Chapter 1

Neuroanatomy

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1.1 Overview

This chapter will provide a brief review of **basic neuroanatomy**, followed by a more detailed description of structures and pathways important for neuropsychiatric practice. The focus will be on the **limbic brain** and the functional anatomy of emotion, memory, cognition and behaviour. A more comprehensive review of **general neuroanatomy** can be found in standard textbooks such as Johns, *Clinical Neuroscience*.[1, 2]

1.2 Review of Basic Neuroanatomy

1.2.1 Overview of the Nervous System

The nervous system is divided into central and peripheral parts. The **central nervous system** (**CNS**) is made up of the brain and spinal cord, encased within the bones of the skull and vertebral column. It is surrounded by three protective membranes or **meninges** (dura, arachnoid, pia). The **subarachnoid space** lies between the inner two layers and is filled with **cerebrospinal fluid** (**CSF**). This contains dissolved oxygen and glucose that nourishes the cerebral surface and helps to cushion and protect the brain.

The **peripheral nervous system** (**PNS**) includes 31 pairs of **spinal nerves** which emerge between the vertebrae and 12 pairs of **cranial nerves** which arise from the base of the brain (Table 1.1, Figure 1.1). At the roots of the upper and lower limbs, sensory and motor fibres are redistributed in the **brachial** and **lumbosacral plexuses** to enter a number of named **peripheral nerves**. The motor component of the peripheral nervous system is further subdivided into **somatic** and **autonomic** parts. The **somatic nervous system** innervates skeletal muscles whilst the **autonomic nervous system** supplies smooth muscle, cardiac muscle and the contractile elements of glands.

1.2.2 Cells of the Nervous System

Neural tissue contains two specialised cell types: **neurons** and **glia**. Neurons are the main functional elements, whilst glial cells offer structural and metabolic support. Modern estimates suggest that the human brain contains approximately 86 billion neurons, with a similar number of glial cells.[3, 4]

Neurons occupy the **grey matter** of the brain and spinal cord. Their axons traverse the **white matter** to reach other parts of the central nervous system. The pale colour of white matter is due to the lipid-rich myelin sheath, which enhances nerve impulse conduction velocity. Discrete collections of neurons are called **nuclei** in the CNS and **ganglia** in the PNS.

1.2.2.1 Neurons

Neurons are **electrically excitable**, process-bearing cells. They are highly specialised for the receipt, integration and transmission of information via rapid electrochemical impulses (**action potentials**). The **cell body** contains the nucleus and biological machinery for protein synthesis and other housekeeping functions. It ranges from 5 to 100 μm in diameter.[5]

Two types of process (or **neurite**) arise from the cell body. A profusely branching 'tree' of **dendrites** (Greek: *dendron*, tree) is specialised to receive and integrate information, typically from many thousands of other neurons. Nerve impulses are triggered in the cell body and transmitted away from the neuron along the slender **nerve fibre** or **axon**. A typical neuron has a single axon which may be up to one metre long in humans.[6] Axons make contact with target cells at swellings called **axon terminals** and often give rise to collateral branches.

Types of Neuron

The cerebral cortex contains two major neuronal types: granular and pyramidal. **Granule cells** have

Table 1.1 The cranial nerves

Name (and fibre types)	**Main functions**
I: Olfactory (sensory)	**Special visceral afferent**: sense of smell
II: Optic (sensory)	**Special somatic afferent**: vision
III: Oculomotor (mixed)	**General somatic efferent**: superior rectus, inferior rectus, medial rectus, inferior oblique (four out of the six extraocular muscles); levator palpabrae superioris (eyelid elevator) **General visceral efferent (parasympathetic)**: sphincter pupillae (pupil constriction), ciliary muscle (accommodation)
IV: Trochlear (motor)	**General somatic efferent**: superior oblique only (depression of the adducted eye)
V: Trigeminal (mixed) V1: Ophthalmic V2: Maxillary V3: Mandibular	**General somatic afferent (V1, V2, V3)**: sensation to facial skin, cornea, nasal mucosa, paranasal sinuses, supratentorial dura; periodontal tissues, teeth, temporomandibular joint (proprioception); buccal cavity, anterior two-thirds of tongue (general sensation) **Special visceral efferent (branchiomotor, V3 only)**: muscles of mastication (masseter, temporalis, medial and lateral pterygoid), anterior belly of digastric, mylohyoid, tensor veli palatini (palate), tensor tympani (middle ear)
VI: Abducens (motor)	**General somatic efferent**: lateral rectus only (abduction of eye)
VII: Facial (mixed)	**General somatic afferent**: sensation to part of the external ear (*) **Special visceral afferent**: taste from anterior two-thirds of tongue (*) **General visceral efferent (parasympathetic)**: submandibular and sublingual salivary glands, lacrimal gland* **Special visceral efferent (branchiomotor)**: muscles of facial expression, stapedius (middle ear), stylohyoid, posterior belly of digastric
VIII: Vestibulocochlear (sensory)	**Special somatic afferent**: vestibular sensation, hearing
IX: Glossopharyngeal (mixed)	**General somatic afferent**: cutaneous sensation from the external ear, tympanic membrane, upper pharynx, and posterior one-third of the tongue **General visceral afferent**: carotid body and sinus (for baroreceptor reflexes) **Special visceral afferent**: taste from posterior third of the tongue **General visceral efferent (parasympathetic)**: parotid salivary gland **Special visceral efferent (branchiomotor)**: stylopharyngeus only
X: Vagus (mixed)	**General somatic afferent**: cutaneous sensation from auricle, external auditory meatus, larynx, pharynx and infratentorial dura **General visceral afferent**: main sensory innervation to thoraco-abdominal viscera **Special visceral afferent**: taste from the epiglottis and soft palate **General visceral efferent (parasympathetic)**: main parasympathetic innervation to heart, lungs and majority of gastrointestinal tract, as far as the splenic flexure **Special visceral efferent (branchiomotor)**: pharyngeal constrictors, intrinsic laryngeal muscles, muscles of the palate (apart from tensor veli palatini), upper two thirds of the oesophagus, therefore important for speech and swallowing
XI: Accessory (motor) XIc: cranial accessory XIs: spinal accessory	**General somatic efferent**: sternocleidomastoid, trapezius (spinal accessory nerve) **Special visceral efferent (branchiomotor)**: muscles of pharynx and larynx (cranial accessory nerve; fibres distributed via the vagus nerve)
XII: Hypoglossal (motor)	**General somatic efferent**: all intrinsic and extrinsic tongue muscles, apart from palatoglossus (the latter is supplied by the vagus nerve)

* Carried in the slender *nervus intermedius*, which joins the main nerve trunk.

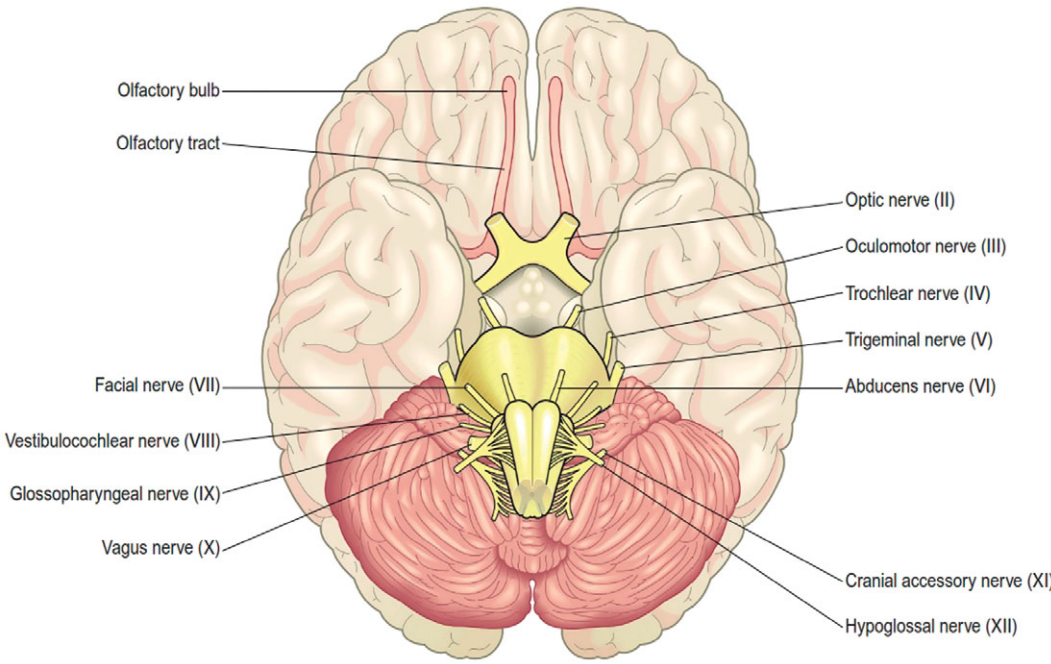

Figure 1.1 Ventral surface of the brain showing the 12 cranial nerves. The olfactory nerve (cranial nerve I) is not seen here; it consists of up to 5 million axonal filaments that arise from the nasal mucosa and synapse in the olfactory bulb. From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014).

small, spherical cell bodies and short axons. They are particularly numerous in areas that receive incoming projections (e.g. the granule cell layers of the hippocampus and cerebellum). Due to the predominance of granule cells, sensory cortices are thinner (e.g. 2 mm in the **primary visual cortex**).

Pyramidal cells have large, pyramid-shaped cell bodies. They predominate in areas that give rise to efferent projections, such as the **motor cortex**. Pyramidal cells require a larger cell body to support their long axons. Motor cortex is therefore thicker (up to 5 mm in the **primary motor cortex**). The largest neurons in the brain are the **giant cells of Betz**, found in the 'leg area' of the primary motor cortex in the medial frontal lobe. They are up to 100 μm in diameter.[7, 8]

The **medium spiny neuron** is the characteristic cell type of the **basal ganglia**. The 'ganglia' part of the term is a misnomer traditionally used to refer to a collection of **basal hemispheric nuclei** which contribute to the control of voluntary movement, cognition and behaviour.

Medium spiny neurons use the inhibitory neurotransmitter **gamma-amino butyric acid** (**GABA**). They have processes with microscopic **dendritic spines** which receive incoming axonal projections. In contrast, the granular and pyramidal cells of the cerebral cortex are excitatory neurons, many of which use **glutamate** as a neurotransmitter. Pyramidal cells also have dendritic spines, whereas granule cells may be spiny or aspinous.

Interneurons influence the activity of nerve cells in the cerebral cortex, subcortical nuclei and cerebellum. The cerebral cortex contains a significant population of **inhibitory interneurons** that use GABA as a neurotransmitter. A modest but functionally important group of cholinergic interneurons is found within the basal ganglia.

Neurons make contact at **synapses** (Greek: *sunapsis*, point of contact) and influence effector structures such as muscle fibres and glands at **neuroeffector junctions**. The point of contact between a somatic motor neuron and a skeletal muscle fibre is the **neuromuscular junction** (**NMJ**).

Neurogenesis

Mature neurons are **post-mitotic** cells, meaning that they are unable to divide and cannot be replaced. The

only location in the human brain that is capable of **neurogenesis** (production of new neurons from **stem cells**) is the dentate gyrus of the **hippocampus**.[9] In other species, a stem cell population in the **subventricular zone** of the lateral ventricle continuously gives rise to new neurons which migrate to the olfactory bulbs. However, this is minimal or absent in humans.[10]

Neurogenesis in the granule cell layer of the dentate gyrus is found in some patients with **temporal lobe epilepsy** (**TLE**) in association with **hippocampal sclerosis**.[11] This is presumably an attempt to replace neurons that have been lost due to seizure activity. It is unclear whether neurogenesis in hippocampal sclerosis is protective or if it exacerbates seizures.[12]

1.2.2.2 Neuroglial Cells

Five main types of **glial cell** provide metabolic and structural support to neurons (Greek: *glia*, glue):

- **Astrocytes**, which are involved in glucose metabolism, neurotransmission, response to injury and induction of the blood–brain barrier
- **Oligodendrocytes**, which invest axons with a myelin sheath in the brain and spinal cord
- **Schwann cells,** the peripheral counterparts of oligodendrocytes
- **Ependymal cells**, which line the cerebral ventricles and central canal of the spinal cord
- **Microglia**, the resident phagocytic and immunocompetent cells of the CNS

Glial cells have a mean diameter of 4–8 μm and are found in a 1:1 ratio with neurons.[13] Unlike neurons, glial cells are able to divide and may therefore give rise to cerebral tumours called **gliomas** (e.g. astrocytoma, oligodendroglioma).

1.2.3 Parts of the Brain

The human brain has a mass of around 1.3 kg and a very soft, gelatinous consistency. It consists of the cerebral hemispheres, diencephalon (thalamic region), brain stem and cerebellum (Figure 1.2).

1.2.3.1 Cerebral Hemispheres

The **cerebral hemispheres** (**cerebrum** or **telencephalon**) are responsible for sensorimotor functions, cognition, language, memory, emotion and behaviour. Sensory and motor pathways are **crossed** so that the left hemisphere is concerned with sensation and movement of the right side of the body. Cognitive functions are **lateralised** so that one hemisphere is said to be dominant for a particular mental faculty such as language or visuospatial ability (Box 1.1).

Cerebral Cortex

The **cerebral cortex** is a 2–5-mm-thick sheet of grey matter that forms the outermost layer of the cerebral hemisphere (Latin: *cortex*, bark). The brains of reptiles, birds and some mammals have a smooth or lissencephalic outer surface, whilst the human brain is thrown into convolutions. These consist of outfoldings (**gyri**) and furrows (**sulci**). The purpose of cortical folding (or **gyrification**) is to maximise the area of cerebral cortex that can be accommodated within the limited confines of the skull. It also enhances intracortical communication by bringing disparate areas into proximity.

Extent of gyrification varies greatly between species, depending on the size and complexity of the brain. It can be quantified as the **gyrification index**. The human brain has a high gyrification index, with approximately two-thirds of the cortical surface lying within sulci.

Two important sulcal landmarks on the surface of the brain are the **lateral sulcus** (**sylvian fissure**) and the **central sulcus** (**fissure of Rolando**). These help to divide the hemispheres into four main **lobes**. The key functional areas of each lobe are summarised in Table 1.2. The main gyri, sulci and functional areas are illustrated in Figure 1.3.

A separate **limbic lobe** is also recognised. This is a ring-shaped convolution that surrounds the corpus callosum and brain stem. It includes the **hippocampus**, a longitudinal roll of cortex in the medial temporal region. The limbic lobe is primarily concerned with emotion and memory and receives strong projections from the **central olfactory pathways**. This might explain why particular smells sometimes evoke vivid memories.

The brain contains two main **fissures** (deeper furrows that are not lined by cortex). These are the **longitudinal fissure** between the cerebral hemispheres and the **transverse fissure** which separates the cerebrum and cerebellum.

