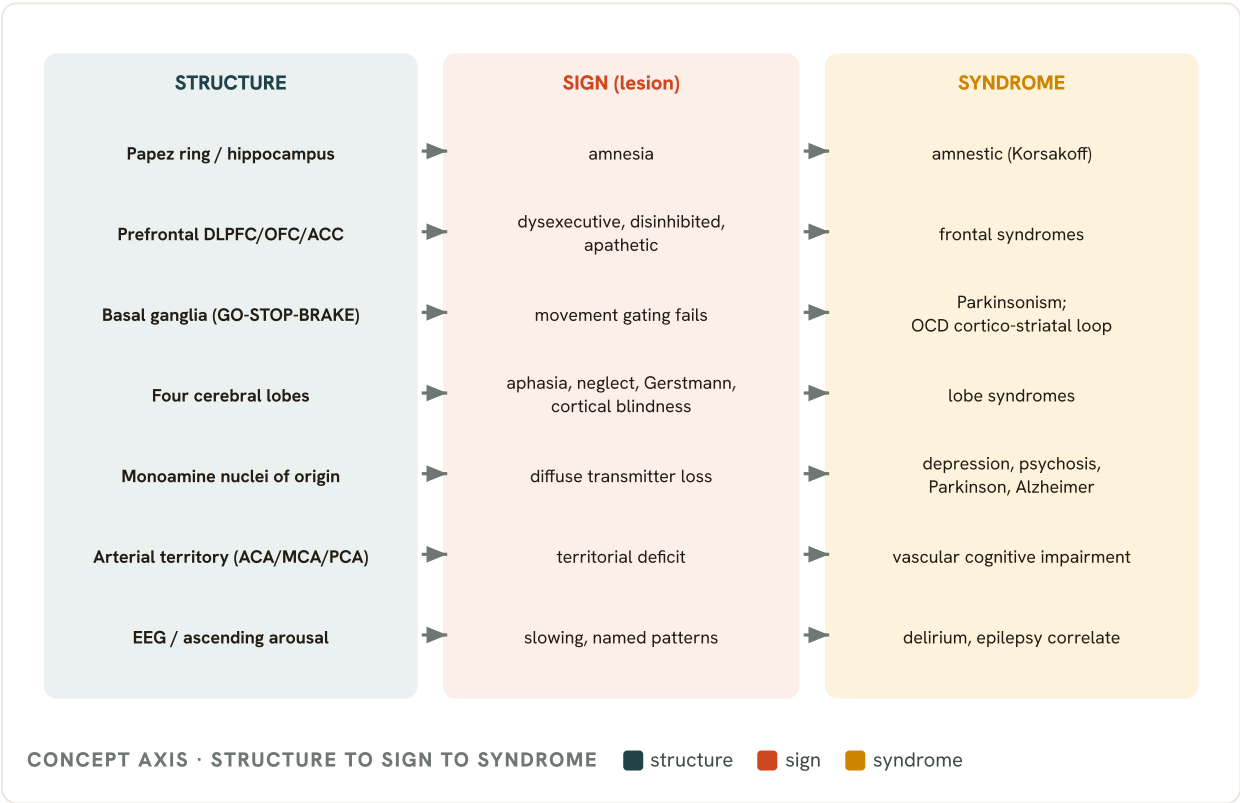



**Fig 1.18** The whole-chapter synthesis map. Every system reduces to one line: a structure, the sign its lesion produces, and the named syndrome. Cover the right two columns and rebuild them from the structure alone; the rows you cannot complete are the topics to reopen.

## 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-$\alpha$, 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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