Health Education England
NW School of Psychiatry

Basic Neurosciences

INTRODUCTION

There are almost 100 billion neurones within the brain and surprisingly 80% are found within the cerebellum despite it only contributing to 10% of brain mass. There are two basic divisions to the nervous system: the **central nervous system** which includes the brain and spinal cord, and the **peripheral nervous system** (PNS). The autonomic nervous system (part of the PNS) has two basic divisions:
The **sympathetic nervous system** is involved in "fight or flight". Preganglionic cell bodies are located from T1-L2 in the spinal cord. Pre-ganglionic neurotransmitter: **acetylcholine** (nicotinic receptors)
Post-ganglionic neurotransmitter: **noradrenaline** (Acetylcholine in sweat glands; muscarinic receptors).

The **parasympathetic nervous system** is often known for its "rest & digest" function. Some effects are in opposition to SNS (e.g. reduced HR/ pupillary constriction etc.) whilst some are complementary (e.g. sexual function). Cranial innervation is via ganglia receiving input from cranial nerves 3, 7, 9 and 10. The vagus nerves supplies thoracic and abdominal organs. Sacral outflow is from pre-ganglionic neurones whose cell bodies are in a column from S2-4. Post-ganglionic neurones are found in pelvic plexus or near target organs.
Pre-ganglionic neurotransmitter: **acetylcholine** (nicotinic receptors)
Post-ganglionic neurotransmitter: **acetylcholine** (muscarinic receptors).

EMBRYOLOGY - DEVELOPMENT OF THE NERVOUS SYSTEM

During gastrulation, the single-layered blastula transforms into the three-layered gastrula. These three germ layers are established by the 2nd week of human embryonic development:
Ectoderm – skin and nervous system
Mesoderm – connective tissue, muscles, bone, urinary & reproductive tracts.
Endoderm - GI system (inc. liver and pancreas) & respiratory tracts.

The nervous system arises from a specialised area of ectoderm called the neural plate during the 3rd week of development when the ectoderm thickens in the midline. The **neural plate** forms a longitudinal groove with a ridge on either side. The lateral edges of this groove fuse dorsally to form **the neural tube** which becomes the brain and spinal cord in a process called **neurulation**. This detaches from the rest of the ectoderm and the mesoderm develops somites (paired blocks of mesoderm arranged alongside the neural groove).

Neurulation starts on day 22 roughly halfway along the neural plate adjacent to the 4th pair of somites. It occurs rostrally and caudally forming a hollow tube with anterior and posterior neuropores. The central cavity in the neural tube becomes the central canal of the spinal cord and ventricles. The anterior neuropore closes by day 25; the caudal by day 27. Failure of the caudal neuropore to close results in ***spina bifida***. This developmental abnormality disrupts overlying structures including the meninges, vertebral arch, paravertebral muscles, and skin (their development is dependent on closure of the neural tube). ***Anencephaly*** results from failure of anterior neuropore closure.

The ridges separate from the neural tube to form the **neural crest** tissue (multipotent cells) which develop into DRG cells, ganglia of the SNS, Schwann cells, melanocytes and the MSK elements of the head and neck (including cardiac septum and semi-lunar valves). Cranial cells develop into various ganglia and contribute to bones of middle ear, jaw, and dental pulp.

BRAIN

The brain arises from the part of the neural tube rostral / cranial to the 4th pair of somites. Following closure of the cranial (anterior) neuropore (week 4) three **brain vesicles** are formed in the cephalic (rostral) portion of the neural tube:

- **P**rosencephalon (forebrain)
- **M**esencephalon (midbrain)
- **R**hombencephalon (hindbrain)

These different parts of the neural tube grow at different rates which results in folding and distortion of the neural tube. Flexures form between the midbrain and forebrain meaning that the cerebral hemispheres and thalamus are rotated forwards at the top of the brainstem.

PROSENCEPHALON	TELENCEPHALON	Cerebral cortex Basal Ganglia Limbic system Hippocampus Olfactory Bulb	Lateral ventricles
	DIENCEPHALON	Thalamus Hypothalamus Subthalamus Epithalamus	3rd ventricle Posterior pituitary
MESENCEPHALON	TECTUM	Superior Colliculi Inferior Colliculi (Corpora quadrigemina)	Cerebral aqueduct (of Sylvius)
	TEGMENTUM	Red nucleus PAG matter	Substantia Nigra
RHOMBENCEPHALON	METENCEPHALON	Pons Cerebellum	
	MYENCEPHALON	Medulla	

SPINAL CORD

The spinal cord develops from the part of the neural tube that is caudal (distal) to the 4th pair of somites.

After neurulation, the lateral walls of the tube thicken and a longitudinal groove called the **sulcus limitans** appears in the lateral walls of the embryonic spinal cord and caudal (hind) part of the brain. Two plates form on either side. A ventral or **basal plate** and the dorsal (or **alar plate**). By week 10 the lumen of the neural tube has narrowed and becomes a small central canal. Nerve cells developing in the alar plate (dorsal) are predominantly sensory and form ascending projections. Nerve cells in the basal (anterior) plate are predominantly motor.

Cells in the thoracic segments of this plate develop into **sympathetic preganglionic neurones**. Cells in the sacral segments develop into **parasympathetic preganglionic neurones**. Grey and white matter differentiate with grey matter located centrally around canal, and the white matter forming an outer coat. During development, the spinal column lengthens more than the spinal cord. This means the spinal cord stops at L1 in adults but L3 in neonates.

FOREBRAIN (PROSENCEPHALON)

Before the cranial neuropore closes, two pairs of lateral outgrowths appear on the sides of the forebrain. One pair forms the **optic vesicles**, the other pair become the **cerebral hemispheres**. The optic vesicles develop into the retina and optic nerve. The forebrain vesicle (**prosencephalon**) develops into:

- **Telencephalon**: Cerebral cortex, commissures, tracts and **basal ganglia**.
- **Diencephalon**: hypothalamus, thalamus, epithalamus and posterior pituitary gland.

TELENCEPHALON - CEREBRAL CORTEX

The **left hemisphere** is usually the dominant hemisphere in nearly all right handers and > 2/3 of left handers. It has a specialist role in language, arithmetic, verbal memory and visual recognition.

The **right hemisphere** is involved in non-verbal perceptual tasks such as visuospatial recognition, emotional expression and elements of speech such as prosody.

Dominance can be assessed through use of functional imaging (fMRI, PET) or invasive methods including the Wada test. The cerebrum is commonly divided into four lobes, the **frontal lobes, parietal lobes, temporal lobes and occipital lobes**. (The limbic system is sometimes referred to as a fifth lobe).

The frontal lobes (largest area of cortex; approx. 40%) have 3 major functions:

1. Motor
2. Speech
3. Personality / social behaviour / emotion regulation (pre-frontal cortex; PFC)

The frontal lobe contains the primary motor cortex (BA 4) (elicits simple movements; contains motor homunculus) and secondary motor cortex (SMA (BA 6) – motor planning; timing & sequencing; Premotor area – similar to SMA but may have role in waiting for external cue; Cingulate motor area – motivational drive for movement – injury can result in lack of spontaneous motor activity and decreased speech).

PFC region	Role	Syndrome
Dorsolateral PFC (DLPFC)	Organising & planning Set-shifting; working memory	**"Disorganised"** - Poor attention / judgement / planning / insight / Rigidity (concrete)
Orbitofrontal (OFC)	Inhibitory; maintains appropriate behavioural responses and facilitates tactful behaviour	***"Pseudo-psychopathic"*** – Disinhibited / Poor impulse control / Explosive outbursts / Inappropriate behaviour
Ventromedial / mPFC	Mood & motivation Part of "default mode network"	***"Pseudo-depressive"*** – Apathetic / Lack of initiation / Poverty of speech / Lack of social knowledge

Other signs of frontal lobe damage include:

- Contralateral hemiplegia
- Anosmia
- Inappropriate mood, inappropriate jocularity (**Witzelsucht** – includes hypersexuality), talkativeness, primitive reflexes.
- Abulia or akinetic mutism
- Utilisation & imitation behaviours (e.g. echolalia).

Tests of frontal lobe function:

- Luria (hand sequence)
- Go-no-go (inhibitory control)
- Similarities (conceptualisation)
- Cognitive estimates (abstraction)
- Letter / category fluency (initiation)
- Alternating patterns (copying squares/triangles) (set-shifting; perseveration)
- Stroop/FAB etc.

Temporal lobes are involved in perception & recognition of auditory information, language production and memory. The *planum temporale* on the upper surface of the temporal lobe shows significant asymmetry in most humans. People with schizophrenia are more likely to lose this asymmetry / have reversal of asymmetry. The **superior temporal gyrus** – primary auditory cortex (in lateral sulcus) / inputs arrive via medial geniculate nucleus from both ears. Auditory association cortex on lateral surface of gyrus. Wernicke's area is on the posterior 1/3 of superior temporal gyrus.