Hemispheric Grey Matter

Collections of subcortical grey matter in the base of the cerebral hemisphere are known as the **basal hemispheric nuclei**. These include the corpus striatum,

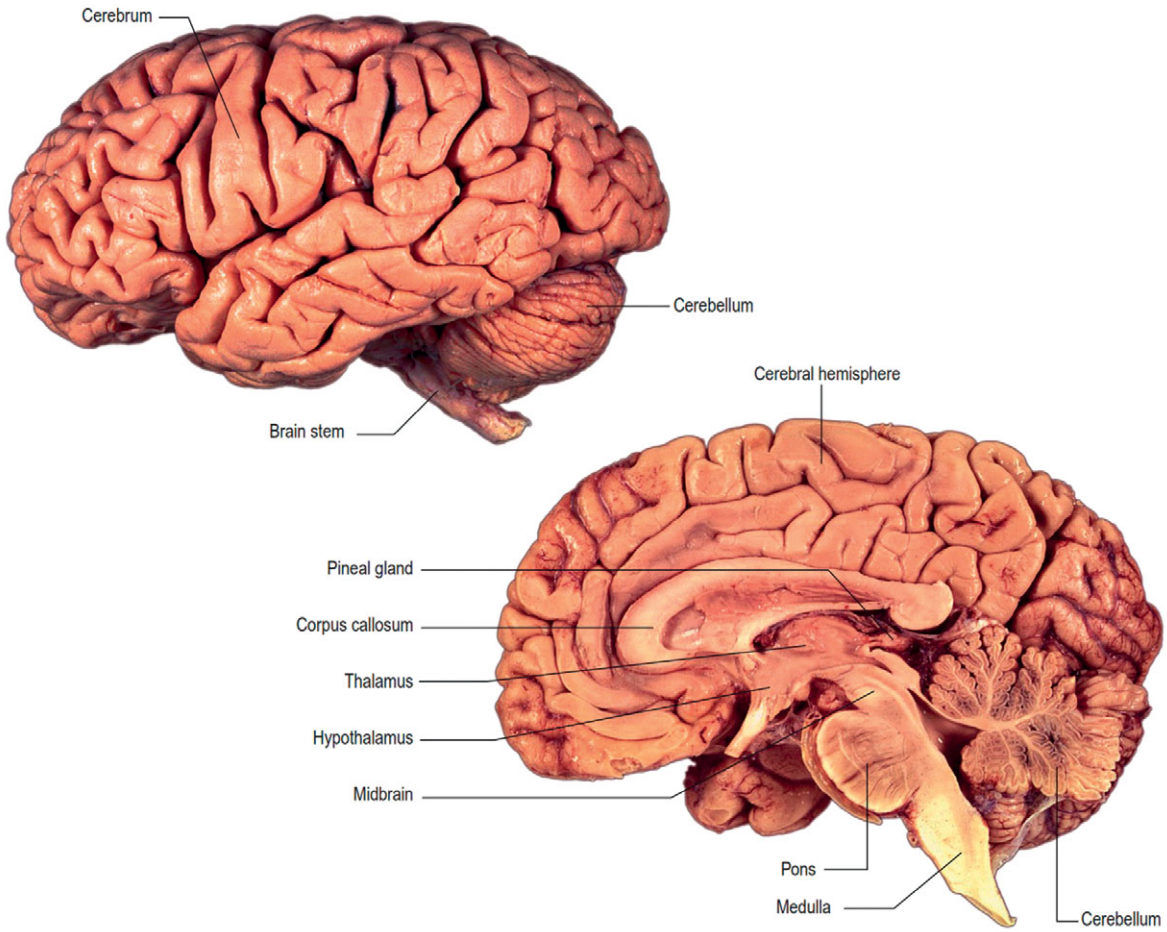

Figure 1.2 Lateral and medial views of a preserved human brain. The three main parts are the cerebrum, cerebellum and brain stem, together with the diencephalon (a small midline portion, which includes the thalamus and hypothalamus). From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014).

amygdala and claustrum, but not the thalamus, which belongs to the diencephalon (thalamic region).

The **corpus striatum** is the largest component of the basal ganglia and consists of the C-shaped **caudate nucleus** and cone-shaped **lentiform nucleus**, which are separated by white matter. The lentiform nucleus is further subdivided into the **putamen** laterally and **globus pallidus** medially.

The **amygdala** is an almond-shaped nuclear group in the medial temporal lobe that is concerned with emotional responses (particularly fear, anxiety and rage) (Box 1.2). The **claustrum** is a thin lamina of grey matter overlying the basal ganglia that is of uncertain function.

The basal nuclei are closely related to the **ventricular system** (Figure 1.4) which forms from the lumen of the embryonic **neural tube** and is filled with cerebrospinal fluid. CSF is as an ultrafiltrate of plasma that is secreted by the vascular **choroid plexuses**. Obstruction of CSF drainage or reabsorption pathways leads to **hydrocephalus** (Greek: *hydro*, water; *kephalē*, head).

Hemispheric White Matter

The subcortical white matter (Figure 1.5) is composed of interlacing **tracts**, defined as groups of axons with a common origin, destination and function. Two or more tracts running in company make up a **fasciculus** (plural: fasciculi).

Pathways linking areas within a hemisphere are called **association fibres**, which may be short or long. **Short association fibres** loop between neighbouring

Box 1.1 Hemispheric Lateralisation

In most individuals the left cerebral hemisphere has a **verbal bias** whilst the right hemisphere is superior for **visuospatial functions**. The hemisphere that controls the preferred hand is said to be **dominant**, and given that approximately 90% of people are right-handed, this is usually the left hemisphere.

Language is traditionally said to be left-lateralised in 95% of right-handed people and in 70% of those who are left-handed; right-hemisphere dominance occurs in just 2%, most of whom are left-handed.[14] This means that the majority of individuals are either **left-lateralised** for language or **co-dominant**. More generally, it has been shown that the strength of left-hemisphere language dominance is almost linearly correlated with the degree of right-hand preference.[15]

Language lateralisation can be assessed using **functional magnetic resonance imaging** (**fMRI**) and quantified as a **lateralisation index**. Another method is **Wada testing**, which was developed by the Japanese neurologist Dr Juhn Wada to assess language function prior to epilepsy surgery.[16] This involves injection of the barbiturate **sodium amobarbital** (**sodium amytal**) into the internal carotid artery to anaesthetise one cerebral hemisphere at a time. In most people, anaesthesia of the left hemisphere leads to transient loss of language function.

Selective left-hemisphere anaesthesia sometimes produces an agitated **acute dysphoric state** or 'catastrophic reaction'. In contrast, suppression of activity on the right-hand side may lead to **euphoria**.[17, 18] An affective lateralisation effect can also be seen following stroke. Left frontal lesions are strongly associated with **depression**, whilst right-sided lesions may lead to **pleasant indifference**, **elation** or **mania**.[19]

Box 1.2 Amygdala and Klüver-Bucy Syndrome

In the 1930s, the German experimental psychologist Heinrich Klüver and American neurosurgeon Paul Bucy reported the behavioural effects of **bilateral temporal lobectomy** in rhesus monkeys, some of which were attributed to ablation of the **amygdala.**[20–22] However, temporal lobectomy destroys many other cerebral structures, reflected in a constellation of neuropsychiatric symptoms.

The features included '**psychic blindness**' (visual agnosia), **emotional changes** (docility), altered **sexual behaviour** (hypersexuality, indiscriminate mating behaviour) and '**oral tendencies**' (excessive eating and oral exploration of objects, possibly due to visual agnosia). The obsolete term **hypermetamorphosis** is similar to what would now be called **utilisation behaviour** (compulsive grasping and utilisation of objects), but this is more typical of frontal lobe lesions.

In the 1950s, an analogous pattern of deficits was identified in humans with bilateral medial temporal lesions. This became known as the **Klüver-Bucy syndrome**, which was influential in the development of the 'limbic system' concept. Similar results had also been reported by Sanger Brown and Edward Albert Sharpey-Schafer in 1888.[23]

gyri, whilst **long association fibres** link more distant areas (e.g. the **superior longitudinal fasciculus**, connecting the frontal and parietal lobes). The **arcuate fasciculus** is a large, arc-shaped branch of the superior longitudinal fasciculus. It connects the inferior frontal and posterior temporal regions and is important for **language**.

Homologous cortical regions communicate across the midline via **commissural fibres** (Latin: *commissūra*, a joining together). The largest is the **corpus callosum**, consisting of 300 million myelinated axons.[24] The anteromedial temporal lobes are linked by the much smaller **anterior commissure**, whilst the **posterior commissure** connects the posterior hemispheres and rostral brain stem.

Axons passing to and from the cerebral cortex (e.g. sensory pathways, motor tracts) are called **projection fibres**. The majority are contained within the **internal capsule**, a massive white matter system composed of 20 million nerve fibres. The internal capsule passes through the corpus striatum, splitting it into the caudate and lentiform nuclei.[25]

1.2.3.2 Diencephalon (Thalamic Region)

The thalamus and hypothalamus belong to the **diencephalon**, which lies between the cerebral hemispheres (Greek: *dia-*, between; *enkephalos*, brain) surrounding the cavity of the **third ventricle**. The thalamic region is best appreciated on a midsagittal section of the brain (see Figure 1.2).

Table 1.2 Lobes of the cerebral hemispheres

Lobe	**Main functional areas** (clinical effects of focal lesions in parenthesis)
Frontal	• **Primary motor cortex**, precentral gyrus (contralateral paresis/paralysis with an upper motor neuron pattern: hypertonia, spasticity, clonus, hyperreflexia, positive Babinski sign) • **Premotor cortex,** lateral frontal lobe (contralateral weakness, apraxia) • **Supplementary motor area**, medial frontal lobe (transient contralateral weakness, akinesia, bradykinesia: 'SMA syndrome') • **Prefrontal cortex**: dorsolateral (dysexecutive syndrome), orbitomedial (behavioural disinhibition), medial prefrontal (apathy, abulia, amotivational state) • **Broca's area**, inferior frontal gyrus, usually left (expressive/non-fluent aphasia); non-dominant lesions may cause subtle deficits in speech comprehension and verbal working memory
Parietal	• **Primary somatosensory cortex**, postcentral gyrus (contralateral anaesthesia or paraesthesia, diminished ability to localise tactile sensations) • **Somatosensory association cortex**, anterior part of posterior parietal cortex (astereognosia) • **Visuospatial association cortex**, posterior parietal lobe (right: contralateral hemineglect; left: apraxia) • **Inferior parietal lobule**, angular and supramarginal gyri (Gerstmann syndrome: left/right confusion, agraphia, acalculia, finger agnosia; alterations in proprioception or body schema)
Occipital	• **Primary visual cortex**, calcarine sulcus (visual field defect: contralateral scotoma, quadrantanopia, hemianopia; cortical blindness with bilateral lesions) • **Visual association cortex** (visual field defect: contralateral quadrantanopia, hemianopia; category-specific visual agnosia, e.g. specific to faces; alexia without agraphia)
Temporal	• **Primary auditory cortex**, transverse temporal gyri (deafness, if bilateral; diminished sound localisation, speech recognition and pitch discrimination, when unilateral) • **Auditory-visual association cortex**, lateral temporal lobe (visual agnosia; semantic memory deficit; impaired verbal memory; word agnosia) • **Fusiform gyrus**, inferior occipito-temporal region (left: visual word-form area, alexia; right: fusiform face area, prosopagnosia) • **Wernicke's area,** posterior third of superior temporal gyrus/temporo-parietal junction, usually on the left (fluent aphasia; non-dominant lesions may cause amusia or aprosodia)

The **thalamus** is an egg-shaped structure containing numerous nuclei that project to different parts of the cerebral cortex. It acts as a relay station for cortical afferent pathways and is sometimes referred to as the 'gateway' to the cerebral cortex. The **hypothalamus** is a tiny, triangular-shaped part of the diencephalon that forms the floor of the third ventricle and the lower part of its side walls. It lies below and in front of the thalamus and is important for homeostasis.

The hypothalamus has ultimate control of the **endocrine system** by modulating hormone release from the underlying **pituitary gland**. It also controls the **autonomic nervous system** and influences behaviour. Other roles include the control of hunger, satiety, thirst and sexual function. Its contribution to **emotional behaviours** is illustrated by the clinical features of hypothalamic **seizures** (Box 1.3).

The **preoptic area** is just in front of the hypothalamus and is important for the regulation of sleep, feeding, body temperature and fever. The medial preoptic area contains the **sexually dimorphic nucleus,** which is significantly larger in heterosexual males and appears to influence sexual orientation and gender identity. Although sometimes said to belong to the hypothalamus, the preoptic area is in fact derived from the telencephalon (cerebral hemispheres).[26]

Two important white matter pathways pass through the hypothalamus. The **columns of the fornix** (part of the hippocampal memory system) traverse the lateral hypothalamus before terminating in the pea-like **mamillary bodies** in the floor of the third ventricle. The **medial forebrain bundle** is an important conduit for fibres passing between the brain stem and cerebral hemispheres, including diffuse neurochemical projections for serotonin, noradrenaline and dopamine.

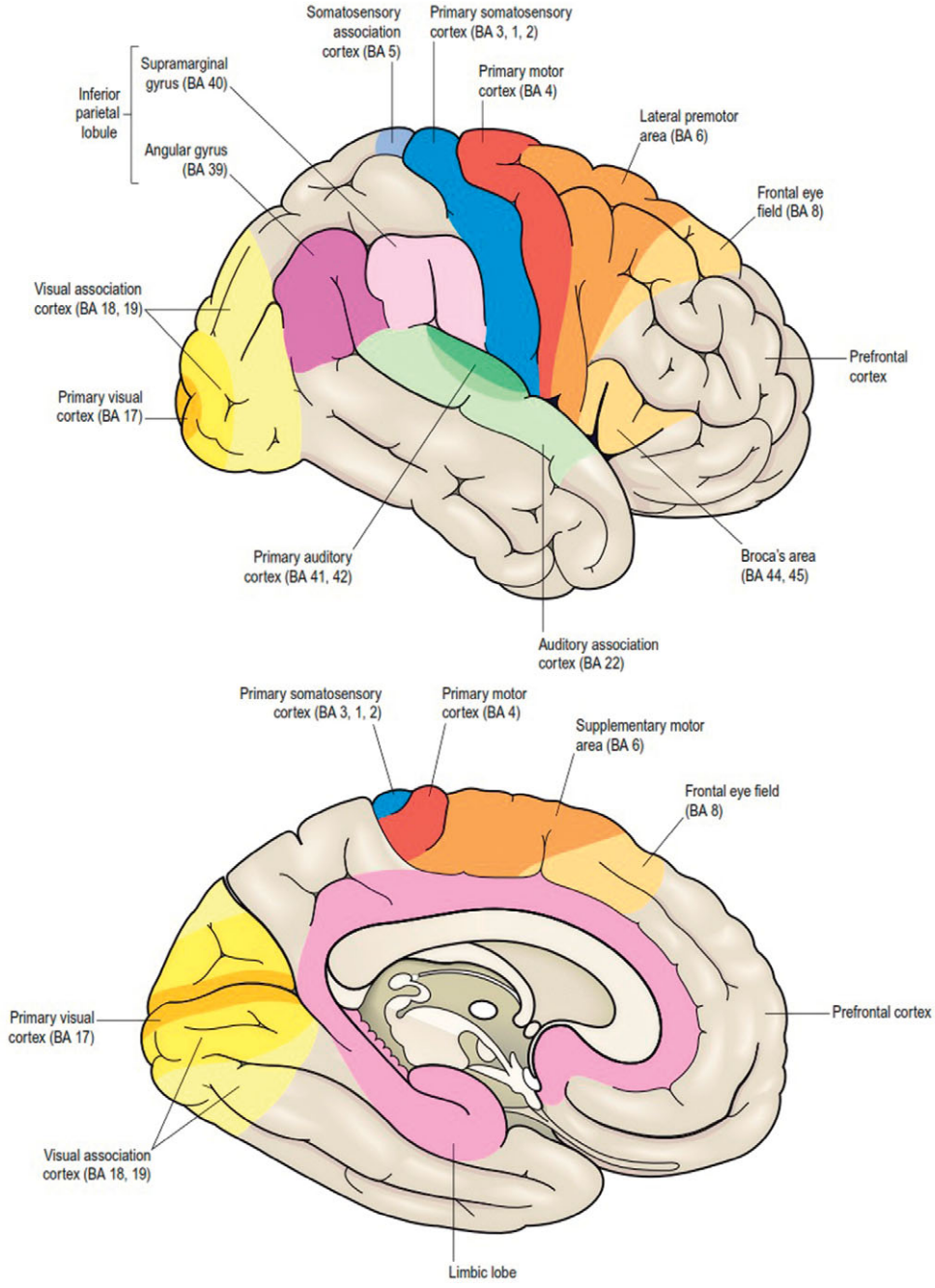

Figure 1.3 Lateral and medial views of the cerebral hemispheres. The main functional regions of the cerebral cortex are indicated; the numbers are Brodmann areas (BA), representing cortical zones with distinct microscopic structure and function. From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014).