Damage to temporal lobes can cause:

- Impaired memory (verbal / visual)
- Wernicke's aphasia
- Anomia
- Visual agnosia
- Dysgraphia (spatial elements with non-dominant)
- Prosopagnosia
- Homonymous upper quadrantopia

HM - famous patient who underwent bilateral MTL resection to treat intractable seizures. He developed severe anterograde and retrograde memory impairment.
Temporal lobe epilepsy (TLE) - autonomic sensations / Dysphasia / Forced thinking / Panoramic memory / Depersonalisation / Déjà vu and jamais vu / absences / lip smacking /

Parietal lobes include the sensory cortex (BA 1,2,3) and process and integrate sensory information. They are involved in praxis and visuospatial processing. They are important for undertaking skilled movements / manipulation of objects in space. Parietal lobe damage can cause:

- Dysgraphia*
- Dyscalculia (L- number alexia / R - spatial)*
- R-L disorientation*
- Finger agnosia*
- Tactile agnosia
- Homonymous lower quadrantopia
- Constructional apraxia (not a true apraxia)
- Neglect / inattention
- Topographical disorientation
- Anosognosia
- Astereognosis

*features of **Gerstmann's syndrome** – usually associated with lesions in dominant hemisphere in area of angular gyrus.

The parietal lobe is the site of the **supramarginal gyrus** (BA 40) and **angular gyrus** (BA 39)

Occipital: location of visual cortex. Medially divided by the calcarine sulcus. Above is the cuneus (wedge) – lower quadrant of contralateral visual field; below is the lingual gyrus (upper quadrant).

Damage can cause:

- Contralateral homonymous hemianopia
- Visual object agnosia
- Visual illusions/hallucinations
- Cortical blindness

Two recognised syndromes are:

- ***Anton's Syndrome*** (or Anton-Babinski) – cortically blind; visual anosognosia (with confabulation)
- ***Bálint's Syndrome*** – bilateral damage to dorsal visual stream. Can be seen in posterior cortical atrophy (Alzheimer's) and watershed infarctions.
  - simultagnosia - not being able to perceive visual field as a whole
  - oculomotor apraxia – difficulty fixating on an object
  - optic ataxia - inability to move hand to specific object using vision

Primary visual cortex (BA 17) – mostly hidden within the calcarine sulcus with a small amount at the occipital pole. It is surrounded by the visual association cortices (BA 18/19) in the cuneal & lingual gyri.

Visual pathways have a retinotopic (point-point) organisation.
Retina → optic chiasm → synapse in lateral geniculate nucleus (of thalamus) → 1° visual cortex (via optic radiations).
In the visual cortex, incoming information is divided into 3 modalities – form/motion/colour.
2 parallel streams arise from occipital lobe:
The dorsal/parietal "where" stream – location, movement & position of objects
The ventral/temporal "what" stream – form & colour

CEREBRAL CONNECTIONS:

Three main types of fibres link brain areas with each other and with different parts of the nervous system.

Commissural fibres: link matching areas in each hemisphere, the largest being the corpus callosum. From the body of the corpus callosum some fibres pass laterally and upward intersecting the corona radiate. Other fibres pass laterally and downward as the tapetum reaching the lower parts of the temporal and occipital lobes. The corpus callosum is divided into *rostrum, genu, body, & splenium.*

Association fibres: interconnect areas lying within one cerebral hemisphere. Short association fibres pass from one gyrus to another within a lobe. Long fibres link one lobe with another.

Superior longitudinal fasciculus
Occipital lobes - frontal lobes

Inferior longitudinal fasciculus

Occipital lobes - temporal lobes

Uncuate fasciculus
Frontal - anterior temporal lobe

Broca's area - Wernicke's area.
Damage is reported to cause conduction aphasia (impairment of repetition)

Cingulum
Underlying the cingulate gyrus

Arcuate fasciculus

Projection fibres: pass from the cerebral cortex and subcortical structures (e.g. thalamus, striatum) and project to distant areas. See motor and sensory system.

MOTOR SYSTEM

Pre-central gyrus: Motor homunculus – both the sensory and motor cortices contain a representation of the body known as a homunculus. The size of the individual area corresponds to nervous innervation. These homunculi are capable of reorganisation following loss of a limb or injury to part of the cortex (e.g. CVA). Other brain areas such as the cerebellum and thalamus have a similar homuncular configuration.

Internal capsule: subcortical structure containing projection fibres which form the corona radiata and contains both motor and sensory projection fibres.

Corticospinal tract: Major motor pathway
Motor axons travel through the internal capsule (posterior limb), midbrain, pons and into the medulla where they form the medullary pyramids. In the medulla approximately 85% decussate (crossover) and descend in the white matter of the contralateral cord as the **lateral corticospinal tract**. They synapse on motor neurones in the anterior horn. Most of these neurones innervate flexors. The 15% non-crossing axons form the **ventral corticospinal tract**. They decussate at the spinal level mainly controlling extensor muscles. The average conduction velocity in the corticospinal tract is 60m/s. Corticospinal fibres are excitatory and use glutamate. Acetylcholine is released at the neuromuscular junction (NMJ).

Other motor pathways:

Tectospinal tract: Visuospinal reflexes - mediates reflex postural movements of the head to visual and auditory stimuli.

Vestibulospinal tract: Maintaining balance

Rubrospinal tract (midbrain) : Negligible role in humans, but the crawling as a baby is controlled by the red nucleus, & arm swinging in walking.

SENSORY SYSTEM

Main sensory pathways: both contain three orders of neurones. 1st order in dorsal root ganglia; 2nd order in dorsal grey matter; 3rd order from the thalamus. Afferent (sensory) fibres join the spinal cord via the dorsal root. The neurones have cell bodies in the dorsal root ganglia (DRG). They are pseudo unipolar type neurones.

Dorsal column – medial lemniscal pathway: Conscious proprioception and discriminative touch. Large sensory neurones enter via the dorsal root (their cell bodies being in the DRG). They travel in ipsilateral cord to synapse in the medulla (dorsal column nuclei). Sensory information from leg and lower body enter gracile nucleus; from arms, neck, and upper body, enters the cuneate nucleus (face - trigeminal nucleus). 2nd neurone cross to the ventral medulla to form the medial leminscal pathway which synapses in the thalamus. Neurones then project to the primary somatosensory cortex.
Tabes dorsalis is a late symptom of syphilis affecting the dorsal columns. Symptoms include sensory ataxia, reduced reflexes and *Charcot's joints*.

Spinothalamic tract: Pain, crude touch, and temperature. Information is carried into the dorsal horn by fast myelinated neurones (Aδ) (sharp pain) and unmyelinated C fibres (dull pain and thermal information).

Aδ fibres terminate in lamina I and V of the dorsal horn; C fibres terminate in layer I & II. The second order neurones cross to the contralateral side and ascend as the Spinothalamic tract.

Minor sensory pathways:
Spinoreticular tract: Involved in wakefulness; emotional aspects of sensation
Spinocerebellar tract: Non-conscious proprioception
Spinotectal: Visuospinal reflex

BASAL GANGLIA

The basal ganglia are a group of five nuclei (grey matter) in the subcortical areas of the forebrain (at the base). They have extensive connections with other brain areas and are involved in motor control (forming the extrapyramidal system) and cognition. These nuclei play a role in ensuring appropriate movements occur relative to the task (correct scaling for handwriting or in repetitive actions such as walking).

Caudate nucleus
Putamen } "Striatum" – both contain identical cell types
Globus pallidus (external and internal) } "Lentiform" nucleus
Substantia nigra
Subthalamic nucleus
} **Corpus striatum**

The striatum receives inputs from the motor, sensory, association, and limbic areas. The projection from the cortex is organised so the putamen is concerned with motor control and the caudate with eye movements and cognition. The striatum projects to the globus pallidus and subthalamic nucleus. The internal segment of the globus pallidus is the major output to the ventrolateral and ventral-anterior nuclei of the thalamus. The external segment projects to and from the **subthalamic nucleus.**

Motor - **P**rogramming of movement (selecting) - **P**utamen
Cognitive - **C**audate nucleus: receives large projection from PFC. Novel motor tasks / learning

The putamen sends a projection to the pars reticulata of the substantia nigra (SN; contains melanin pigment so appears black). The substantia nigra is divided into the ***pars compacta*** (projects to striatum) and ***pars reticulata*** which projects to the globus pallidus. There are no direct connections with motor neurons in the spinal cord or brainstem. The basal ganglia modify the output of cortical neurons through two pathways:

1. **Direct pathway** - **D**ecreases inhibition / **disinhibits** the thalamus which increases stimulation of the motor cortex. Striatum→GPi→thalamus.
2. **Indirect pathway** - **Inhibits** the thalamus reducing excitation to the motor cortex. Straitum→GPext→subthalamic nucleus→GPi→thalamus.

These two pathways have an opposing action which explains the motor symptoms of common movement disorders. The direct pathway promotes movement, the indirect suppresses oppositional movements.

Parkinson's disease (PD): the inhibitory dopaminergic pathway from the SN (pars compacta) is impaired which effectively enhances activity in the ***indirect*** (and **i**nhibitory) motor pathway as dopamine (D_1) inhibits the indirect pathway. The result is more inhibition (by indirect pathway) of the VA/VL thalamus meaning the motor cortex is LESS ACTIVE.

There is some compensation for loss of dopamine neurons as existing cells release more dopamine and striatal receptors increase in number. These mechanisms fail at about 80% of cell loss. Drug treatment of PD aims to increase the function of the remaining dopaminergic neurones or antagonise the cholinergic interneurons (antimuscarinics).

Huntington's Disease (HD)

Degeneration of the striatum (mainly caudate) with selective loss of GABAergic neurons. Effect is opposite to the changes in PD (too much motor activity).