1.2.3.3 Brain Stem

The **brain stem** as a whole can be divided longitudinally into basal and tegmental regions (Figure 1.6). The **base** of the brain stem is anterior and contains descending axons (e.g. the corticospinal motor tract). The **tegmentum** is the central core of the brain stem. It contains cranial nerve nuclei, the reticular formation and numerous long tracts passing between the

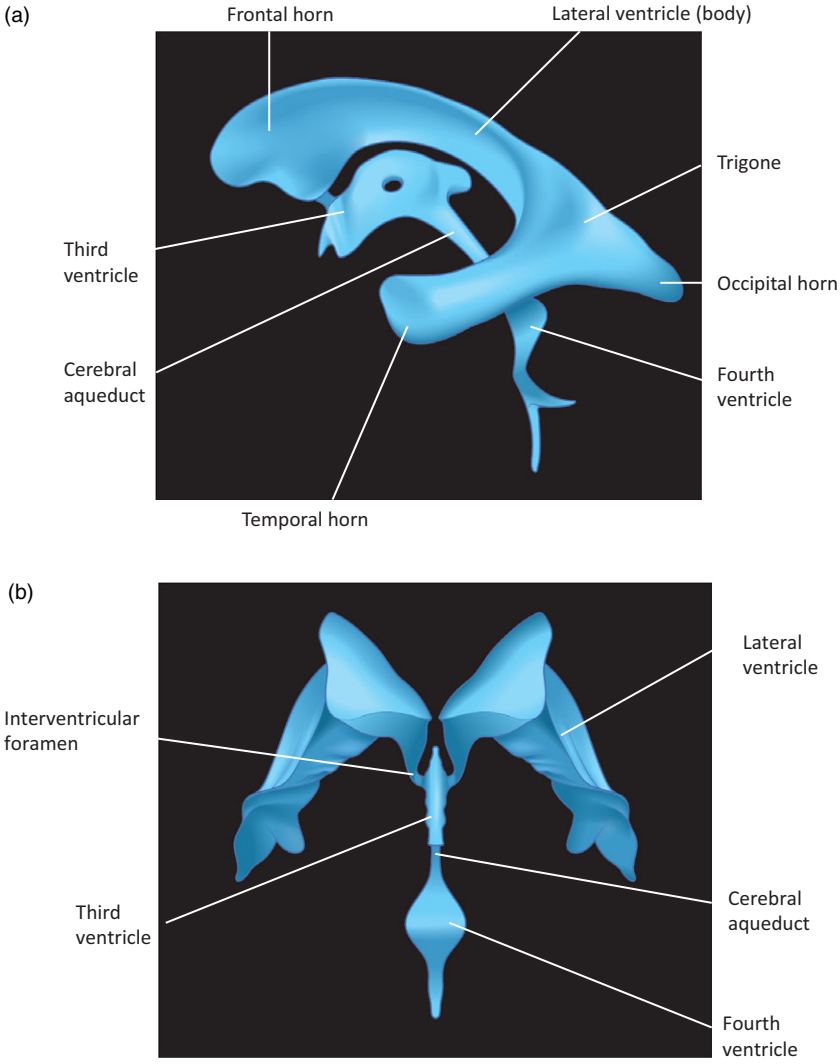

Figure 1.4 The ventricular system from (A) lateral and (B) anterior aspects. Note that the third ventricle appears large and impressive from the side, but when viewed from the anterior aspect, it can be seen to be a slit-like cavity that is only a few millimeters wide.

spinal cord and cerebral hemispheres. The brain stem consists of the midbrain, pons and medulla oblongata.

Midbrain

The **midbrain** is the most rostral part of the brain stem. It contains the **cerebral aqueduct**, which connects the third and fourth ventricles. The **tectum** or 'roof' of the midbrain (Latin: *tectum*, roof) is the small part that lies dorsal to the aqueduct. The remainder of the midbrain consists of the left and right **cerebral peduncles**. These resemble stout Roman pillars and make up almost half of the midbrain on each side. They are separated by the **interpeduncular fossa** (Latin: *fossa*, ditch or grave).

The term 'cerebral peduncle' is often used to describe the most anterior part of the midbrain, which contains the corticospinal tract. However, the proper name for this region is the **crus cerebri** (plural: crura) or base of the cerebral peduncle (**basis cerebri pedunculi**). The cerebral peduncle is a much larger region (almost half of the midbrain) that includes the tegmentum, substantia nigra and crus.

The tectum bears four smooth elevations called **colliculi** (Latin: *colliculus*, little hill). The **superior colliculi** (or **optic tectum**) give rise to the **tectospinal tracts** which co-ordinate head, neck and eye movements during orientation reflexes (e.g. involuntary turning to a novel stimulus). The **inferior colliculi**

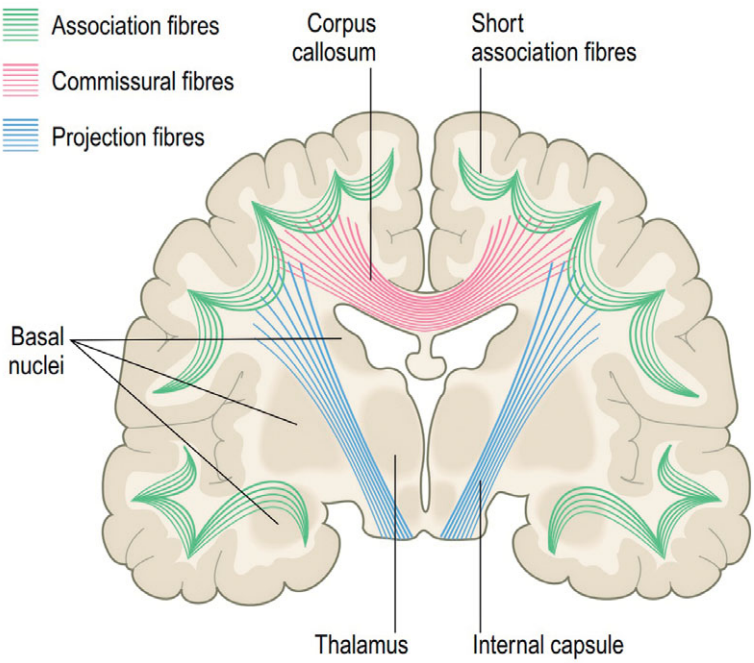

Figure 1.5 Types of subcortical white matter. The corpus callosum is the main commissural pathway linking the cerebral hemispheres. The internal capsule is a massive white matter bundle consisting of fibres passing to and from the cerebral cortex. From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014).

Box 1.3 Hypothalamic Seizures

Discrete lesions in the **hypothalamus** may be associated with **focal seizures** that have predominantly emotional manifestations such as laughter or crying.[27] The most common cause is a **hypothalamic hamartoma**. This is a benign, tumour-like congenital malformation with a prevalence of less than 1 in 100,000. It may be associated with **gelastic seizures**, characterised by paroxysms of uncontrolled laughter; or **dacrystic seizures**, in which there are episodes of uncontrolled weeping, with facial grimacing and lacrimation. The **emotional behaviours** in each type of seizure are divorced from the subjective mood state, and the patient (who remains conscious) typically experiences fear and panic rather than amusement or sadness. This underscores the dichotomy between emotional experiences (**feelings**) and their behavioural accompaniments (**emotional expression**), which are, respectively, cortical and hypothalamic in origin.[28, 29]

are part of the central auditory pathway from the cochlea to the **primary auditory cortex**.

A transverse slice through the midbrain reveals the deeply pigmented **substantia nigra** (Latin: black substance). It has **compact** and **reticular parts** (**SNc**, **SNr**), but only the compact portion is pigmented. The latter supplies dopamine to the basal ganglia via the **nigro-striatal tract**. The pars reticularis belongs to the globus pallidus and takes part in a basal ganglia loop involved in eye movement control. Just medial to the substantia nigra, but not visible with the naked eye, is the much smaller **ventral tegmental area**. This provides dopamine to the **ventral** (**limbic**) **striatum**.

The tegmentum of the midbrain is the large portion of the cerebral peduncle that is posterior to the substantia nigra, whilst the crus cerebri is the smaller portion in front of it. The tegmentum contains cranial nerve nuclei, long tracts and part of the reticular formation.

Pons

The **pons** is the middle portion of the brain stem. When viewed from the front, it appears to bridge the cerebellar hemispheres (Latin: *pons*, bridge). It is divided into basal and tegmental regions.

The anterior two-thirds of the pons is the **base** (or **basilar pons**). This transmits bundles of descending corticospinal tract fibres that have already passed through the internal capsule and crus cerebri on their way to the spinal cord. It also contains the **pontine**

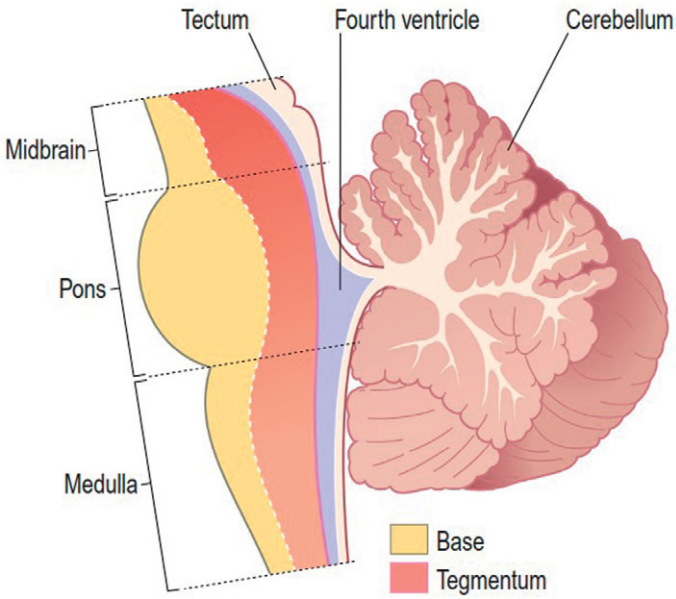

Figure 1.6 Midsagittal view of the brain stem and cerebellum. The tectum is the roof-plate of the midbrain, dorsal to the cerebral aqueduct; the corresponding region in the pons and medulla is occupied by the cerebellum, which forms the roof of the fourth ventricle. From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014).

nuclei, which give rise to axons that project to the opposite cerebellar hemisphere. These cross the midline as the **transverse pontine fibres**.

The dorsal third of the pons is the tegmentum, the posterior surface of which contributes to the floor of the **fourth ventricle**. The tegmentum contains the pontine reticular formation, together with several cranial nerve nuclei and long tracts. The paired **loci coerulei** (singular: locus coeruleus) are found in the rostral pons, just beneath the floor of the fourth ventricle. These are pigmented nuclei (Latin: *locus*, place; *coeruleus*, dark blue) that give rise to a diffuse projection for **noradrenaline**.

Medulla Oblongata

The **medulla** (or **medulla oblongata**) is the lowermost portion of the brain stem, which is continuous with the spinal cord at the level of the **foramen magnum**. The upper third of the medulla is splayed open dorsally, contributing to the rhomboid-shaped floor of the **fourth ventricle**. The lower two-thirds does not contribute to the ventricle and is described as closed.

The **pyramids** of the medulla are tapering columns of white matter in the anterior midline. They are equivalent to the basilar regions of the midbrain and pons and transmit axons of the corticospinal tract. For this reason the primary motor pathway is also known as the **pyramidal tract**.

The **olives** are two ovoid prominences in the upper part of the medulla, just lateral to the pyramids. They project to the opposite cerebellar hemisphere via the **olivo-cerebellar tract**. This pathway contributes to **motor learning** by signalling unexpected events (e.g. dropping a ball whilst juggling). Olivary afferents provide a 'training signal' to the cerebellum which induces **long-term depression** (**LTD**), altering synaptic weightings in such a way that the error is less likely to be repeated.

CSF escapes from the ventricular system into the subarachnoid space surrounding the medulla via three **exit foramina** in the **fourth ventricle**. These are the single **median** and paired **lateral apertures**. Cerebrospinal fluid is ultimately reabsorbed into the venous system via the **arachnoid granulations**. These project into the **superior sagittal sinus** along the dorsal aspect of the cerebral hemisphere.

Reticular Formation

The **reticular formation** is a polysynaptic network of widely branching neurons in the tegmentum of the brain stem. It contains **vital centres** (respiratory and cardiovascular) and mediates airway-protective **brain stem reflexes** (e.g. cough, sneeze, gag).

It also coordinates feeding reflexes via connections with the cranial nerve nuclei. These include salivating, chewing, swallowing and vomiting. Other activities include control of (1) bladder emptying (the

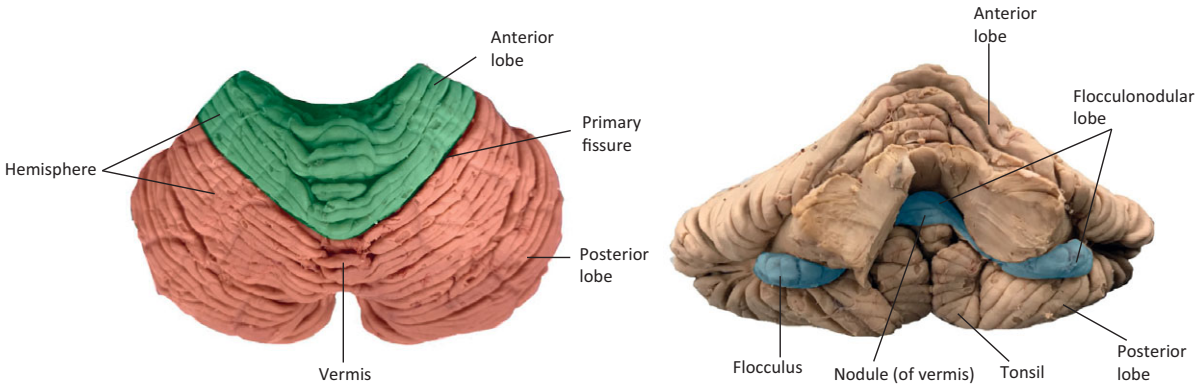

Figure 1.7 Three lobes of the cerebellum. The anterior (*green*), posterior (*red*) and flocculonodular (*blue*) lobes are defined by the primary and posterolateral fissures. (The posterolateral fissure, which is not labelled, lies immediately below the flocculonodular lobe.)

micturition reflex), (2) conjugate gaze (via the **vertical** and **horizontal gaze centres** of the midbrain and pons) and (3) posture, muscle tone and gait.