Other disorders with a basal ganglia aetiology or dysfunction include:

- ***Obsessive compulsive disorder***
- ***PANDAS*** – paediatric autoimmune neurological disorder associated with streptococcus
- ***Tourette's***
- ***Fahr's disease*** - rare genetic neurological disorder characterized by abnormal deposits of calcium in the basal ganglia. Symptoms include unsteady gait, dysarthria, difficulty swallowing, and involuntary movements. Seizures and neuropsychiatric symptoms may occur.

Other basal ganglia circuits:
The limbic loop from the OFC through the nucleus accumbens (ventral striatum) and ventral pallidum back to the inferior PFC via thalamus. Plays a role in emotional expression & reward behaviours. It is rich in dopamine and dysfunction may account for the mask-like face characteristic of Parkinson's disease.

The oculomotor loop commences in the frontal eye fields and posterior parietal cortex (area 7). It coordinates voluntary saccades through interaction with the superior colliculi. Involves caudate nucleus and also important for visual attention & cognition.

LIMBIC SYSTEM

Hippocampus	**A**utonomic control
Parahippocampal gyrus	**D**rives
Amygdala	**E**motion
Cingulate gyrus	**M**emory
Anterior thalamus	**O**lfaction
Hypothalamus	**N**euroendocrine control
Mamillary bodies	(courtesy of https://psychmnemonics.wordpress.com/category/neuroscience/)

The Cingulate Cortex – loops around the limbic system. The anterior cingulate cortex plays a role in social interaction. The posterior aspects are involved in memory function. The limbic system forms a "limbus" or ring in the medial aspects of the temporal lobes surrounding the upper part of the brainstem. It is the "nervous system" of emotion and behaviour. It has a complicated structure but can be divided into two key circuits:
Hippocampal circuit – involved in learning and memory (Papez circuit)
Hippocampus (CA3 pyramidal neurones) →via fornix→mamillary bodies→anterior nucleus of thalamus→cingulate cortex→ entorhinal cortex → hippocampal formation (dentate gyrus)
Damage to mammillo-thalamic tract, ventral anterior nucleus, and ventral lateral nucleus can result in memory and language impairment.

Amygdaloid circuit – involved in processing of emotion and modulating our responses (including neuroendocrine). Amygdala is an almond-shaped nucleus found in the poles of the temporal lobe anterior to the hippocampi. Stimulation can cause feelings of fear and a corresponding response in the sympathetic nervous system. Lesions of the amygdala impair face recognition.

Klüver–Bucy syndrome results from bilateral lesions of the anterior temporal lobe (including amygdala and hippocampus). Symptoms include hyperphagia, hypersexuality, hyperorality, visual agnosia, hypermetamorphosis, amnesia, and placidity (with loss of fear or anger).

DIENCEPHALON

Thalamus – major relay for sensory & motor information. Role in consciousness and alertness (as part of reticular activating system – intralaminar nucleus).
Hypothalamus

Epithalamus : includes Pineal gland – small endocrine gland below thalamus which releases melatonin.
Subthalamus

Hypothalamus – located below thalamus in walls of the third ventricle. Part of limbic system. Role in autonomic nervous system and homeostatic functions (body temp / circulation) and sexual behaviour, hunger, thirst and sleep. Parvocellular cells release other hormones into the hypophyseal portal system which travels to the anterior pituitary causing release of secondary hormones.

Ventromedial hypothalamus – "satiety centre"; damage results in hyperphagia & weight gain
Lateral hypothalamus – "hunger centre"; damage results in reduced food/fluid intake

The pituitary is a small gland which sits within the bony *sella turcica* (Turkish saddle). The **anterior pituitary** is glandular and develops as an ingrowth of ectoderm from the hard palate (Rathke's Pouch). The **posterior pituitary** (or neurohypophysis) is comprised mainly of magnocellular cells extending from the paraventricular and supraoptic nuclei of the hypothalamus.

Hypothalamic area	Hypothalamic hormone	Anterior Pituitary	Posterior Pituitary
Paraventricular nucleus	CRH (+ve)	ACTH (also B-lipotropin)	
	Thyrotropin releasing hormone (TRH) (+ve)	Thyroid stimulating hormone Prolactin	
Preoptic area	Gonadotrophin releasing hormone (+ve)	FSH LH	
Arcuate nucleus (infundibular nucleus)	Dopamine (-ve)	Prolactin	
	GH releasing hormone (+ve)	Growth hormone	
Periventricular nucleus	Somatostatin (-ve)	Growth hormone	
		Thyroid stimulating hormone	
Magnocellular neurosecretory cells in the paraventricular & supraoptic nucleus			Antidiuretic hormone/ vasopressin
			Oxytocin

Learn about the (hypothalamo-pituitary-adrenal axis) HPA axis and its abnormality in illness e.g. depression!

Blood supply

Internal carotid arteries and basilar artery (from vertebral arteries) form a circular anastomosis at the base of the brain known as the Circle of Willis which is composed of the:

Anterior cerebral arteries
Anterior communicating artery
Internal carotid arteries
Posterior cerebral arteries
Posterior communicating arteries
Basilar artery.

Internal carotids arise from common carotid arteries and enter the middle cranial fossa lateral to the optic chiasm. The *posterior community artery* is a branch of the internal carotid before it finally divides.
The *anterior cerebral* arteries provide the anterolateral part of the Circle.
The middle cerebral artery does not contribute to the Circle.

Significant inter-individual variation exists in the Circle of Willis. The Circle of Willis encircles the optic chiasm and the floor of the midbrain. The Circle of Willis is a common site of cerebral aneurysm formation. The Circle of Willis is designed to potentially give the ability of the brain to maintain its blood supply in the event of an arterial occlusion in a feeding vessel.

Anterior cerebral artery: Medial aspects of frontal and parietal lobes; anterior part of corpus callosum and external capsules.

Disruption can cause leg weakness and cortical sensory loss. Other symptoms may include a grasp reflex, and frontal lobe symptoms.

Left ACA: transcortical aphasia may be seen if the prefrontal cortex and supplemental motor areas are involved.
Right ACA: Left hemineglect if the prefrontal cortex and non-dominant association cortex are involved.

Small penetrating branches of the ACA and MCA supply subcortical structures. These are known as the striate and lenticulostriate arteries - small perforating arteries.

Middle cerebral artery: Lateral surface surface of the hemispheres. Supplies most of pre- and post-central gyri other than upper and medial aspects which are supplied by anterior cerebral artery. Doesn't supply the inferior parts of the temporal lobe which is supplied by PCA.

Left MCA - nonfluent (Broca's) aphasia. Other deficits include a fluent (Wernicke's) aphasia due to damage to Wernicke's area. Right MCA - Left hemineglect (variable) due to damage to non-dominant association areas.

The Lateral Lenticulo-striate arteries – supply most of basal ganglia.
Interruption of blood supply can cause pure motor hemiparesis due to damage to the basal ganglia (globus pallidus and striatum) and the genu of the internal capsule. Larger infarcts extending to the cortex may produce cortical deficits such as aphasia.

Posterior cerebral artery: The posterior cerebral arteries arise from the basilar artery which itself is a conjunction of the left and right vertebral arteries (at the lower pons). The PCA enters the skull through the foramen magnum. The basilar artery divides in to the two PCAs at the upper border of the pons.

Branches of PCA supply: Midbrain and thalamus (posterior thalamo-perforating arteries), posterior internal capsule and optic radiation. Cortical branches supply the infero-medial part of the temporal lobe, occipital pole, visual cortex, and splenium of the corpus callosum.

Contraleteral homonymous hemianopia.
Extension to the splenium of the corpus callosum therefore interfering with communication between the two visual association areas can cause alexia without agraphia. Larger infarcts involving the internal capsule and thalamus may cause hemisensory loss and hemiparesis due to disruption of the ascending and descending information passing through these structures.

Venous System:
The brainstem and cerebellum drain into the dural venous sinuses.
The cerebral hemispheres drain via the external veins into the superior sagittal sinus – transverse sinus – lateral sinus – internal jugular vein.
The internal cerebral veins drain the subcortical structures of the hemispheres to the Great Cerebral Vein (vein of Galen) into the straight sinus.

Blood-brain barrier (BBB):
The BBB is formed by an interaction of capillary **endothelial cells** and astrocytes. It functions to maintain a constant chemical environment and provide immunological protection. It protects neurons from

- Tight junctions between endothelial cells which unlike those elsewhere in the body don't allow transcellular movement of molecules (such as sodium and potassium ions) without being transported.
- Close association with astrocyte end-feet which form a barrier from the neurones.
- Effective barrier to water-soluble substances
- Some lipid soluble molecules can enter the brain (e.g. ethanol).
- Small hydrophilic molecules transported
- Glucose uses facilitated diffusion*

Not all areas of the CNS have blood brain barrier such as the ***area postrema*** (aka Chemoreceptor trigger zone located on surface of medulla oblongata in floor of fourth ventricle which can detect toxins in the blood) – these areas are named *circumventricular organs* and contain fenestrated capillaries.