The **ascending reticular activating system** (**ARAS**) arises from the brain stem and diencephalon and has a general excitatory effect on the cerebral cortex. It receives afferents from all sensory pathways and promotes cortical excitability by the release of acetylcholine, noradrenaline and histamine. Interruption of this ascending projection is responsible for **coma** in rostral brain stem injury. Given that it does not arise from the reticular formation, it is better referred to as the **ascending arousal system**.

1.2.3.4 Cerebellum

The **cerebellum** (Latin: diminutive of cerebrum) clasps the brain stem from behind and forms the roof of the fourth ventricle. The paired **cerebellar hemispheres** are connected in the midline by the narrow **vermis**, which is said to resemble a garden worm (Latin: *vermis*, worm). The cerebellum is large and impressive in the human brain, having expanded during evolution in proportion to the cerebral cortex.[30]

The **cerebellar cortex** is arranged in parallel ridges called **folia**, separated by creases called **fissures**, and has a comparatively simple three-layered structure. It contains two major neuronal cell types. **Granule cells** are small, spherical neurons which receive incoming projections, whilst **Purkinje cells** have large cell bodies and long axons that project out of the cerebellar cortex.

The cerebellar white matter has a branching pattern that resembles a tree in midsagittal section (see Figure 1.6) and is referred to as the **arbor vitae** (Latin: living tree). Several nuclei are buried in the cerebellar white matter. The largest is the **dentate nucleus** which has tooth-like serrations (Latin: *dentalis*, bearing teeth) and is the principal efferent nucleus.

Lobes and Fissures

The cerebellum is divided into three lobes (Figure 1.7). The **primary fissure** defines a small V-shaped **anterior lobe** and a much larger **posterior lobe**. The latter includes the **cerebellar tonsils**. The diminutive **flocculonodular lobe** lies at the anterior aspect of the cerebellum and is composed of the paired **flocculi** laterally (Latin: *flocculus*, tuft of wool) together with the **nodule** of the vermis in the midline. The boundary between the posterior and flocculonodular lobes is the **posterolateral fissure**.

In contemporary neuroanatomy the cerebellum is divided into 10 **cerebellar lobules** (each with components in the vermis and cerebellar hemisphere). These are named using Roman numerals: anterior lobe (lobules I–V), posterior lobe (lobules VI–IX) and flocculonodular lobe (lobule X).

Three pairs of white matter bundles connect the cerebellum to the brain stem: the **superior**, **middle** and **inferior cerebellar peduncles**. These communicate, respectively, with the midbrain, pons and medulla. The inferior and middle peduncles contain mainly afferent fibres, whilst the superior cerebellar peduncle is the principal outflow pathway.

Cerebellar Functions

The cerebellum is traditionally regarded as a 'motor structure' because it contributes to balance, muscle

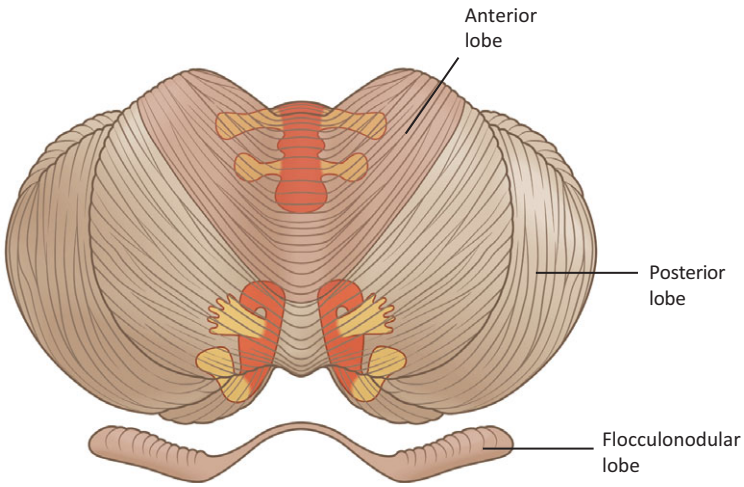

Figure 1.8 Diagram indicating the parts of the cerebellum with motor and sensory functions. The sensorimotor and vestibular portions of the cerebellum are small. The vast majority of the cerebellum has non-motor roles, contributing to cognition, language, visuospatial ability, behaviour and emotional regulation.

Box 1.4 Clinical Effects of Cerebellar Lesions

The portion of the cerebellum that is involved in **vestibular** and **sensory/motor functions** is relatively small, consisting mainly of the **flocculonodular lobe** and the medial part of the **anterior lobe**, together with a second sensorimotor representation in the ventral cerebellum.

The classic **cerebellar motor syndrome** (gait ataxia, limb dysmetria, dysarthria) is mainly associated with anterior lobe lesions (e.g. superior cerebellar artery stroke). The **cerebellar vestibular syndrome** (disequilibrium, vertigo, nystagmus) typically follows damage to the flocculonodular lobe and/or oculomotor vermis (e.g. due to an infarct in the territory of the anterior inferior cerebellar artery).

Lesions restricted to the **posterior lobe** (e.g. following a posterior inferior cerebellar artery stroke) produce disturbances of cognitive-executive function, language and visuospatial ability, often without significant motor features. Alterations of mood and behaviour are more specifically associated with damage to the **posterior vermis** ('limbic cerebellum').

The constellation of non-motor cerebellar features is known as the **cerebellar cognitive affective syndrome** or **Schmahmann syndrome**, named after the American neurologist Jeremy Schmahmann.[36–38] Just as the cerebellar motor syndrome is associated with **limb dysmetria**, it is proposed that Schmahmann syndrome represents **dysmetria of thought** and **emotion**. As such, it has been described as the third cornerstone of clinical ataxiology.[37]

In keeping with the remarkably uniform structure of the cerebellar cortex, it has been suggested that the function of the cerebellum is the same for all cortical regions that it influences: the **universal cerebellar transform**.[39] Its overall role can be summarised as the maintenance of cortical functions 'around a homeostatic baseline, automatically, without conscious awareness, informed by implicit learning, and performed according to context'.[40]

tone and coordination. However, it is embryologically an alar (sensory) plate derivative, and most of its connections are **non-motor**, contributing to the regulation of cognition, language, visuospatial ability, emotion and behaviour (Figure 1.8).[31–34]

Its overall contribution to motor and non-motor functions is to act as an '**oscillation dampener**', rapidly and automatically optimising cognitive and motor performance according to context.[35] Cerebellar lesions therefore tend to produce erratic excursions in the control of movement, cognition and emotion (Box 1.4).

1.2.4 Spinal Cord

The spinal cord is continuous with the brain stem and lies within the bony **spinal canal**, surrounded by meninges. It is 40–50 cm in length, up to 1.5 cm in width and contains approximately 200 million neurons.[41] The considerable sensory and motor supply to the upper and lower limbs is reflected by the presence of **cervical** and **lumbar enlargements**.

The spinal cord is significantly shorter than the vertebral column, terminating at the lower border of the first lumber vertebra (L1/2) as the tapering **conus**

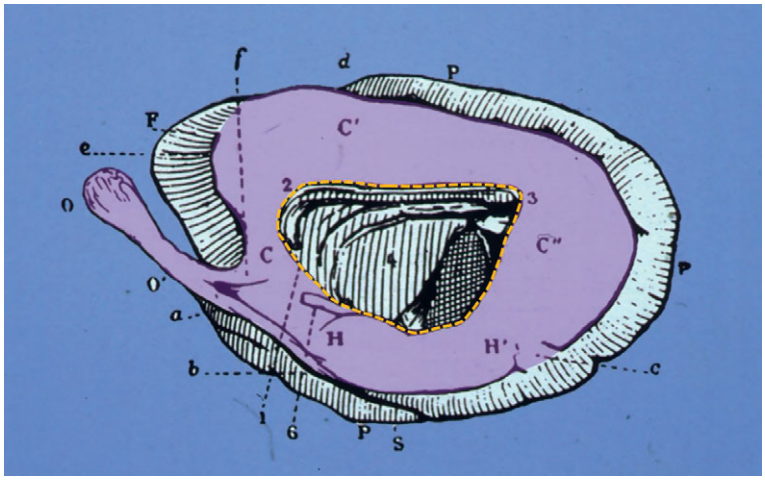

Figure 1.9 Depiction of the limbic lobe. Note the resemblance to a tennis racket, with the handle represented by the olfactory bulb and tract. The medial edge (limbus) of the cerebral cortex is indicated in orange. Modified from Paul Broca (1878) (please ignore the letter labels in the image).

medullaris. Due to this length discrepancy, the upper roots leave the cord horizontally, whilst the lower roots follow a progressively more oblique course. Below the conus medullaris, the roots form an almost vertical leash called the **cauda equina** (Latin: horse's tail).

The 31 pairs of spinal nerves are attached to the cord via the **dorsal** (**sensory**) and **ventral** (**motor**) **roots** which arise from a series of rootlets. Each dorsal root bears a **dorsal root ganglion** which contains the cell bodies of **primary sensory neurons**. Dorsal root ganglia neurons are derived from the **neural crest**, a transient population of cells at the dorsolateral margins of the **neural tube**.

The spinal cord contains a central, H-shaped core of grey matter (with **dorsal** and **ventral horns**) that is surrounded by a thick layer of white matter. The white matter is arranged in three longitudinal **columns** (or **funiculi**) that contain ascending and descending tracts. The **posterior columns** are located between the dorsal roots and are separated by the **dorsal median sulcus**. The **anterior columns** lie between the ventral roots and are separated by the **ventral median fissure**. The **lateral columns** are situated between the attachments of the dorsal and ventral nerve roots on each side.

The spinal cord coordinates simple reflexes. For instance, the **stretch reflex** maintains normal muscle tone and tendon reflexes, whilst the **flexor reflex** mediates withdrawal from a painful stimulus. More complex neuronal networks called **central pattern generators** (**CPGs**) are responsible for semi-automatic actions such as walking and are recruited by descending projections from the brain.

1.3 Limbic and Paralimbic Cortex

The **limbic lobe** (which includes the **hippocampus**) is a band of cortex that encircles the corpus callosum and brain stem, surrounding the medial border of the cerebral cortex (Figure 1.9). It is concerned with olfaction, emotion and memory, and has a microscopic structure that differs from that of the neocortex. The limbic lobe is a central component of what was formerly referred to as the 'limbic system' (Box 1.5). Non-neocortical areas lying outside of the limbic lobe (e.g. posterior orbital region, anterior insula) are referred to as **paralimbic cortex**.

1.3.1 Cortical Types

The cerebral cortex is classified into three major types (Figure 1.10). The majority of the cerebral surface (e.g. sensory, motor and association cortices) is composed of **neocortex**. Areas concerned with olfaction, emotion and memory (including the entire limbic lobe) are non-neocortical, consisting of **allocortex** and **mesocortex**.

1.3.1.1 Neocortex

At least 90% of the cerebral surface is composed of **neocortex**. This is evolutionarily more recent than limbic brain regions (Greek: *neos*, new) having emerged with the appearance of early mammals in the late Triassic period.[50] It is also referred to as **isocortex** because it has a uniform structure with six identifiable layers throughout (Greek: *isos*, equal). The neocortex is arranged in horizontal **laminae** with alternating layers of **granular** and **pyramidal** neurons. Sensory areas (e.g.

Box 1.5 Historical Origins of the Limbic System

The term **limbic system** was coined in the 1950s by the American neuroscientist Paul MacLean,[42] replacing his earlier term **visceral brain.**[43] He had been influenced by a 1937 paper written by the American neuroanatomist James Papez (pronounced 'paypz'), entitled 'A Proposed Mechanism of Emotion', which sought to delineate the anatomical basis of emotional experience.[44]

Papez was influenced in turn by the brain transection studies of Walter Cannon and Philip Bard, which suggested a **hypothalamic** origin for emotional behaviours.[45, 46] This contrasted with the **peripheral feedback** theory proposed independently by William James and Karl Lange,[47–49] which posited that subjective emotional feelings reflect activity of the **autonomic nervous system** (e.g. trembling, pounding heart, butterflies). Papez cited the behavioural effects of thalamic and cingulate gyrus lesions and noted the involvement of the hippocampus in rabies, which is associated with intense emotional symptoms (Latin: *rabies*, rage).

The anatomy of the so-called **Papez circuit** reflected the view that conscious experience depends on reverberating thalamocortical circuits. It centred on the **hippocampus** (and its efferent pathway, the **fornix**) and included a series of connections passing in turn through the mamillary bodies, anterior thalamus, cingulate gyrus and entorhinal cortex, before returning to the point of origin. This assembly was claimed by Papez to 'constitute a harmonious mechanism which may elaborate the central functions of emotion, as well as participate in emotional expression'.[44]

MacLean sought to disseminate and popularise this theory and expanded on it by incorporating evidence from the neuroscience literature (e.g. the Klüver-Bucy syndrome) and his studies of **psychomotor epilepsy**. This led to the addition of the **amygdala** and **septal area** as core elements of his 'emotional brain'. However, it should be emphasised that most of the assumptions underlying the limbic system concept have since been disproved, and the idea is now of little practical value.

(A)

Isocortex (neocortex)	6 layers	90% of cerebral hemisphere (sensory, motor and association areas)
Mesocortex	3-6 layers	Majority of limbic lobe (e.g. cingulate/parahippocampal gyri)
Allocortex	3 layers	Hippocampal formation (archicortex) Primary olfactory areas (paleocortex)

(B)

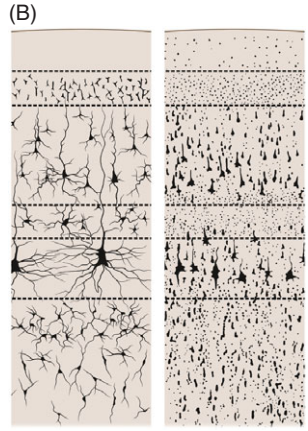

Figure 1.10 Cortical types. (A) There are three main types of cortex. Isocortex (neocortex) is found in the majority of the cerebral hemisphere, whilst non-neocortical areas are located in the limbic lobe and 'paralimbic' areas such as the posterior orbital region. (B) Diagram illustrating the laminar architecture of the neocortex, which consists of six well-defined layers of granular and pyramidal neurons (*left*: Golgi stain; *right*: Nissl stain).

primary visual cortex) have prominent granule cell layers, whilst motor areas (e.g. primary motor cortex) have conspicuous pyramidal cell layers.

1.3.1.2 Allocortex

The hippocampus and primary olfactory areas are composed of **allocortex** (Greek: *allos*, other) which is thinner than neocortex and has only three layers. Hippocampal allocortex is also known as **archicortex**, whilst the primary olfactory areas are referred to as **paleocortex**. The hippocampal and olfactory cortices differ in structure but are nevertheless grouped together, as they are different from ('other than') the neocortex. The terms *paleocortex* and *archicortex* reflect the fact that allocortex is evolutionarily ancient (Greek: *palaios*, ancient; Latin: *archi-*, early).

Box 1.6 Neuroanatomy of Dementia

Dementia (from the Latin, meaning loss of mind) is characterised by a marked **decline in mental faculties** such as memory, intellect or personality.[53–56] Most cases are due to a **neurodegenerative process** characterised by the formation of **pathological inclusions** within neurons. The entorhinal cortex, hippocampus and amygdala are often severely affected,[57] and the pathology usually progresses in a predictable anatomical sequence, enabling disease **staging**.[1]

This is illustrated by the step-wise development of neurofibrillary tangles in **Alzheimer's disease** (**AD**) in which six **Braak stages** can be identified.[58] Tangles first appear in the **entorhinal cortex** and **hippocampus** (preclinical stage: I–II), with progression to the **limbic mesocortex** (limbic stage: III–IV) and **neocortex** (symptomatic stage: V–VI). A similar step-wise progression of Braak stages is described in **Parkinson's disease dementia** (**PDD**) and **Dementia with Lewy Bodies** (**DLB**).[59]

In some cases cortical features are less prominent and the clinical picture is dominated by generalised slowing of thought or **bradyphrenia** (Greek: *bradys*, slow).[60] This is usually accompanied by impaired reasoning and decision-making and is referred to as 'subcortical-type' dementia. The underlying cause in these cases is often **cerebrovascular** and is associated with loss of subcortical white matter.[61]

1.3.1.3 Mesocortex

The term **mesocortex** describes an intermediate cortical zone between the neocortex and allocortex (Greek: *mesos*, middle). It has between three and six layers and accounts for much of the limbic lobe, including the **cingulate** and **parahippocampal gyri**. The posterior orbital region, anterior insula and temporal pole are also mesocortical. Damage to these 'paralimbic' regions is often seen in **traumatic brain injury**, which may account for some of the neuropsychiatric sequelae.[51, 52] Limbic and paralimbic cortices are particularly vulnerable to **neurodegeneration** and are affected in the majority of dementias (Box 1.6).

1.3.2 Cortical Parcellation and Brodmann Areas

The cerebral cortex can be **parcellated** into a patchwork of around 50 **Brodmann areas** (**BA**). This is based on regional differences in laminar architecture and neuronal packing density, termed **cytoarchitectonics**. Each area has a distinct microscopic structure, connectivity and function.

The numbering system (e.g. primary motor cortex, BA4; primary visual cortex, BA17) is based on a map published by the German neurologist and neuroanatomist Korbinian Brodmann in 1909,[62] but has since been modified and refined.[63, 64]

Modern cortical parcellation incorporates **myeloarchitectonics** (variations in cortical myelination) and **chemoarchitectonics** (distribution of neurotransmitter receptor subunits).[65–67] Cortical boundaries were traditionally determined by visual inspection using **light microscopy**, but can also be identified automatically via a computer algorithm.[68]

1.3.2.1 Granular, Dysgranular and Agranular Cortex

Identification of **cortical layer IV** (the **internal granule cell layer**) is an important step in the cytoarchitectonic classification of cortical zones. Areas with a conspicuous layer IV are referred to as **granular cortex**. This layer receives incoming projections from the thalamus and is therefore prominent in sensory cortices.

In some regions layer IV is virtually impossible to identify by light microscopy (e.g. the motor/premotor areas of the frontal lobe), and these are referred to as **agranular cortex**. The term **dysgranular cortex** is used when layer IV is present but indistinct. Some parts of the limbic lobe lack clear lamination and are referred to as **dyslaminate**.

1.3.3 Limbic Lobe: Topographical Anatomy

The limbic lobe is a ring-shaped convolution surrounding the medial edge or 'limbus' of the cerebral cortex (Latin: *limbus*, border or edge). It includes the **cingulate** and **parahippocampal gyri**, which encircle the corpus callosum and brain stem (Figure 1.11).

The term 'cortical limbus' was coined by the English physician and anatomist Thomas Willis in 1664,[69] whilst the first detailed account of the limbic lobe itself was provided by the French physician and anatomist Paul Pierre Broca in 1848.[70] The limbic

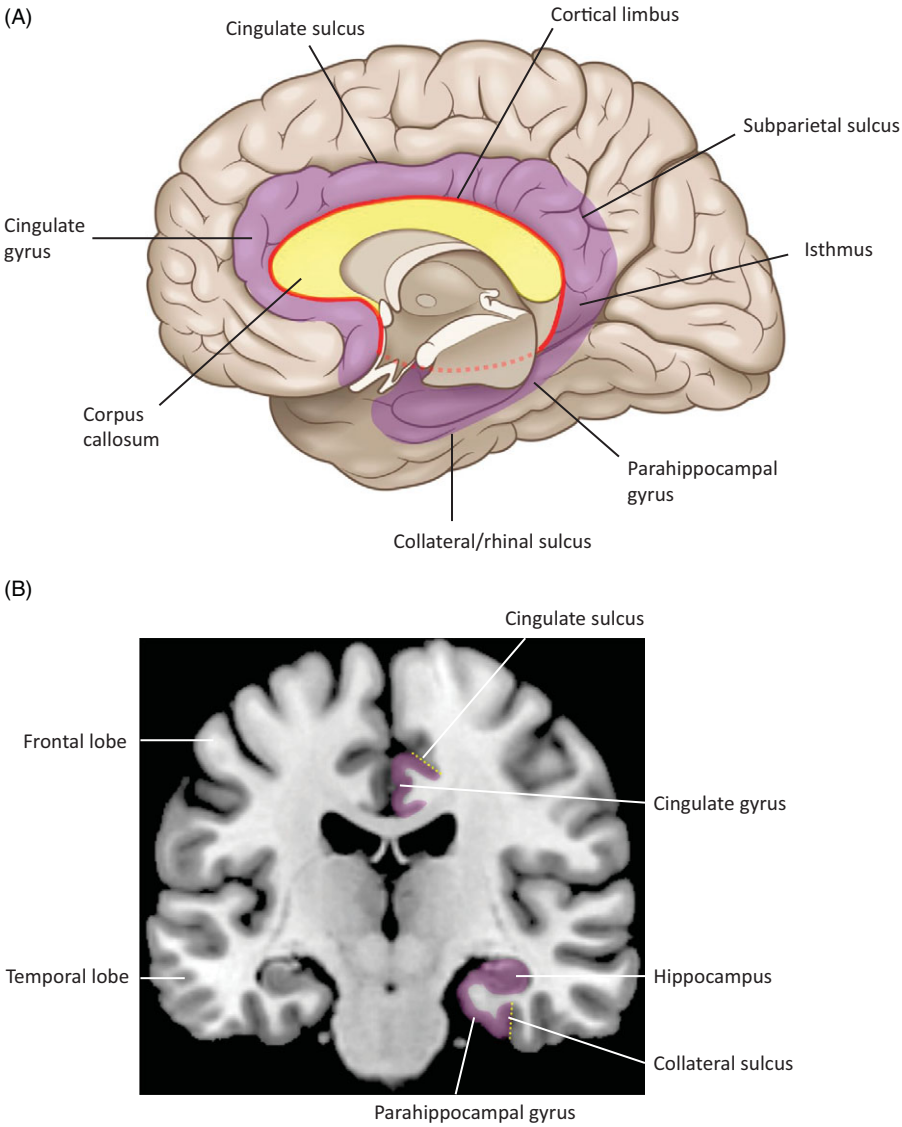

Figure 1.11 The limbic lobe. (A) Diagram showing the ring-shaped limbic lobe (*purple*). This consists of the cingulate and parahippocampal gyri, together with the hippocampus (not shown). The limbic lobe surrounds the cortical limbus or medial edge of the cerebral cortex (*red*). (B) Coronal MRI scan showing the limbic lobe and its lateral sulcal boundaries.

lobe is separated from the surrounding frontal, parietal and temporal regions by the **limbic fissure**, a discontinuous furrow that is composed of several separate sulci (described later in the chapter).

1.3.3.1 Cingulate and Parahippocampal Gyri

The **cingulate gyrus** is named for its belt-like distribution as it wraps around the corpus callosum on the medial hemispheric surface (Latin: *cingulum*, belt). Its boundary with the overlying frontal lobe is the **cingulate sulcus** which sweeps along the medial hemispheric surface in parallel with the corpus callosum. The cingulate gyrus is separated from the medial parietal lobe by the horizontal part of the H-shaped **subparietal sulcus**. The posterior cingulate gyrus passes behind the splenium of the corpus callosum before terminating as the tapering **isthmus** (**retrosplenial area**).

The limbic lobe continues into the medial temporal region as the **parahippocampal gyrus**, which is

Box 1.7 The Rise and Fall of the Limbic System

The **limbic system** or 'emotional brain' concept[71] is an outdated idea from the 1950s that has not stood up to scientific scrutiny.[72–75] For instance: (1) the hippocampus is concerned with **episodic memory** and **spatial navigation** rather than emotion;[76] (2) MacLean's 'triune brain theory' (positing the **sequential evolution** of reptilian, paleomammalian and neomammalian brains, corresponding to the basal ganglia, limbic system and neocortex) is false;[77] (3) the **cortical primordium** is present in the entire vertebrate line and did not evolve in mammals;[78] and (4) the **basal ganglia** (MacLean's so-called reptilian brain) cannot function independently of the cerebral cortex, but instead rely on **cortical-subcortical re-entrant loops**.[79]

The limbic system idea has been eroded further by its **ever-expanding boundaries** (e.g. Nauta's limbic midbrain area, the greater limbic system of Nieuwenhuys) and the **lack of a consistent definition**.[80] This was encapsulated by the view of Swedish neuroanatomist Lennart Heimer, who noted that the limbic system is 'a concept in perpetual search for a definition' and that defining it may be impossible 'without enlisting practically the entire brain, including the cerebellum'.[79]

It is also undermined by the observation that, unlike other neural systems (e.g. visual, auditory, motor), the limbic 'system' **lacks a clearly defined purpose**. It has been variously claimed to be responsible for olfaction, emotion, pain perception, empathy, social cognition, maternal love, motivation, reward-based learning, implicit learning, episodic memory and spatial navigation. In recent years the validity of the concept has repeatedly been called into question, and many authors have recommended that it should be **abandoned altogether**.[77, 81–87]

bordered laterally by the **collateral sulcus**. The anterior segment of the collateral sulcus is renamed the **rhinal sulcus**. The rostral portion of the parahippocampal gyrus that lies medial to the rhinal sulcus is the **entorhinal cortex**, which forms reciprocal connections with the hippocampus.

Anteriorly, the medial part of the parahippocampal gyrus gives rise to a backwardly projecting, hook-like eminence called the **uncus** (Latin: *uncus*, hook) (see Figure 1.15, later in the chapter). This belongs to the hippocampus and is also known as the **uncus hippocampi**. The presence of the uncus gives the parahippocampal gyrus the overall appearance of a question mark or swan's neck.

1.3.3.2 Hippocampus and Cingulum

The **hippocampus** (discussed further below) is an in-rolling of allocortex in the medial temporal region. It forms a longitudinal prominence in the floor of the temporal horn of the lateral ventricle. The cortex of the hippocampus is continuous with that of the parahippocampal gyrus and is formed by three successive cortical folds. The process of folding gives the hippocampus the appearance of two interlocking C-shapes when viewed in coronal section.

The cortex of the limbic lobe is interconnected by a central core of white matter called the **cingulum**. This consists of **association fibres** that travel in both directions and allow communication between different parts of the cingulate and parahippocampal gyri. The **dorsal cingulum** lies beneath the cingulate gyrus, whilst the **ventral cingulum** is related to the parahippocampal gyrus. The limbic lobe and cingulum form the core of what was formerly known as the 'limbic system' (Box 1.7).

1.4 Cingulate Region

The cingulate gyrus is traditionally divided into the **anterior cingulate cortex** (**ACC**) and **posterior cingulate cortex** (**PCC**).[88] However, these are large heterogeneous cortical regions that have been subdivided into four major subzones.[89, 90]

1.4.1 The Four-Region Model of Vogt

A large body of converging evidence (e.g. comparative anatomy, lesion studies, electrical stimulation, fMRI) has identified four functionally distinct areas within the cingulate gyrus (Figure 1.12):[91]

- **Anterior cingulate cortex** (**ACC**)
- **Midcingulate cortex** (**MCC**)
- **Posterior cingulate cortex** (**PCC**)
- **Retrosplenial cortex** (**RSC**)

The functions of the anterior and midcingulate regions are **emotional-motivational** (including the experience of pain and empathy) and are of most relevance to neuropsychiatric disorders. The posterior cingulate and retrosplenial regions are involved in **visuospatial functions** including visual imagination,

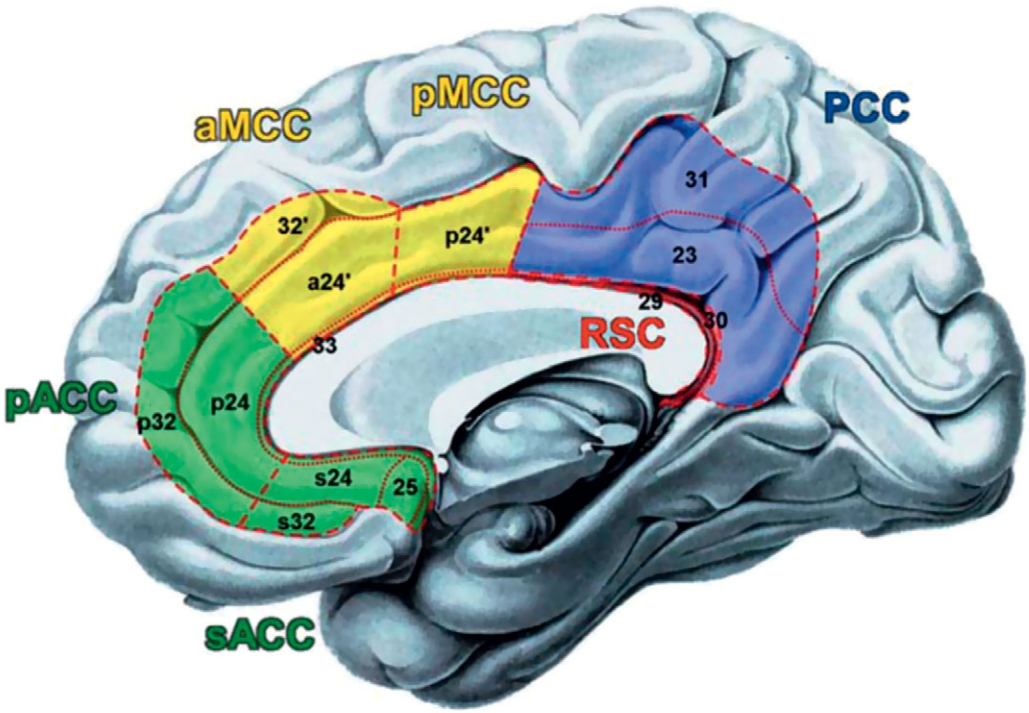

Figure 1.12 Functional areas within the cingulate region. Note that the midcingulate cortex (MCC, *yellow*) can be divided into anterior and posterior parts (aMCC, pMCC). The retrosplenial cortex (RSC, *red*) is a small area that lies posterior to the splenium of the corpus callosum. The numbers designate Brodmann areas. Reproduced with permission from Hoffstaedter F, Grefkes C, Caspers S, Roski C, Palomero-Gallagher N, Laird AR, Fox PT, Eickhoff SB. The role of anterior midcingulate cortex in cognitive motor control: evidence from functional connectivity analyses. *Hum Brain Mapp*. 2014;35 (6):2741–2753.

episodic memory recall and the mental projection of self into past and future.

1.4.1.1 Anterior Cingulate Cortex

The anterior cingulate cortex has pregenual and subgenual parts. The **pregenual region** (**BA33** and the anterior parts of **BA24** and **BA32**) is in front of the genu of the corpus callosum. The **subgenual area** (**BA25**) lies below the genu. The pregenual ACC has strong links with the amygdala and other limbic brain regions and has mainly **emotional** and **affective functions** (e.g. emotional experience, pain, suffering, empathy). The subgenual area is specifically implicated in **negative emotional states** and **depression**.