MENINGES

Dura mater (literally hard mother): Tough membrane that closely adheres to skull and vertebrae. In the skull it is innervated by trigeminal nerve supratentorially and upper cervical nerves infratentorially.
The dura has a superficial (periosteal) layer and a deep meningeal layer. These two layers separate in the dural folds with the meningeal layer forming protrusions into the cranial cavity:

The tentorium cerebelli – separates the cerebellum and brainstem from occipital lobes
The falx cerebri – in the longitudinal fissure separates the two cerebral hemispheres.

Subdural haematoma – blood between dura and arachnoid membrane. Cause by torn bridging veins. Usually crescent shaped. Classic cause of pseudo-dementia.
Extradural haematoma *(or epidural haematoma)* – forms between the inner surface of skull and periosteal layer of dura. Usually due to trauma and found with fracture. Torn meningeal artery (usually middle meningeal artery). Typically **biconvex** and are limited by cranial sutures. Cause mass effect.

Arachnoid mater (spider-like mother): Separated from the pia mater by the web-like sub-arachnoid space in which CSF flows. Sits around the brain unlike the pia mater. The arachnoid has villi which protrude through the dura into the venous sinuses allowing CSF to exist the subarachnoid space. The subarachoid space contains the major arteries which project through the pia mater into the CNS.

Pia mater (tender mother): adheres closely to the brain and follows contours of gyri and sulci. Thin fibrous membrane. Impermeable to water. In the cord attaches to the dura/arachnoid tube via the denticulate ligament.

Ventricular system

The cerebral hemispheres contain paired lateral ventricles within the cerebral hemispheres which connect to the 3rd ventricle through interventricular foramina (of Munro). The lateral ventricles lie directly below the corpus callosum. The anterior horns are separated by a thin membrane extending down from the corpus callosum called the **septum pellucidum**.

Thalamus and hypothalamus form the walls of the third ventricle. Caudally joins cerebral aqueduct (of Sylvius) which extends through the midbrain. Stenosis of aqueduct (congenital, compression) can result in communicating hydrocephalus.

4th ventricle found bounded by pons and medulla with the "roof" formed by the cerebellum. It is diamond-shaped in cross section. Contains a median aperture (foramen of **M**agendie) which drains into the cisterna magna and two lateral apertures (foramina of **L**uschka) which drain into another cistern (widening of subarachnoid space). CSF then circulates around the brain or down into spinal cord. It can also pass directly into the central canal of the spinal cord via the obex.

Cerebrospinal Fluid (CSF)

Up to 500 mL/day of CSF produced. Approx 150mL always in circulation.

CSF is produced mainly by the choroid plexus; a significant amount is also produced by the pia mater and ventricular ependymal surfaces and arachnoid membrane. The choroid plexi are vascularised processes projecting into each ventricle and are lined with ependymal cells.

CSF moves from ventricles and cerebellum to subarachnoid space via three foramina in the 4th ventricle. It enters the circulation via the arachnoid granulations – small protrusions of the arachnoid through the Dura mater into the venous sinuses (largest in the superior sagittal sinus). The arachnoid granulations function as one-way valves driven by the higher pressure of CSF compared to venous system.

Component	Normal	Bacterial Meningitis	Viral Meningitis
Appearance	Clear	**Cloudy & turbid**	Usually clear
Cells / mm³	0 - 5 all lymphocytes	**10- 100 000 granulocytes**	**15 - 2000 lymphocytes**
Glucose (mmol/L)	2.8 - 4.4	**low**	Normal
Protein (g/L)*	0.15 - 0.5	**0.5 - 5.0**	**0.45 – 5.0**
*normally 60-70% of plasma level			

CSF is similar to plasma but contains less protein and glucose. It cushions and supports the brain and spinal cord. It plays a role in the transport of nutrients, chemical messengers and waste products

Hydrocephalus – an increase in CSF volume (or pressure): **Non-communicating hydrocephalus:** If CSF flow is blocked within the ventricles (e.g. congenital abnormalities such as aqueduct stenosis) or mass lesions (tumour; haematoma). **Communicating hydrocephalus (non-obstructive):** caused by impaired CSF reabsorption. Maybe due to impairment of arachnoid granulations in superior sagittal sinus. Caused by SAH, meningitis, infections, or congenital absence of villi.
Normal pressure hydrocephalus (NPH) is a form of communicating hydrocephalus – characterised by enlarged ventricles. Classic symptoms are cognitive impairment (typically sub-cortical), gait changes and urinary incontinence (later feature).

MICROANATOMY

There are two basic cell types in the nervous system:

1. **Neurones**
2. **Glial cells** (or neuroglia)

NEURONES – specialist excitable cells which can transmit impulses. Neurones can be classified by their shape (morphology) depending on the number of neurites (processes arising from cell body) they have:

- ***Multipolar*** – (most common) single axon and many dendrites to integrate information (motor axons and inter-neurones)
- ***Bipolar*** – Single axon and dendrite; found in the retina mainly.
- ***PseudoUnipolar*** - single axon and dendrite appear to arise from same stem. Sensory pathways – e.g. sensory neurones of dorsal root ganglion.

Neurones can also be classified by their size as **Golgi Type 1** which have a long axon and **Golgi Type 2** neurones which have a short or no axon. Afferent axons (arrive) – carry information into the CNS. Efferent axons (exit) – carry information out of the CNS/away from a structure.

Major neuronal types in brain:

CELL TYPE	Pyramidal Cells	Granule / Stellate cells
Morphology	Large-triangular cells bodies 20-50μm	Star-shaped 10μm Can be spiny or smooth
Function	Excitatory	Excitatory or inhibitory
Classification	Multipolar Golgi Type I	Multipolar Golgi Type II (short axons)
Location	Motor/pre-motor areas Hippocampi / amygdala	Sensory cortex

Betz cells are large pyramidal cells (~100μm diameter) found in layer V of cerebral cortex.

Neurones have large surface areas which increases as the number of dendrites increase. (Neurones have high energy requirements for the Na^+/K^+ ATPase pump – around 2/3 of energy requirement). Ion channels within the membrane allow transmission of action potentials.

The cell body of a neurone is known as the **soma**. Other constituents of neurones include:
NISSL substance – consists of granular (rough) endoplasmic reticulum for protein synthesis; only found in cell body.
Golgi apparatus – processes and packages proteins (e.g. ion channels/receptor proteins) – mainly in cell body
Microtubules – role in axonal flow. Tubular polymer of α- and β-tubulin which are stabilised through binding with microtubule associated proteins (MAPs) including Tau. Diameter approx. 50 μm. Microtubules facilitate axoplasmic flow of macromolecules and small organelles in both directions. Neurones transport proteins, lipids, and other macromolecules, from the cell body to the synapses as the ribosomes and endoplasmic reticulum are in the cell body – **axonal transport.**

Dendrites of many neurones are covered in microscopic spines. Each spine is the site of a synapse. These spines are believed to play a role in synaptic plasticity.

Neuronal membranes are lipid bilayers. It contains proteins that form ion channels, voltage-gated channels, receptors or function as ion pumps. The membrane is fluid allowing proteins to float freely in the "lipid sea". Carbohydrates are found only on the external surface attached to proteins or lipids. The membrane allows lipid-soluble, small and non-charged molecules to diffuse passively through the membrane. Ions and polar molecules are reliant on carriers or ion channels. Membranes have a high rate of turnover. This means neurones accumulate non-digestible by-products within residual lysosomal bodies – lipofuscin ("age pigment") and neuromelanin granules.

Structural proteins, such as:
Neurofilaments - 10 nanometer filaments which are important part of neuronal cytoskeleton giving axon support and regulating axonal diameter. Made up of chains of polypeptides arranged orthogonal to axon.
Microfilaments: ~7nm double-stranded protein strands of actin.

NEUROGLIA - play a role in physical support of neurones, formation of myelin, regulating the extracellular environment, removing NTs, involved in blood-brain barrier (BBB) and may have a nutritive function for neurones. They are capable of cell division. There are two main classes of glial cells:

1. **Microglia** (CNS) are macrophages found in the CNS. They make up around 10-15% of the total glial cells within the brain. Small cells with rod-shaped nuclei.
2. **Macroglia** – Astrocytes & oligodendrocytes (in the CNS), and Schwann cells (PNS) and Satellite cells (ANS).

Macroglial cells	Function
Astrocyte	Support neurones & synapses. Scaffolding of the brain. Important role in formation of BBB (end-feet make contact with neurones & capillaries). Convert glucose → lactate for neuronal use. Regulate ECF (K^+ ion concentration); absorb excess NTs (e.g. GABA, glutamate). Involved information of scar tissue and phagocytosis.
Oligodendrocyte (CNS)	Formation of myelin sheath around some myelinated neurones and structural support of neurones (physical & metabolic) in CNS. One oligodendrocyte will myelinate more than 1 axon (c.f. Schwann cells).
Schwann cells (PNS)	Structural support and formation and maintenance of the myelin sheath in the PNS around single neurones.
Satellite cells	These cover the surface of nerve cell bodies in sensory, sympathetic and parasympathetic ganglia. They are derived from the neural crest of the embryo during development.
Ependymal cells (CNS) "ependymocytes"	Cuboidal cells found in the ventricles and central canal of the spinal cord. Form a thick epithelium-like lining and have cilia on their surface. They are important to circulation of CSF and absorption of solutes.