Emotion, Pain and Empathy

Increased cerebral blood flow has been demonstrated in the anterior cingulate cortex in association with emotional states of both positive and negative valence[92] including physical pain and psychological or emotional distress.[93–96] Activity in the ACC is observed in **empathic states**,[97–99] but this is typically attenuated or abolished in people with sociopathy or psychopathy, in the context of **antisocial personality disorder**.[100–102]

Troublesome ruminations in patients with **obsessive-compulsive disorder** (**OCD**) are also accompanied by increased anterior cingulate activity.[103, 104] This provided the rationale for surgical lesions in this region (**anterior cingulectomy**) or within the underlying white matter (**anterior cingulotomy**) in severe, treatment-refractory OCD.[105–107]

Anterior cingulate lesions have also been used to ameliorate intractable **chronic pain**.[108–110] In the latter a state of **pain asymbolia** may result, in which the patient continues to experience pain but is no longer bothered by it, having lost the aversive emotional component of the experience.[111]

Motivation and Apathy

The role of the ACC in **motivational drive** is underscored by the behavioural effects of substantial

anterior cingulate lesions (e.g. anterior cerebral artery stroke, parafalcine meningioma). These may lead to behaviourally inert states of **apathy**, **anhedonia**, **abulia**[112, 113] or **akinetic-mutism**.[114–116]

The anterior cingulate gyrus forms part of the so-called **salience network** which is engaged during circumstances that are important to the individual and demand concentrated attention.[117–119] The salience network also includes the **anterior insula**, which is connected to the cingulate region by a hook-shaped fronto-temporal white matter pathway, the **uncinate fasciculus**.

Subgenual Area 25

The subgenual area belongs to the ACC subregion but has distinct connections and functions. It is the origin of powerful autonomic effector projections to the hypothalamus and brain stem, by which it mediates the expression of behavioural, autonomic and neuroendocrine accompaniments of negative emotional states (e.g. sorrow, grief). As such, it is an effective target for **deep brain stimulation** (**DBS**) in patients with severe intractable **depression**.[120–123]

1.4.1.2 Midcingulate Cortex

The midcingulate cortex (consisting of the posterior parts of **BA24** and **BA32**) lies immediately below the **supplementary motor area** of the medial frontal lobe. The MCC contains the **cingulate motor areas** which lie in the crease of the cingulate sulcus.

Voluntary Action

The midcingulate cortex appears to take part in a **voluntary motor pathway** by which the intention to act is transformed into an actual movement.[124, 125] It receives afferents from the anterior cingulate cortex (which may provide the **emotional drive** to act) and projects in turn to the **supplementary motor area**. The pathway continues from the SMA to the **primary motor cortex**, from which voluntary movement is initiated. The SMA takes part in a basal ganglia loop that is involved in movement initiation, selection and execution. It therefore represents an important 'middle stepping-stone' in the pathway between intention and action.

Emotional Facial Expression

The **face area** of the cingulate motor cortex receives strong projections from the **amygdala**, contributing to emotional facial expressions.[126, 127] This explains the difference between a genuine **Duchenne smile**, which is initiated via the limbic lobe, and a voluntary or **non-Duchenne smile**, which is executed effortfully via the pyramidal tract. This dichotomy is seen in some stroke patients who have paralysis of the contralateral hemiface but are able to smile spontaneously.[128] This is also of relevance to the lack of emotional expression (**facial amimia**) in Parkinson's disease, in which amygdala pathology is usually prominent.[129]

1.4.1.3 Posterior Cingulate and Retrosplenial Cortices

The **posterior cingulate cortex** (**BA23 and BA31**) lies below the precuneus (medial parietal lobe) and in front of the visual association cortex. The adjacent **retrosplenial cortex** (**BA29 and BA30**) occupies the isthmus of the cingulate gyrus, just below and behind the splenium of the corpus callosum.

The posterior cingulate cortex has been implicated in **visuospatial imagination** and **sense of self** in relation to the environment.[130–132] Similar functions have been attributed to the neighbouring **precuneus**.[133] The posterior cingulate and retrosplenial cortices, which border the parahippocampal gyrus and hippocampal tail, also contribute to recall of **autobiographical memory**.[134]

Structural and functional abnormalities in the cingulate region have been identified in patients with **schizophrenia** and are particularly associated with negative symptoms such as depression, apathy and social withdrawal (Box 1.8).

1.5 Hippocampus and Entorhinal Cortex

The **hippocampus** belongs to the limbic lobe and consists of three-layered allocortex. It occupies the medial temporal region and is continuous with the adjacent parahippocampal gyrus. The name *hippocampus* is the genus name of the seahorse. This reflects its appearance when dissected free from the brain, together with its arch-shaped outflow pathway, the **fornix** (Latin: *fornix*, arch) (Figure 1.13).[148]

The **entorhinal cortex** (BA28) can be regarded as the 'interface' with the hippocampus. It occupies the anterior part of the parahippocampal gyrus, just medial to the rhinal sulcus. The hippocampus and entorhinal cortex together form a structural-functional unit, the **hippocampal formation**, that is crucial for **episodic memory** and **spatial navigation**.[149, 150]

Box 1.8 Schizophrenia and the Cingulate Gyrus

Schizophrenia is a chronic and severe disorder of thought, perception and behaviour that affects 1 in 200 people worldwide.[135] It is a **psychosis**, in which hallucinations and delusions (**positive symptoms**) are core features.[138] These are typically accompanied by depression, social withdrawal, apathy and cognitive deficits (**negative symptoms**). The latter are typically treatment-resistant and may be more debilitating.[136, 137]

Abnormalities of the **cingulate region** have consistently been reported in patients with schizophrenia in association with negative symptoms. These include cortical thinning, hypometabolism and reduced recruitment during cognitive tasks or in response to emotional stimuli. [139–142]

Alterations in hemispheric asymmetry have also been described.[142] For instance, duplication of the cingulate gyrus is a normal anatomical variant that is twice as common in the left cerebral hemisphere.[143] In schizophrenia, the normal leftward asymmetry is commonly lost.[144, 145]

Another area that normally shows strong leftward asymmetry is the language-associated **planum temporale** (the flat, uppermost surface of the posterior temporal lobe). This asymmetry is frequently reversed in schizophrenia, hinting at a more generalised disturbance of hemispheric lateralisation that is not limited to the cingulate region.[146, 147] Abnormalities of other brain regions implicated in schizophrenia (e.g. fronto-temporal cortex, insula, amygdala) are discussed in a later section.

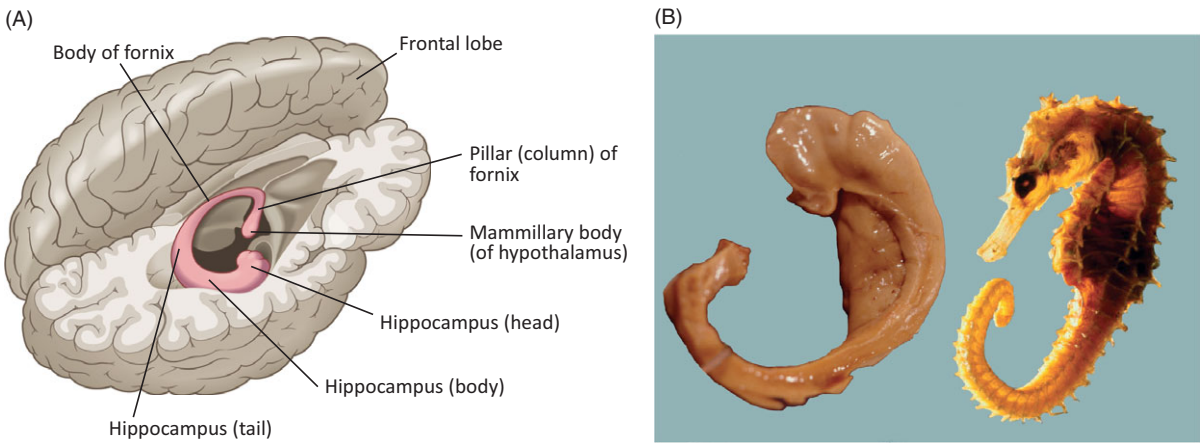

Figure 1.13 The hippocampus. (A) Illustration of the right cerebral hemisphere showing the position of the hippocampus and fornix. (B) Dissection of the hippocampus and fornix, demonstrating its resemblance to a seahorse. (Courtesy of Professor László Seress.)

1.5.1 Anatomy of the Hippocampus

The hippocampus forms a longitudinal bulge in the temporal horn of the lateral ventricle and is therefore submerged in CSF. It is approximately 4–5 cm in length and has a head, body and tail.[151] The head of the hippocampus bears several shallow grooves or digitations so that it resembles a lion's paw, and is also known as the **pes hippocampi** (Latin: *pes*, foot).

The hippocampi have a gentle curvature (concave medially) and are reminiscent of a pair of thick brackets, flanking the brain stem on either side in the medial temporal lobe. The hippocampus is covered by a thin sheet of white matter called the **alveus** (Latin: *alveus*, riverbed). This contains hippocampal efferent fibres which leave the hippocampus by entering the fornix.

1.5.1.1 Hippocampal Subregions (Figure 1.14)

The hippocampal allocortex consists of the **dentate gyrus** and **Ammon's horn** (within the ventricle) together with the **subiculum** below (Latin: *subicere*, to place underneath). Ammon's horn (also known as the **hippocampus proper**) contains large pyramidal neurons arranged in three zones: **CA1**, **CA2** and **CA3**. The terminology derives from the Latin form of Ammon's horn, **cornu ammonis** (**CA**). A CA4 subregion was previously described but was found to belong instead to the dentate gyrus.

The internal connections of the hippocampus include a linear sequence of three neurons arranged in series. This is known as the **trisynaptic pathway**, which has been intensively studied in animal models of memory.[152] The hippocampal connections form a

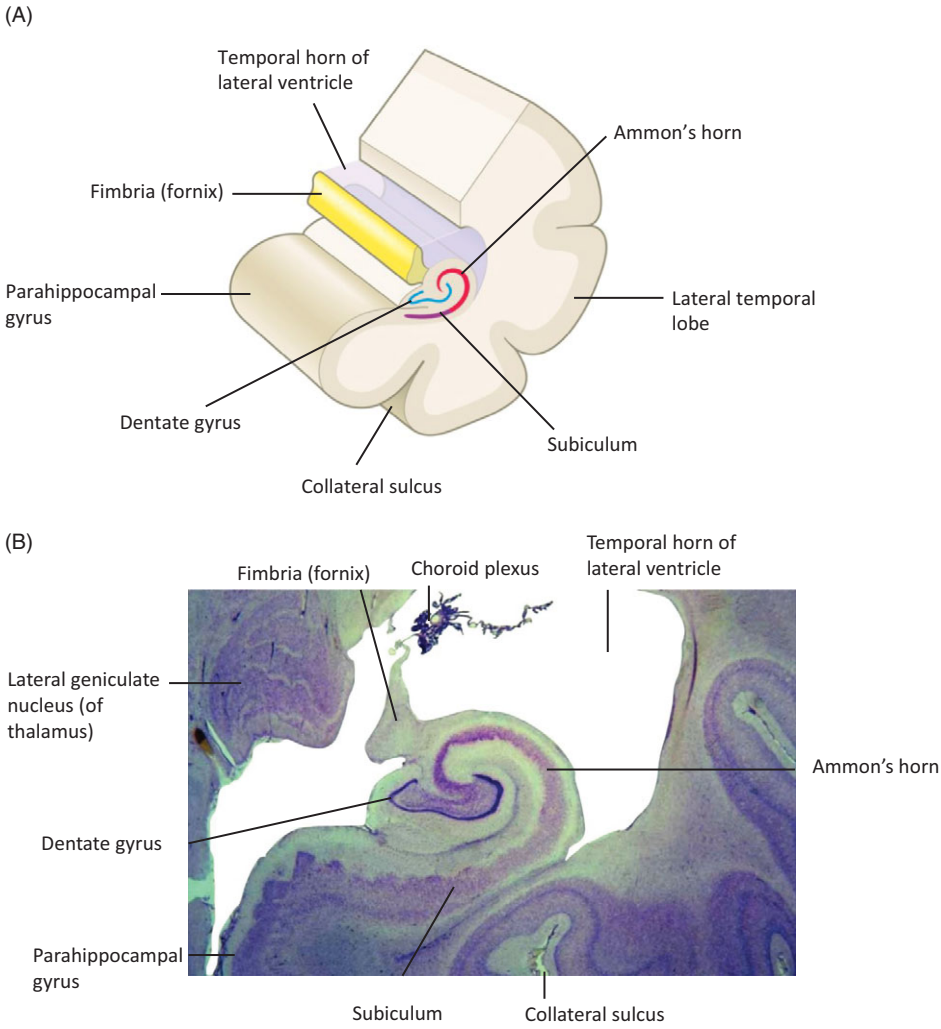

Figure 1.14 Hippocampal subregions. (A) Illustration of the right temporal lobe showing the three parts of the hippocampus: dentate gyrus (*blue*), Ammon's horn (*red*) and subiculum (*purple*). From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014). (B) Medium-power microscopic view of the hippocampus. (Courtesy of Professor Roy Weller.)

closed loop that arises and terminates in the entorhinal cortex. Hippocampal pyramidal neurons also give rise to projections that leave the hippocampus (via the fornix) to reach the mamillary bodies, septal area, ventral striatum and rostral midbrain. Terms used to describe the hippocampus are discussed in Box 1.9.

1.5.2 Entorhinal Cortex

The **entorhinal cortex** occupies the anterior part of the parahippocampal gyrus (Figure 1.15). It has a unique cytoarchitecture consisting of **internal** and **external principal cell layers** separated by a horizontal sheet of white matter, the **lamina dissecans**. The latter replaces cortical layer IV (the internal granule cell layer).

The surface of the entorhinal cortex bears numerous wart-like elevations, the **verrucae hippocampi.** These correspond to discrete groups of neurons in cortical layer II (called **pre-alpha clusters**) that give rise to the **perforant path**.[154] The latter is the main input stream to the hippocampus, which terminates in the granule cell layer of the dentate gyrus.

The entorhinal cortex is classified as mesocortex and represents the cortical interface with the hippocampus. It forms **reciprocal connections** with the

Box 1.9 Terms Used to Describe the Hippocampus

In clinical and radiological practice the word **hippocampus** is sometimes used rather loosely to refer to the longitudinal prominence in the temporal horn of the lateral ventricle.

A strict **cytoarchitectonic definition** of the hippocampus includes the dentate gyrus, Ammon's horn and subiculum, all of which are composed of three-layered **allocortex**. The term **hippocampus proper** refers specifically to **Ammon's horn** (CA1–CA3).

The **hippocampal formation** consists of the hippocampal allocortex (dentate gyrus, Ammon's horn, subiculum) together with the entorhinal mesocortex. Although cytoarchitectonically distinct, these cortical regions are grouped together because they form a functional unit that is crucial for memory formation.[153]

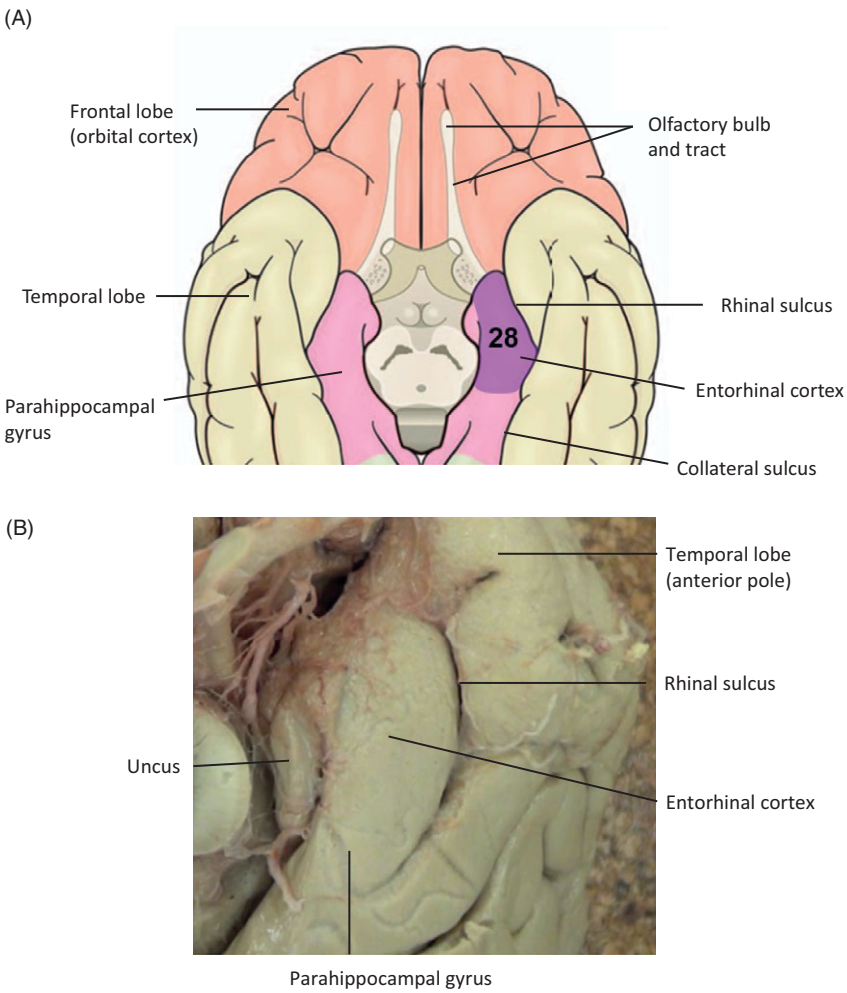

Figure 1.15 The entorhinal cortex. (A) A diagram showing the entorhinal cortex (Brodmann area 28) in the anterior part of the parahippocampal gyrus. (B) A corresponding photograph of a preserved human brain specimen. Note the hook-like uncus which gives the parahippocampal gyrus the appearance of a question mark.

orbitomedial prefrontal cortex, cingulate gyrus, anterior insula, temporal pole, inferior and lateral temporal lobe, and the visual association cortex. It also receives fibres from the olfactory tract, septal area and amygdala. Information from these disparate brain regions is integrated by the entorhinal cortex and transferred to the hippocampus for consolidation as **memory traces**.

Neurons forming the pre-alpha clusters in layer II of the entorhinal cortex are affected early in the course of **Alzheimer's disease**, resulting in a smooth entorhinal cortex that lacks verrucae.[155] This is associated with loss of the perforant path, which originates from the pre-alpha clusters. As a result, the hippocampus is effectively 'disconnected' from the rest of the brain, accounting for the prominent disturbance of episodic memory and spatial orientation in this type of dementia.

1.5.3 Alveus, Fimbria and Fornix

Hippocampal efferent fibres leave the alveus to enter a slender white matter bundle called the **fimbria**. This is triangular in cross-section and runs in an anteroposterior direction along the upper medial edge of the hippocampus (Latin: *fimbria*, fringe) (see Figure 1.14). As it emerges from the posterior hippocampus, the fimbria is renamed the fornix.

1.5.3.1 Parts of the Fornix

The **fornix** is a white, cord-like structure that leaves the posterior hippocampus and sweeps upwards towards the midline to form an arch beneath the body of the corpus callosum. The portion that emerges from the hippocampal tail is the **crus** (plural: crura). The left and right crura unite beneath the corpus callosum to form the **body** of the fornix, which divides again anteriorly to form the paired **pillars** (or **columns**) (Figure 1.16).

The columns of the fornix dive almost vertically downwards, passing through the substance of hypothalamus (in the lateral wall of the third ventricle) before terminating in the **mamillary bodies**. These are paired, pea-like structures in the floor of the third ventricle (Latin: *mamilla*, nipple). The mamillary bodies project in turn to the **cingulate gyrus**, via the anterior thalamus. The fornix also gives rise to a separate contingent of fibres that passes anteriorly to reach the **septal area**. It also projects to the preoptic area, ventral striatum, amygdala and midbrain.

Disruption of the mamillary bodies, hippocampus or fornix often leads to selective episodic memory loss. This is seen in **Wernicke-Korsakoff syndrome**, which is characterised by profound **anterograde amnesia** with **confabulation** (in which memory lapses are filled with distorted or imagined accounts of events). It is caused by micro-haemorrhagic damage to the mamillary bodies due to **thiamine deficiency**, often in association with alcoholism.[156, 157] The classification of memory is discussed in Box 1.10.

1.5.4 Hippocampal Functions

Bilateral hippocampal damage is associated with **anterograde amnesia**, characterised by the inability to form new episodic memories.[159] Established memories are generally preserved in the absence of neocortical disease. However, there is usually a variable degree of **retrograde amnesia**, suggesting that the

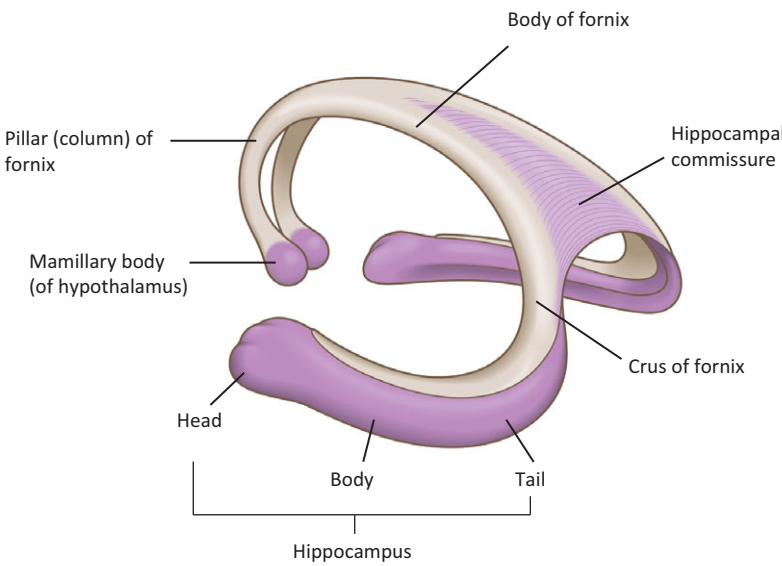

Figure 1.16 Hippocampus and fornix. Since the brain is bilaterally symmetric, there is a hippocampus and fornix on both sides, terminating in the paired mamillary bodies (of the hypothalamus) in the floor of the third ventricle.

Box 1.10 Classification of Memory

Memory can be categorised as **short term** (minutes or hours) or **long term** (weeks, months or years), but this is of limited value in terms of mapping onto neuroanatomical structures.[92] Inability to form new memories is termed **anterograde amnesia** whilst loss of existing memories is referred to as **retrograde amnesia**.

Long-term memories are categorised as **declarative** and **non-declarative**. Declarative (**explicit**) memories are those that can be put into words. They are further subdivided into semantic and episodic types. **Semantic memory** includes abstract facts and information, such as knowledge of capital cities and anatomical terms, and is distributed throughout the neocortex. **Episodic memory** is a day-to-day record of personal experiences (episodes) and involves the hippocampus. **Autobiographical memory** consists of personal experiences (episodic memories) together with factual knowledge such as one's name and address (semantic memories).

Non-declarative (**implicit**) memory encompasses various forms of semi-automatic learning that are only partially accessible to consciousness. An example is **procedural memory** which underlies the acquisition of motor skills. Other types include **associative learning** (e.g. classical conditioning) and **priming** (unconscious behavioural bias due to prior exposure to a stimulus, as used in advertising). The anatomical substrate for implicit memory is not well defined.

Short-term memory (as measured by **digit span**) is a component of **working memory**. This refers to the ability to 'hold in mind' and manipulate information whilst completing a cognitive task. It correlates with activity in the **dorsolateral prefrontal cortex** (specifically the **middle frontal area**, **BA46**). Studies suggest that working memory capacity is a fundamental component of general intelligence and may be a performance-limiting factor in IQ tests.[158]

hippocampus stores memories temporarily prior to **consolidation** in the neocortex.[160–162] It has been suggested that this may take place during dreaming, which is most likely to occur during the **rapid eye movement** (**REM**) phase of sleep.[163, 164]

The hippocampal formation contains **spatial maps** of the world that support navigation. This is achieved by populations of neurons that encode spatial characteristics of the environment: **place**, **border** and **grid cells**.[165–167] The role of the hippocampus in spatial navigation is underscored by the observation that the posterior hippocampus is significantly larger in licenced London taxi drivers.[168]

The link between episodic and spatial memory is **context dependence**. In other words, both types of memory have a spatial and temporal context: *where* was an event or location and *when* did the experience happen. This is not true of **semantic memories** (e.g. knowledge of capital cities or names of geometric shapes) which are context independent.

The hippocampus does not encode semantic memories, which are thought to be distributed throughout the neocortex. Categorical semantic memory (the hierarchical classification of objects) appears to be especially associated with the lateral temporal lobe. This is reflected in the pattern of memory loss in patients with semantic dementia (a variant of **fronto-temporal dementia** or **FTD**). These patients have marked lateral temporal atrophy associated with semantic memory loss and word-finding difficulty. There is therefore a distinction between medial temporal lobe syndromes that preferentially affect episodic memory and lateral temporal syndromes in which sematic memory loss predominates.[169, 170]

It is often said that patients with Alzheimer's disease have loss of **short-term memory**, but this is not correct. Short-term memory is a component of **working memory** and is a function of the **dorsolateral prefrontal cortex** rather than the medial temporal lobe. Short-term memory is usually spared in early Alzheimer's disease[171, 172] but may be affected later due to involvement of the frontal lobes.

In medial temporal lobe amnesia, implicit (e.g. procedural) memory is also usually preserved.[173, 174] As a consequence of this dissociation, it would therefore be possible for a patient with medial temporal lobe amnesia to learn how to drive or play the piano without any recollection of the lessons.

1.6 Central Olfactory Pathways

Loss of the sense of smell (**anosmia**) occurs in several neuropsychiatric disorders. It is an early feature of **Parkinson's disease** that may precede motor symptoms by several years.[175, 176] It is also associated with

mild cognitive impairment and **dementia**[177, 178] and is a consistent finding in **psychotic disorders**, including **schizophrenia**.[179, 180]

1.6.1 Olfactory Nerve and Tract

The **olfactory nerves** (**CN I**) consists of up to 5 million axonal filaments on each side, which arise from the olfactory epithelium in the nasal mucosa.[181] These enter the cranial cavity by passing through the cribriform plate of the ethmoid bone, before synapsing in the **olfactory bulb**. This in turn gives rise to the olfactory tract.

The **olfactory tract** (Figure 1.17) passes posteriorly within the olfactory sulcus to reach the posterior orbital region, where it flattens out into a broad triangle, the **olfactory trigone**. This is flanked on either side by the **medial** and **lateral olfactory striae**. An intermediate stria (and its target, the olfactory tubercle) are barely discernible in the human brain.

The **medial olfactory stria** projects to the contralateral olfactory bulb via the **anterior commissure**. In animals with a highly developed sense of smell this facilitates localisation of olfactory stimuli via **lateral inhibition**.[182, 183] A projection from the medial stria to the septal area is present in other mammals but not in humans.[2]

The **lateral olfactory stria** sweeps laterally towards the sylvian fissure to reach the **ventral insula**. It then makes a sharp hairpin bend, passing posteriorly towards the medial temporal lobe, and extends as far as the cortex overlying the amygdala. Its fibres terminate in the **primary olfactory cortex**. The central olfactory pathways feature prominently in Broca's original description of the limbic lobe or 'nostril brain' (Box 1.11).

1.6.2 Primary Olfactory Cortex

The primary olfactory cortex is known as the **piriform cortex** (also spelled **pyriform**). It is composed of three-layered **olfactory allocortex** (**paleocortex**) and receives direct olfactory tract projections. The term 'piriform' derives from carnivores, which have a conspicuous pear-shaped **piriform lobe** (Latin: *pirum*, pear) on the ventral hemispheric surface which receives olfactory afferents (Figure 1.18).

In animals such as the domestic cat, the piriform lobe receives the bulk of olfactory tract projections. However, a contingent of fibres terminates just in front of the piriform lobe, in an area called the **prepiriform cortex**. The portion of the olfactory cortex that lies within the piriform lobe itself is called the **periamygdaloid cortex** because it overlies the amygdala.

In the older literature, the human brain was also said to have 'prepiriform' and 'periamygdaloid' regions,[185] but this makes little sense in the absence of a piriform lobe.[186] In modern terminology, the corresponding olfactory areas in the human brain are referred to as the **frontal piriform cortex** (**PirF**) and **temporal piriform cortex** (**PirT**). These are

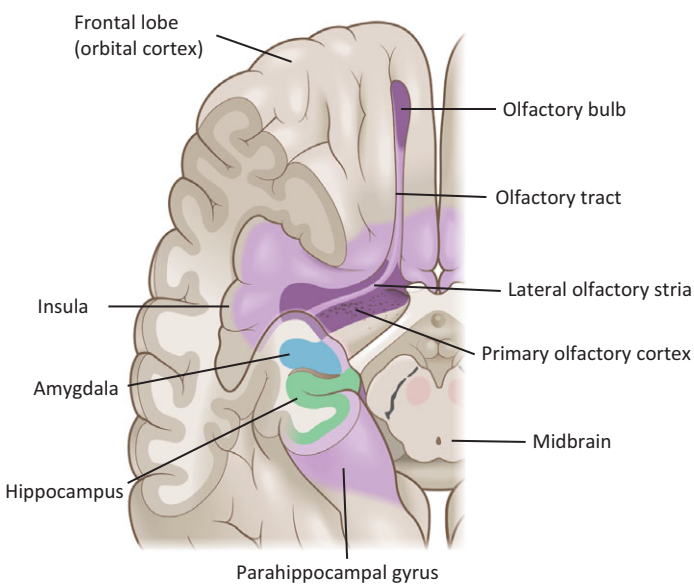

Figure 1.17 View of the basal hemispheric surface with the insula exposed. The olfactory bulb and primary olfactory cortex are shown in dark purple. The magenta areas represent non-neocortical (paralimbic) zones. The hippocampus and amygdala are also indicated, in the medial temporal region.

Box 1.11 Broca's Nostril Brain

The French neurologist and neuroanatomist Paul Pierre Broca is best known for his contribution to language localisation, but he also published a major comparative anatomical study of 17 mammalian species in 1878 in which he provided the first detailed description of the **limbic lobe**.[70]

Broca identified a common **fornicate** (arch-shaped) or **circumannual** (ring-shaped) convolution at the medial border or limbus of the cerebral hemisphere in all mammals. He referred to it as the **greater limbic lobe** (*le grand lobe limbique*), as it transcended normal lobar boundaries, crossing the conventional anatomical borders of the frontal, parietal and temporal lobes.

He noted a prominent input from the **olfactory peduncle** (olfactory tract), likening it to the handle of a tennis racket (the limbic lobe itself representing the head). This is reflected in the obsolete term **rhinencephalon** or 'nostril brain' (Latin: *rhinos*, nose) which became synonymous with the limbic lobe in 19th-century France.[184]

However, it became clear that only a small part of the limbic lobe receives olfactory input and that it is prominent even in species with a poorly developed sense of smell (including **anosmic** mammals, such as the dolphin). Broca doubted that the limbic lobe could be devoted entirely to the sense of smell and, in the human, identified it with **animalistic instincts** (*l'homme brutale*).