CORTICAL STRUCTURE: The cerebral cortex is arranged in both layers and columns. The cerebral cortex is made up of 6 layers of cells (unlike the cerebellum which has 3 – Molecular/Purkinje/Granular) – known as ***isocortex***. >50% of surface area hidden in sulci. Thickness varies from 2-4mm. Thickest in motor and association areas.

LAYER	NAME	COMMENTS
1	Molecular layer	Glial cells. Dendrites from deeper neurones.
2	External granular layer	Granule cells.
3	External pyramidal layer	Association fibres. Small and medium pyramidal cells.
4	Internal granular layer	Granule cells. Stellate cells. Sensory information (afferents)
5	Internal pyramidal layer	Large pyramidal cells. Outputs. Betz cells. Afferent inputs.
6	Fusiform (multiform) layer	Mixed cell types.

Pyramidal neurones (triangular shaped cells) account for most cortical neurones with stellate cells present in all layers except layer 1.

Betz cells found in layer 5 are the largest in the central nervous system. They are found in the motor cortex.

Some brain areas only have 3 layers (e.g. hippocampus) – ***allocortex***. ***Mesocortex*** – found in transitional areas (inc. limbic lobe) has an intermediate number of layers.

The columns (~500μm) make up functional "units" extending through the layers (laminae). Cells within these columns are modality specific.

ACTION POTENTIALS

Neurones are excitable cells. They have a resting membrane potential of -70mV.
The potential difference is maintained by selective permeability to ions and by the Na^+-K^+ ATPase pump which brings potassium into the cell in exchange for sodium (2 K^+↔ 3 Na^+). At rest, voltage gated Na+ channels are closed, but there is a gradual loss of:

- K^+ - down concentration gradient.
- Cl^- - down electrical gradient

The cytoplasm contains large anionic proteins – the cell membrane (plasmalemma) is impermeable and they are unable to leave the cell down their electrochemical gradient.

	Intracellular fluid	Extracellular fluid	
Sodium (Na^+)	15 mmol/L	150 mmol/L	Voltage-gated channel closed; Na^+-K^+ pump active.
Potassium (K^+)	150 mmol/L	5.5 mmol/L	Loss through membrane & K^+ channel
Chloride (Cl^-)	9 mmol/L	125 mmol/L	Slow loss through leakage
Protein$^-$	150 mmol/L	5 mmol/L	Membrane impermeable

Neurones can be excited by a sufficient stimulus resulting in the formation of an **action potential**. This is a brief, rapid change in membrane potential which propagates along a neuronal axon.

Graded potentials (short-distance signals)(resulting from stimuli) spread towards an axon where an action potential (long-distance signal) is generated. An action potential usually arises at the axon hillock when the **threshold potential** is reached. An action potential is an "all or none" response. An action potential occurs through 3 main changes:

1. Opening of voltage-gated Na^+ channels **allowing sodium into the cell** to reach threshold potential (and swing of membrane potential towards positive).
2. Spontaneous decrease in sodium permeability as potential difference towards 0mV.
3. Opening of voltage-gated K^+ channels: K^+ leaves cell down electrochemical gradient with downswing in AP
4. The cell then becomes less positive as membrane potential returns towards resting state – **repolarisation**.

Following an action potential a cell has two refractory periods:

- *Absolute refractory period* – the neuronal membrane has reversed polarity so that conduction/initiation of another AP is impossible (due to Na channel inactivation)
- *Relative refractory period* – during which because it is more difficult to reach the threshold potential because of hyperpolarisation and prolonged increased in potassium permeability.

An action potential is **propagated** along an axon in one direction only (orthodromic). In non-myelinated axons the depolarisation must travel through adjacent areas of membrane. In myelinated axons, the action potential can jump between the **nodes of Ranvier** which results in faster transmission (**saltatory conduction;** *saltare* – to jump or skip). Loss of myelin can cause conduction block.
Conduction velocity is fixed in any axon. It is proportional to nerve diameter (the **larger the faster**).
Local anaesthetics block sodium channels and therefore stop action potentials! Decreases in temperature can slow nerve conduction.

TYPE		MYELINATED	SIZE (μm)	SPEED (m/s)	MAIN FUNCTION
I	Aα	YES	15-20	75-120	Proprioception / motor
II	Aβ		6-12	35-75	Proprioception / touch / pressure
	Aγ		3-6	15-30	Motor to muscle spindles
III	Aδ		1-5	5-35	Crude touch / pain / temperature
	B	YES	1.5-3.5	3-15	Autonomic preganglionic efferents
IV	C	NO	<1	<2	Dull pain / temperature

SYNAPSES & NEUROMUSCULAR JUNCTIONS

Neurotransmission is the process of information transfer between neurones and occurs at synapses.
Synapses are the junctions between neurones. Neuromuscular junctions (NMJs) are the junction between neurones and muscle fibres. Neurones have specialised adaptations at synapses.

Terminal bulb/bouton – expansion of the afferent axonal fibre into a bulb.
Synaptic cleft: a gap between the pre- and post-synaptic membranes.

Chemical – neurotransmitter (NT) released by pre-synaptic terminal to communicate with post-synaptic membrane (usually of another neurone). Receptor activation can be inhibitory (causes hyperpolarisation) or excitatory (causes depolarisation of post-synaptic membrane).

200 angstroms
Transmit one-direction only (uni-directional)
1ms delay
Modifiable activity

Electrical:

Faster than chemical (instant)
20-40 angstroms (2-4 nM)
Bi-directional transmission
On or off

Neurotransmitter release:
NTs are stored in vesicles in the pre-synaptic terminal. Vesicular release occurs via vesicle bonding with the terminal membrane and exocytosis. The process requires calcium (Ca^{2+}) influx via voltage-gated calcium channels which results in membrane fusion. Following release, the vesicles are recycled via endocytosis. Important membrane proteins involved in docking are SNARES, NSF, and SNAP.

Neurotransmitter receptors are classified by their mechanism of action:

Metabotropic Receptors	Ionotropic receptors
G protein coupled receptors (guanine nucleotide binding)	Ligand-gated ion channels
Slower	Faster

Transmembrane protein (spans 7 times) Linked to ion channel or uses 2nd messenger system Enzymes phospholipase C or adenylate cyclase	Usually 5 protein subunits (form rosette shaped protein complex) Inhibitory – chloride channels / Excitatory – Ca^{2+} e.g. $GABA_A$, NMDA, $5\text{-}HT_3$

The neuromuscular junction with skeletal muscle is known as a motor end plate. The terminal bouton is covered by a Schwann cell but is not myelinated and lies within a dip of the muscle membrane. The area of the muscle fibre in association is known as the sole plate. The membrane here is heavily folded. Transmission at the NMJ is via release of acetylcholine which diffuses rapidly across the synaptic cleft (<0.3 μs). ACh binds to a nicotinic (ion-channel) receptor which results in depolarisation of the muscle membrane via triggering of voltage-gated Na^+ channels resulting in an endplate potential. The depolarisation depolarises adjacent sodium channels and if a threshold is reached an action potential in the muscle is initiated. ACh is broken down in the synaptic cleft by cholinesterases and reabsorbed into the neurone.

- *Botulinum toxin* prevents ACh release at the NMJ by interfering with exocytosis.
- Organo-phosphates (non-reversible AChE inhibitors) can prevent the breakdown of ACh.
- Myasthenia gravis, an autoimmune disorder causing weakness and fatigue, is caused by formation of antibodies to skeletal muscle ACh receptors.

NEUROTRANSMITTERS

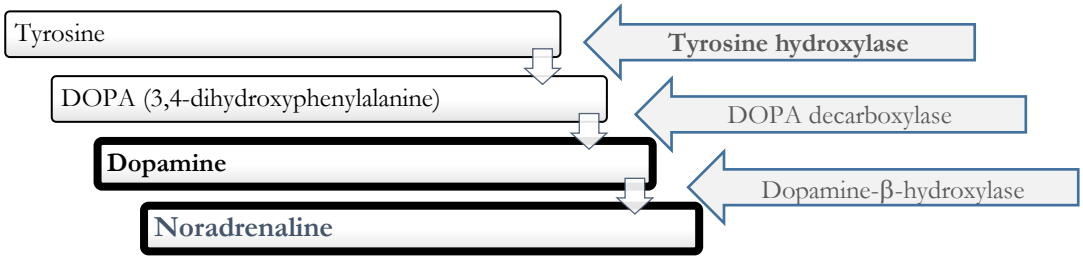
Neurones typically contain one main type of neurotransmitter:

1. **Amino acids –** e.g. **GABA, glutamate** (most), glycine, aspartate.
2. **Peptides** – e.g. Neuropeptide Y, somatostatin, CCK
3. **Amines** - e.g. Histamine, the **catecholamines** (**dopamine, noradrenaline**); **serotonin** (an indolamine), melatonin (synthesised from tyrosine),
4. **Other – e.g. Acetylcholine**

DOPAMINE: Involved in increasing awareness of important stimuli and attention. Dopamine containing cells bodies are found in three main areas – the substantia nigra and ventral tegmental area in the midbrain and the hypothalamus. These neurones form 4 major dopaminergic pathways:

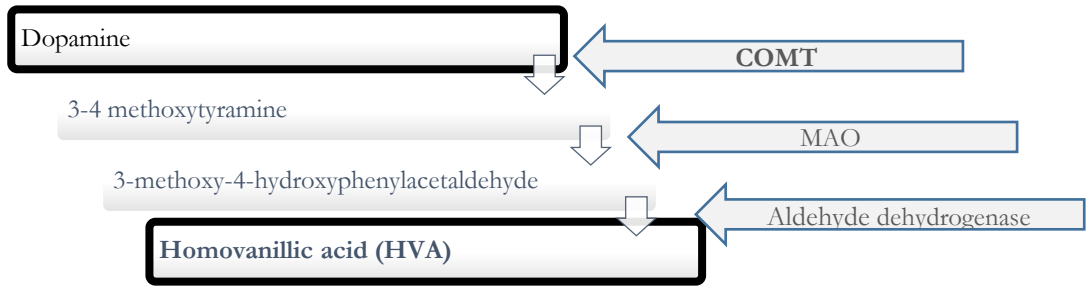
1. ***Mesolimbic Pathway*** – ventral tegmentum (VTA)→limbic (esp. nucleus accumbens & amygdala).
2. ***Mesocortical Pathway*** - VTA to the PFC. Both of these pathways are involved in motivation and reward behaviours.
3. ***Nigrostriatal Pathway*** – substantia nigra pars compacta (midbrain) → striatum (caudate/putamen). Roles in motor planning and purposeful movement. Dysfunction via disease or dopamine antagonism causes parkinsonism/EPSEs.
4. ***Tuberoinfundibular*** - dopamine neurons in the arcuate nucleus (tuberal region of hypothalamus) → pituitary median eminence ('infundibular region'). Dopamine inhibits the release of prolactin.

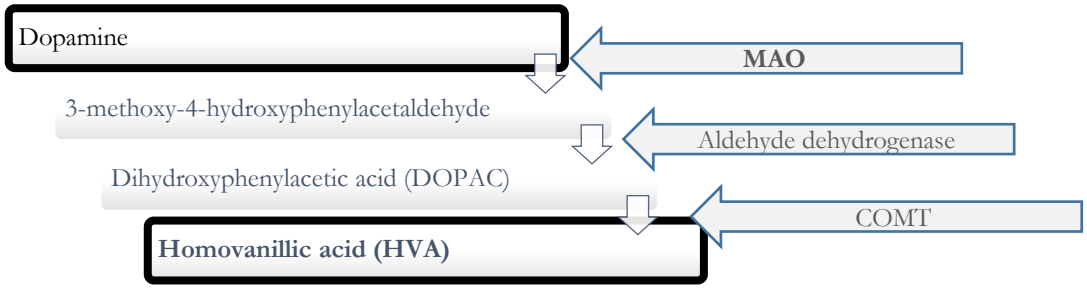
Dopamine is synthesised from tyrosine and is a precursor in the synthesis of noradrenaline. The **rate-limiting** step is conversion of tyrosine to DOPA.



Dopamine release is subject to auto-receptor feedback (D_2 & D_3). Dopamine is transported back into the presynaptic cell by the dopamine transporter (DAT). It is metabolised in pathways starting with **MAO_A**

and MAO_B (mitochondrial) or catechol-O-methyltransferase (**COMT**) (membrane bound) both resulting in the formation of **homovanillic acid (HVA).**





Receptor type	Mechanism	Comments / Mechanism
D1-like family	G-protein	D1 (most common subtype) and D5 (**stimulate** adenylyl cyclase via G_S/ increasing cAMP)
D2-like family	G-protein	**D2** (most common subtype), D3, and D4 (**inhibit** adenylyl cyclase via G_I decreasing cAMP).

NOREPINEPHRINE / NORADRENALINE: NA is important for arousal and alertness. Most cell bodies are found in the locus coeruleus (pons) and project extensively into the cortex and other brain areas via the dorsal bundle. Some cell bodies are found in the medulla (lateral tegmentum) and project to the forebrain via the ventral noradrenergic bundle). Both areas project to the hypothalamus, cortex and limbic system.

The pathway for noradrenaline synthesis was shown above. Dopamine β-hydroxylase is only found in noradrenergic / adrenergic neurones.

Amphetamines cause release of norepinephrine from vesicles. Reuptake can be inhibited by SNRIs, TCAs, cocaine, and amphetamine. Norepinephrine (noradrenaline) is taken back into presynaptic terminal by a noradrenaline reuptake transporter (NAT). NA release is subject to auto-receptor feedback (α_2 receptors).

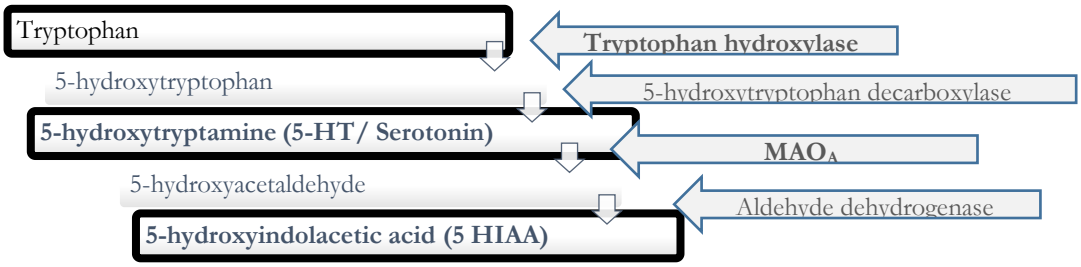
Receptor type	Mechanism	Comments / Mechanism
α_1 receptors	G-protein	Post-synaptic excitatory (Inositol phosphate) Smooth muscle contraction; heart; brain; vas deferens
α_2 receptors	G-protein	Pre and postsynaptic; inhibitory(adenylate cyclase; inhibits cAMP) Found in brain, intestines (relaxation)
β_1 receptors	G-protein	Excitatory; adenylate cyclase; increase cAMP β1 receptors - increase heart rate; found in brain β2 receptors- bronchodilation & blood vessel relaxation β3 receptors – adipose tissue

NB: Remember the mnemonic – 1 heart (β_1), 2 lungs (β_2).

Noradrenaline is metabolised by MAO (mainly MAO_A) or COMT. The two **main end products** of noradrenaline catabolism are vanillyl mandelic acid (VMA) (in the periphery) and **3-methoxy-4-hydroxyphenylgycol (MHPG) in the CNS**.

SEROTONIN (5-HT): Plays a role in attention, arousal, mood, emotion, body temperature and sleep amongst others. Most serotonin is found in GI tract with smaller amounts in blood vessels and CNS. It does not cross the BBB (unlike tryptophan). In brain the main cell bodies are the median and dorsal raphe nuclei which have widespread cortical projections via the median forebrain bundle (MRN – hippocampus; DRN to frontal & limbic cortices). There are also descending projections to the dorsal horn of the spinal cord and play a role in descending inhibition of pain.

The primary biosynthetic and catabolic pathways for serotonin are straightforward. The rate limiting step is the action of tryptophan hydroxylase (which is specific to 5-HT neurones). 5-HT is stored in vesicles bound to serotonin-binding protein and protected from MAO. 5-HT action is terminated mainly through reuptake by the specific monoamine transporter for 5-HT, SERT, on the presynaptic neuron. Reuptake of serotonin is inhibited by SSRIs, SNRIs, tricyclics and cocaine. 5-HT release is subject to auto-receptor feedback at $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptors.

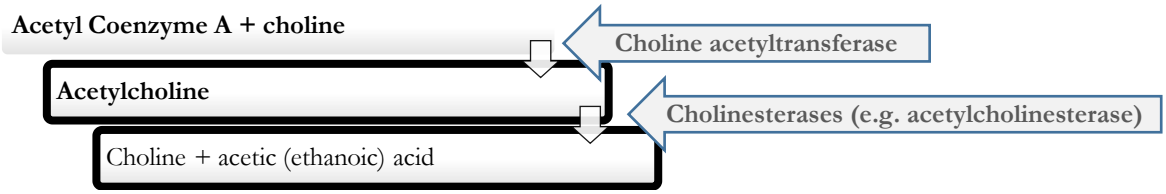


Metabolism is intraneuronal. The breakdown product of 5-HT (5-HIAA) diffuses out of neurones into the CSF and is actively transported across the BBB.

Receptor	Mechanism	Comments / Mechanism
$5HT_1$	**G-protein**; Inhibitory; negatively coupled to adenylate cyclase.	Function as both auto-receptors and post-synaptic. 1_A – role in antidepressant activity (agonist), anxiolytics (partial agonist) 1_B - Aggression
$5HT_2$	**G-protein**; Excitatory – (phospholipase C/inositol phosphate pathway)	2_A – LSD acts as partial agonist; antipsychotics (antagonist) 2_C – role in feeding & anxiety Post-synaptic / stimulation causes anxiety/agitation/insomnia/sexual dysfunction
$5HT_3$	**Ligand-gated ion channel**	Excitatory – found in area postrema Antiemetic (e.g. ondansetron, a 5-HT3 antagonist)
$5\text{-}HT_4$	**G-protein**; positively coupled to adenylate cyclase	
$5\text{-}HT_5$		
$5HT_6$		Possible antipsychotic/antidepressant action (antagonist)
$5HT_7$		Regulation of circadian rhythm; role in depression
There are 14 known serotonin receptor subtypes in 7 families.		

There is an inverse association between serotonin levels and aggression. Lower levels of 5-HIAA found in violent suicides and those with history of aggression. In chronic use, ecstasy (3,4-methylenedioxy-methamphetamine) reduces 5-HT levels.

ACETYLCHOLINE is important for attention/arousal, memory and as the NT at the neuromuscular junction. It is synthesised from acetyl CoA and (dietary) choline and is store in vesicles.



Main pathways are:

- Nucleus basalis of Meynert projecting to cortex and lateral septum which projects to the hippocampus.
- Ascending system of cholinergic neurons originating in the reticular formation (pons) project to thalamus.

Many brain areas also contain cholinergic interneurons.

Muscarinic ACh receptors	**Nicotinic ACh receptors (nAChRs)**
G-protein coupled (metabotropic)	Ionotropic; fast & excitatory 5 subunits (pentameric) forming different subtypes
Most common	Less common
M_1, M_3, & M_5 – promote IP_3 M_2 & M_4 – inhibit cAMP M_1 (memory); M_3 (exocrine glands)	Mediate attention; neuromuscular junction

Breakdown of ACh is via hydrolysis by cholinesterase enzymes which are abundant in the synaptic cleft. Choline is actively taken back up into the presynaptic neurone for recycling. Neurotoxins can inhibit the action of AChE causing bradycardia or prolonged muscle contractions. Other toxins work by competing with acetylcholine at the post-synaptic receptor. Botulinum toxin works by interfering with release of acetylcholine from the nerve terminal.

GLUTAMATE: is the brain's excitatory (amino acid) neurotransmitter. It is widespread in neurones and glial cells throughout the brain. Pyramidal cells (motor cortex; hippocampus) contain glutamate. Monoamine nuclei in the brain stem are innervated by glutamatergic axons from the cortex. Glutamate is synthesised via the citric acid cycle and is present in all CNS neurones; only those expressing vesicular glutamate transporters store glutamate. Glutamate is taken back up into neurones by specific glutamate transporters and can be recycled. Also absorbed by astrocytes; converted to glutamine and returned to neurones for recycling into glutamate.

Receptor types	**Mechanism**	**Comments**
NMDA N-methyl-D-aspartate	Ligand-gated ion channel	4 protein subunits; Na^+ & Ca^{2+} Blocked by Mg^{2+}
AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic	Ligand-gated ion channel	4 protein subunits Na^+
Kainate	Ligand-gated ion channel	4 protein subunits
mGLuR	Metabotropic (G-protein linked) IP3DAG`	Group 1: mGluR1 & mGluR5 Group 2: mGluR2 & mGluR3 Group 3: mGluR4/6/7/8

GABA (γ-aminobutyric acid): is synthesised from glutamate (by glutamic acid decarboxylase and B_6 as cofactor) and is the brain's major inhibitory neurotransmitter. It is stored in synaptic vesicles prior to release. It is distributed widely in interneurones particularly the basal ganglia and limbic system. The

GABAergic striato-pallidal pathway is an important part of the indirect motor pathway which is affected by Huntington's disease.
After synaptic release, GABA is taken up the neurone or glial cells and is metabolised into glutamate (or α-oxoglutarate) by GABA transaminase (GABA shunt).

Receptor types	Mechanism	Comments
$GABA_A$	Ligand-gated ion Cl^- channel; cause hyperpolarisation	5 subunits; Separate binding sites for barbiturates & benzodiazepines.
$GABA_B$	Metabotropic receptor; increase K^+ conductance & inhibit adenylate cyclase	Pre & post-synaptic. Site of action of baclofen.

BRAINSTEM

The **brainstem** continues the basic structure of the spinal cord but in addition carries the ascending and descending tracts. The brainstem includes the medulla, pons and mesencephalon. The brainstem is important in providing most of the motor and sensory innervation to the face and neck via the cranial nerves. 10 pairs of cranial nerves arise in the brainstem.

The major motor and sensory pathways also pass through the brainstem. The brainstem is important in regulation of cardiac and respiratory function. It is also involved in maintaining consciousness and regulating the sleep cycle.

MIDBRAIN (MESENCEPHALON)

The **midbrain** doesn't alter much from the basic alar/basal plate structure. The central canal becomes narrow forming the aqueduct of Sylvius (midbrain).

Tectum: The colliculi form by migration of the alar plates. The colliculi are important in the processing of sensory information. The **superior colliculi** (L: *upper hill)* also known as the **optic tectum** is a paired structure in the midbrain. It is important in visual processing and control of eye movements (including saccades). The **inferior colliculi** (L: *lower hill*) is the principal midbrain nucleus of the auditory pathway and receives input from several peripheral brainstem nuclei in the auditory pathway, as well as inputs from the auditory cortex.

Tegmentum: The **red nucleus** and **substantia nigra** develop from the basal plates and are involved in **motor** processing.

The **periaqueductal grey (PAG)** is a grey matter area surrounding the cerebral aqueduct. It is important in the descending inhibition of pain. It receives sensory information from spinothalamic tract via spinomesencephalic fibres. It connects with the serotonin neurons in the raphe nuclei resulting in endorphin release at spinal cord level [descending inhibition of pain / gate control theory of pain].

HINDBRAIN (RHOMBENCEPHALON)

The two division of the rhombencephalon are the metencephalon which forms the pons and cerebellum, and the myelencephalon which forms the medulla. The **pons** is formed by the thick band of fibres that connect the frontal lobes, basal ganglia, & thalamus with the cerebellum in a motor processing loop.

The **cerebellum** develops from the most posterior parts of the alar (dorsal) plate above the level of the medulla. The two sides fuse in the midline. Migrating cells from the alar plate form the cerebellar cortex.

The main cell types found in the cerebellum are:

1. Purkinje cells
2. Granule cells

The cerebellum forms the "roof" of the 4th ventricle. It is composed of 3 main areas – the vermis, cerebellar hemispheres, and the flocculonodular lobe. It's gyri are known as folia and the sulci as fissures.

The **vermis** along with the flocculonodular lobe is important for vestibular function/balance/reflex eye movements (connects to vestibular nuclei) in brain stem.

The cerebellar peduncles are white matter bundles which join the cerebellum to the brainstem:
Superior – major efferent output from cerebellar hemispheres and **dentate nucleus** to contralateral thalamus and then motor areas of frontal lobe. Important in control of movement (acting as a regulator through feedback mechanisms); also has role in control of tongue & larynx. ***Middle*** – afferent from contralateral frontal lobe; crosses in the pons – hence cerebellar signs are ipsilateral. The superior & middle cerebellar peduncle form part of the pathways linking cerebellum with cerebrum.
Inferior – afferent from medulla – ascending sensory information carried in the **spinocerebellar tract** – carries proprioceptive information with information about posture and gait etc.

Cerebellar lesions: Dysdiadochokinesia / **A**taxia / **N**ystagmus / **I**ntention tremor (and past-pointing) / **S**lurred speech / **H**ypotonia → DANISH.

The **medulla** has a similar structure to the spinal cord with posterior sensory groups and anterior motor groups. As the medulla becomes flatter around the floor of the fourth ventricle, the posterior (sensory) cells move laterally (resulting in sensory nuclei being lateral to motor nuclei) – some migrate to form the **olivary bodies** which have superior and inferior nuclei. The inferior olivary nucleus is part of the olivo-cerebellar system and is mainly involved in cerebellar motor-learning and function.

Lateral medullary syndrome –due to unilateral lesion in the medulla. It causes contralateral sensory loss in the body (spinothalamic) and ipsilateral facial and sensory loss (trigeminal nucleus). This *crossed finding is diagnostic* for the syndrome.
Other symptoms include dysphagia, slurred speech, ataxia (with inferior cerebellar peduncle damage), diplopia (6th nerve), lesions of cranial nerves 9 and 10, and Horner's syndrome (miosis, ptosis and anhidrosis).

ELECTROENCEPHALOGRAPHY (EEG)

- Electrical activity produced by brain; Summed activity of post-synaptic currents
- Spatial orientation perpendicular to skull
- "International 10-20 system" - electrodes placed with measurements made from specific landmarks. The proportion of scalp distances are 10% or 20%, and midline electrodes are denoted by the subscript z.

Mu partly overlaps other frequencies. May reflect activity in mirror motor neurones.

Spikes – transient high peaks <80ms
Sharp waves – sharply defined waves that rise quickly/fall slowly; >80ms
Vertex waves / V Waves – electronegative sharp waves over vertex. Evoked by auditory stimuli.

Wave	Frequency	Comments
BETA **B**enzodiazepines↑	13-30 Hz	**Bilateral, frontal** Low-amplitude waves Seen in **alert** stage
ALPHA Alcohol↑	8 – 13 Hz	Bilateral and **occipital** - Higher amplitude on the dominant side Seen in relaxed state with **eyes closed** / attenuated with attention
THETA	4 – 7 Hz	Seen in **young children** **Transient theta can be seen in up to 15% of the normal pop.**

DELTA	<4 Hz	High-amplitude waves **Seen in slow-wave sleep of adults** **Abnormal in awake EEG** – sign of pathology
Mu	7 – 11 Hz	**Associated with motor activity** and seen in precentral areas Attenuated with contralateral limb movement
Lambda		**Single sharp waves in occipital region** Associated with ocular movement (visual attention)
Gamma	>30 Hz	**Associated with cognitive and motor functions**

In adults alpha usually occurs posteriorly / beta anteriorly; but generalised low amplitude beta may be present. When drowsy intermittent alpha/theta appears.

>60 years
Slowing of alpha rhythm
Increased theta activity (esp L temporal)
Decreased delta activity

>80 years
Diminished beta activity

Diffuse slowing – most common abnormality.
Focal slowing – mass lesion
Of those with delirium 90% have abnormal traces.

Event-related potentials (ERPs)
Stereotyped change in brain activity with direct temporal relationship to stimulus ("event") or absence of expected stimulus. ERPs are characterised by:

- Polarity (N or P)
- Latency (e.g. P300 response; 300ms)
- Scalp distribution

ERPs can be:

- Early ("evoked potentials") – used to study sensory pathways (e.g. Brainstem EPs in response to sound)
- Mid-latency: these occur after brainstem EPs. They show habituation.
- Late: Used to study cognitive processes (e.g. decision making).

The P300 signal is measured most strongly over the parietal lobe. Reduced P300 response is a replicated finding in schizophrenia and relates to negative symptoms, poor attention, and grey matter volume deficits.

DISORDER	CHANGES
CJD	Generalised periodic spike-wave complexes Myoclonic jerks
Delirium	**Usually slowing** or loss of posterior dominant rhythm Generalised theta or delta activity No changes to eye opening / closing
Delirium tremens	Normal or **fast activity** (beta)
HIV	**Mild diffuse slowing**
Alzheimer's disease	Mostly abnormal **Decrease in alpha & beta;** increase in slow waves (later)
Encephalitis	Diffuse irregular slow waves; scattered sharp waves Reduced alpha.
Head Injury	Suppression of alpha

RETICULAR SYSTEM

Brainstem reticular formation – mass of neurones forming the core of the brain stem. It is arranged in diffuse columns/nuclei containing serotonergic, noradrenergic, acetylcholine and dopaminergic neurones. The neurones have long axons and contact with virtually all parts of the CNS.
Functions:

1. Motor: reticulospinal tract – modulation of spinal interneurons.
2. Sensory: role in gating of pain (modulation) through contact with ascending fibres
3. Autonomic functions: respiratory centres (medullary chemosensitive area); effects on heart rate.
4. Consciousness – **Reticular activating system**. Role in maintaining attention and transition from sleep to wakefulness.

Midline – Median Raphe nuclei: major sources of **serotonergic** projections. All parts of CNS grey matter permeated by serotonin neurones – largest distribution of any CNS neurone.
Paramedian – Magnocellular neurones. Mainly efferent – ascending and descending.
Lateral (parvocellular) – mainly afferents from all sensory pathways including special senses.

Dopamine – tegmentum of midbrain. Mesocortical/mesolimbic/nigrostriatal projections.
Norepinephrine – 90% of somas in locus coeruleus (violet spot on floor of fourth ventricle): wide spread projections.

SLEEP

Wakefulness is promoted by brainstem (RAS) & hypothalamus. During sleep the RAS shuts down under influence of hypothalamus. Cholinergic neurones are active during REM sleep and cause rapid eye movements by action on ocular motor nuclei.

Hypothalamus- important as control centre for sleep and wakefulness. Histaminergic neurones in tuberomamillary nucleus project widely to cerebral cortex.
The anterior hypothalamus contains the **suprachiasmatic nucleus** . Controls circadian rhythms. It maintains synchronisation through signals from **melanopsin**-containing retinal ganglion cells. In the absence of light input – the 24hr sleep-wake cycle approaches 26 hours ("free-running"). The SCN is reset daily by light signals and **melatonin** secreted by the **pineal gland**. A **sleep switch nucleus in the ventrolateral hypothalamus** induces sleep through inhibition of the RAS.
Orexins (hypocretins): neurosecretory peptide released by lateral hypothalamus. Highly excitatory and stimulate brain nuclei important for wakefulness/ absence causes narcolepsy. Also play role in stress response and hunger (causes craving). Act on OX_1 and OX_2 receptors.

Neurotransmitters that promote sleep/wakefulness:

Brain region	Sleep promoting	Wakefulness
Thalamus	**GABA**	
Basal Forebrain	Adenosine Nitric oxide GABA	Acetylcholine Glutamate
Hypothalamus	Modulating neuropeptides e.g. **Galanin** **GABA**	**Histamine** **Orexin** (hypocretin)(lateral/posterior)
Brainstem		**Norepinephrine** **Dopamine** **Serotonin** **Acetylcholine**

Average sleep time being 7.5 hrs
Sleep is composed of NREM and REM sleep with NREM making up ¾ of sleep in adults.
It was previously classified under stages 1-4 and NREM sleep. They are now known as
N1-3 and stage R (REM). N3 incorporates stages 3 and 4. It lasts 30-45 mins before reversion to N2.
REM sleep has a latency of 90 minutes.

Sleep spindles: groups of waves. Occur especially during stage 2. High frequency (13-15Hz) short duration (<1s). Waveform resembles a spindle. Usually symmetric and most obvious in parasagittal regions.
K Complex: large amplitude low frequency waves sometimes with a sharp apex. Most prominent frontally. Associated with partial arousals.

NREM Sleep 75% (high-voltage; low frequency EEG)

- Increased parasympathetic activity - decrease in BP / HR / RR / CBF
- Loss of tendon reflexes; Upward ocular deviation with minimal movements
- Reduced recall of dreaming if awoken

Stage	Proportion	Feature	EEG
Awake			Rapid low-amplitude waves
N1	5%	**Transitional stage between sleep and wakefulness**	Waves with frequency of 3-7Hz Theta & vertex sharp waves
N2	45%	**Fragmentation of thought processes**	**K-complexes** **Sleep spindles** Theta waves
N3	25% [S3 12% S4 13%	**Slow-wave sleep**	Delta waves 0.5-1Hz Stage 4: **delta waves**>50%. Physiological functions lowest.
R	25%	**Occurs every 90 minutes; increasing length** High brain & physiological activity Ocular movements; otherwise paralysed Increased sympathetic activity Increased dream recall if woken	Mixed frequency Saw-tooth waves Low-voltage waves Similar to awake state

Parasomnias in NREM:

- Sleep terrors
- Confusional arousals (sleep drunkenness)
- Nocturnal panic attacks
- Somnambulism (familial; males>female)
- Periodic limb movement disorder – repetitive stereotyped movements of limbs in sleep

Risk factors: alcohol; stress; medication; febrile illness

Parasomnias in REM

- REM Sleep Behaviour Disorder (association with PD/DLB) – can be treated with clonazepam
- Nightmare disorder
- Recurrent isolated sleep paralysis

Hypersomnias

e.g. Narcolepsy – fall asleep easily; cataplexy; hypnopompic & hypnogogic hallucinations; sleep paralysis. Results from deficiency of **hypocretin-1 (orexin)** in hypothalamus.

Sleep changes with age:

Reduced overall sleep duration / Reduced SWS as get older and decreased quality / Attenuated delta waves / Disappearance of stage 4 / Decreased REM latency and duration / Increased stage 1 sleep / Increased arousals / fragmented sleep / leg movements / daytime naps / snoring / apneoic episodes

NEUROPATHOLOGY

Syndrome	Atrophy/early changes	Protein/pathology	**Genetics** (chromosome)
bvFTD	Anterior cingulate Frontoinsular (von Economo neurones) Knife-blade gyri	**Tau** **TDP-43** Pick bodies Pick cells (ballooned neurones)	MAPT (17) Progranulin (17); C9ORF72 (9)
Semantic dementia	Anterior temporal	**TDP-43 (69%)** AD (25%) Tau (6%)	Progranulin MAPT
Progressive non-fluent aphasia (PNFA)	Left posterior frontoinsular	**Tau (52%)** AD (25%) TDP-43 (19%) Other 4 %	MAPT Progranulin
Logopenic	Left posterior perisylvian; inferior parietal	**AD (50%)** TDP-43 (38%) Tau (12%)	
Alzheimer's disease	Medial temporal (hippocampus); posterior cingulate; precuneus	**Aβ42 / Tau** **Neuritic plaques & NFTs** Lewy neurites (CA region) Amyloid angiopathy Hirano bodies Astrogliosis & microglial activation	APP (21), PS1 (14), PS2 (1) (APOε (19))
Dementia with Lewy Bodies	Nigrostriatal changes; ascending NT networks	**α-synuclein; Lewy bodies** & Lewy neurites (CA2; brainstem)	(SNCA-α-synuclein; LRRK-2)
Parkinson's disease	Nigrostrial pathways	**Lewy bodies**	
Progressive supranuclear palsy	Pallidum / nigrostriatal / superior colliculus / dentate	**Tau** **Globose tangles** Thorny astrocytes	MAPT
Corticobasal degeneration	Asymmetrical – frontoparietal cortical, basal ganglia…..	**Tau positive Pick cells** TDP-43 Thorny astrocytes	MAPT Progranulin
Huntington's disease	Caudate; frontal	**Huntingtin**	HTT (4) [CAG repeat]
"Normal ageing"	Brain atrophy; esp. frontal lobes; caudate; hippocampus; cerebellum (Purkinje cell loss)	Neuritic plaques (limbic only) NFTs (hippocampal area only) Hirano bodies Lipofuscin (ageing pigment) Lewy bodies (SN/locus coeruleus)	
References: Bonner et al, 2011; Macedo, Kim & Seeley, 2009			

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