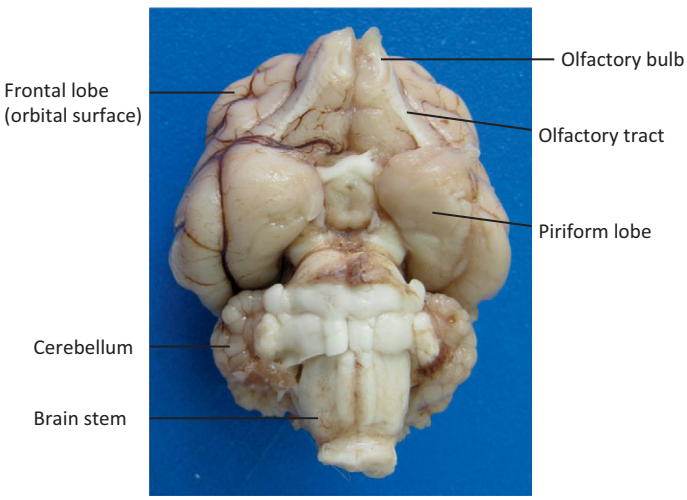

Figure 1.18 Ventral aspect of the domestic cat brain. The pear-shaped piriform (olfactory) lobe is indicated, which receives strong projections from the ipsilateral olfactory bulb and tract. (Courtesy of Professor Brian Summers.)

found in, respectively, the posterior orbitofrontal and medial temporal regions, encroaching on the ventral part of the insula.[187]

In addition to the main fronto-temporal piriform cortex, several other areas receive direct projections from the olfactory tract and are therefore also classified as **primary olfactory cortex** (Figure 1.19). These include the cortical nucleus of the amygdala, periamygdaloid cortex and lateral entorhinal cortex.[188] A potential source of confusion is that any brain region receiving direct olfactory tract fibres (e.g. the periamygdaloid cortex) can be described as 'piriform cortex', meaning 'primary olfactory cortex'. However, only one among them is specifically named *the* piriform cortex (PirF, PirT). This is analogous to the distinction between New York State and New York City.

The olfactory cortex is evolutionarily ancient, representing a phylogenetically conserved **paleocortex**, sharing common characteristics with the three-layered general cortex of reptiles.[189] This presumably accounts for the fact that smell-related afferents gain direct access to the olfactory cortex without passing through a thalamic relay. Nevertheless, a **secondary olfactory area** is present in the posterior orbital region which receives afferents via the mediodorsal nucleus of the thalamus.

1.7 Insula and Claustrum

The **insula** or island of Reil (Latin: *insula*, island) is a triangular cortical region that is hidden within the depths of the lateral sulcus and is not visible from the

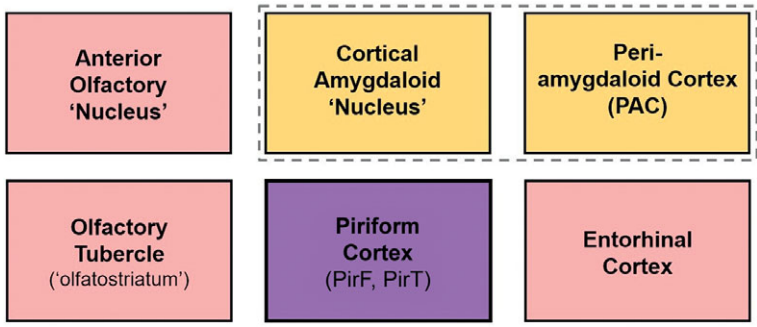

Figure 1.19 Primary olfactory areas in the human brain. Each of these areas receives olfactory tract projections and is therefore regarded as 'piriform' (primary olfactory) cortex, but only one among them is specifically named the piriform cortex. The dashed box indicates areas lying within the amygdala.

external surface of the brain. In order to expose the insula, it is therefore necessary to retract or dissect away the overlying **frontal** and **temporal opercula** of the sylvian fissure (Latin: *operculum*, lid or covering). The **claustrum** is a thin lamina of grey matter that lies immediately beneath the insula. For this reason the insula is sometimes called the claustrocortex.

1.7.1 Insular Lobe

The insula has an approximately triangular profile, with the **apex** lying inferiorly (Figure 1.20). The insula overlies the central core of the cerebral hemisphere which contains the basal ganglia, thalamus and internal capsule. It is demarcated from the frontal, parietal and temporal lobes by the **circular sulcus**. The insular cortex is divided into **anterior** and **posterior insular lobules** by the **central sulcus of the insula**, which passes obliquely downwards and forwards.

The insula resembles a mountain that has been tipped over on its side, with the summit (or apex) projecting laterally. The apex is therefore the most lateral part of the insular lobe and is also the most inferior. The anterior insula lobule consists of three **short gyri** which converge on the apex. The posterior insula contains two or three **long gyri** which have an elongated, finger-like disposition.

When approached from the ventral hemispheric surface, the apex forms a narrow 'entrance' to the insular region which widens out posteriorly and dorsally. For this reason the apex is also known as the **limen** of the insula (Latin: *limen*, entrance or threshold).

Cytoarchitectonic analysis of the insular cortex reveals that its anterior two-thirds is **non-neocortical**, consisting of **dysgranular** and **agranular mesocortex**.[190] These areas have strong connections with other limbic brain structures and have been implicated in visceral, autonomic and nociceptive functions.[191, 192] The posterior third of the insula is neocortical.

1.7.2 Insular Functional Zones

Various lines of converging evidence, including fMRI, functional connectivity analysis and lesion studies, have identified three functional areas within the insula:[191, 193, 194]

- **Ventral anterior insula** (**vAI**)
- **Dorsal anterior insula** (**dAI**)
- **Posterior insula** (**PI**)

1.7.2.1 Ventral Anterior Insula

Activity in the **ventral anterior insula** is associated with emotional experiences and visceral sensation[195–197] including nausea, vomiting and disgust.[198, 199] It is one of several brain regions that responds to **pain**.[200, 201] This is not limited to physical pain but encompasses emotional suffering and distress, including **empathic responses** to pain and discomfort in other people.[98, 202, 203] Attenuation of this response has been documented in **psychopathy**.[204]

The ventral anterior insula shows increased activity during voluntary acts and may contribute to the sense of personal agency or 'free will'.[205, 206] This is often disturbed in patients with schizophrenia, who may experience passivity phenomena, in which they feel that their actions are being controlled by an external force.[207, 208]

1.7.2.2 Dorsal Anterior Insula

The **dorsal anterior insula** borders the dorsolateral prefrontal cortex. It is engaged during higher cognitive functions and is associated with attention, working memory and language.[209–212] It has been noted that patients with expressive aphasia often have lesions that extend beyond Broca's area into the

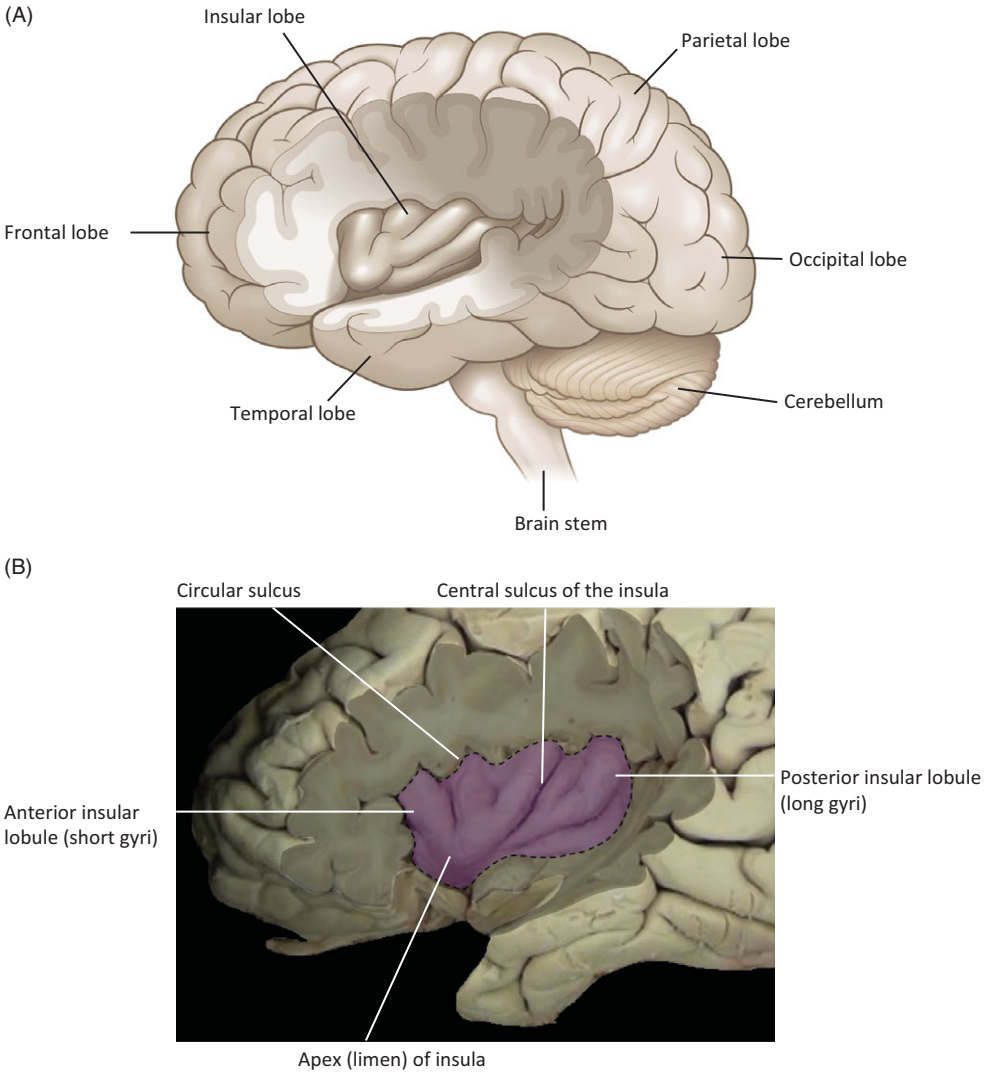

Figure 1.20 The insular lobe. (A) Diagram showing the position of the insula in the left cerebral hemisphere, following removal of the frontal, parietal and temporal opercula that surround the sylvian fissure. (B) Corresponding dissection of the insular region, with the main topographical features indicated.

dorsal insula and adjacent white matter[213, 214] including Broca's original cases, Leborne and LeLong.[215, 216] Furthermore, lesions restricted to Broca's area typically do not produce classic **expressive aphasia**.[217, 218] This raises the possibility that the dorsal insula may be the true site of Broca's expressive language area.

1.7.2.3 Posterior Insula

The **posterior insula** is neocortical. It collects interoceptive and proprioceptive information concerning the current visceral and somatic state of the body, including afferents related to warmth, touch and vestibular sensation.[219] This reflects the activity of the insula as a whole, which seems to gather information relating to **self versus non-self** including the current emotional, cognitive and intentional states.[220–222] It appears that the insula constantly integrates these afferents to create an ever-changing 'snapshot' of the global mental state.[223]

1.7.3 Insular Functions and Role in Psychosis

The insula appears to contribute to a coherent **sense of self**[223] and to the **perception of time**.[224, 225] This

Box 1.12 Neuroanatomy of Schizophrenia

Although schizophrenia is traditionally regarded as a **neurodevelopmental disorder** with both genetic and environmental elements,[233, 234] there is evidence for ongoing **neurodegeneration**. This includes progressive cortical atrophy and enlargement of the cerebral ventricles.[235]

However, the presence of a degenerative component is contested, and the effects of **antipsychotic medication** may be a confounding factor. For instance, observed changes in the size of the thalami (decreased) and caudate nuclei (increased) may be secondary to neuroleptic exposure.[236] It is also likely that schizophrenia is a heterogeneous group of disorders rather than a single entity with a common aetiology, pathophysiology and anatomy.[237]

Nevertheless, several structural abnormalities have consistently been described in treatment-naïve patients.[238, 239] These include an overall reduction in **brain size** and **grey matter volume**, together with a more modest loss of hemispheric white matter and thinning of the corpus callosum. Reduced cortical thickness is particularly evident in the **cingulate gyrus**, **fronto-temporal region** and **insula**. There is also a more general reduction in the size of the **temporal lobes** and **hippocampus**, especially in the left hemisphere. In keeping with a putative neurodevelopmental origin, studies have reported abnormalities of **cortical folding** (reduced gyrification, abnormal sulcation)[240] and loss of normal hemispheric asymmetry (e.g. of the cingulate gyrus and planum temporale, discussed earlier).

Several studies have reported structural or functional abnormalities of the insular lobe, including a report of monozygotic twins who are discordant for schizophrenia. This showed bilateral **reduction of insular volume** in the affected twin.[241] Insular abnormalities appear to be specifically associated with **positive symptoms** including hallucinations, delusions and somatoparaphrenia (the belief that a body part belongs to someone else).[242] Abnormal insular responses have also been observed during self-generated motor tasks,[243, 244] imagined first-person speech[245] and in patients who struggle to recognise themselves in photographs or in the mirror.[246] Many of these findings are consistent with disturbance of the ability to distinguish between self and non-self.

view is supported by accounts from patients with so-called **ecstatic seizures** caused by ictal activity in the anterior insula.[226, 227] Ecstatic seizures are typically preceded by an aura characterised by blissful **mental clarity** and **heightened sense of self**, together with altered **time perception** (time dilation). Another feature of ecstatic seizures is a sense of **absolute certainty**, which has implications for belief formation and **delusional thinking**.[228]

Various structural and functional abnormalities of the insula have been documented in patients with **schizophrenia** and other psychoses.[229-231] This may account for some of the core features such as fixed false beliefs, misattribution of self, passivity phenomena and distorted time perception. For instance, auditory hallucinations might represent a failure of the insula to 'tag' normal internal mental dialogue as egocentric, so that it is incorrectly attributed to an external source.[232] The insula lobe is one of several brain regions that have been found to show structural and functional abnormalities in schizophrenia (Box 1.12).

1.7.4 Claustrum

The claustrum is a thin lamina of grey matter underlying the insular lobe. It is sandwiched between two layers of white matter: the **extreme capsule** on its outer aspect and the **external capsule** medially (Latin: *claustrum*, enclosed; as in claustrophobic) (Figure 1.21).

The claustrum is present in all mammals and has a homogenous, non-laminated architecture. The **dorsal claustrum** forms neocortical connections, whilst the **ventral claustrum** blends with the amygdala and communicates with limbic brain areas. The claustrum is reciprocally connected to all parts of the cerebral cortex, with each cortical region projecting to the nearest portion. Furthermore, any two cortical areas that are strongly interconnected converge on a common point in the claustrum. Interhemispheric fibres link the left and right claustrum across the midline, via the anterior commissure.[247]

The function of the claustrum is uncertain. However, based on its architecture and connectivity, it has been postulated to play a role in **conscious awareness** by helping to synchronise disparate neuronal processes. It has therefore been proposed to act, as it were, like the conductor in a neural orchestra.[248] As such, it has been offered as a solution to the so-called **binding problem** in neuroscience.[249] This refers to the paradox that various properties of a stimulus (e.g. shape, colour, movement) are analysed in different parts of the brain, and at different speeds, yet are experienced as a single unified percept.

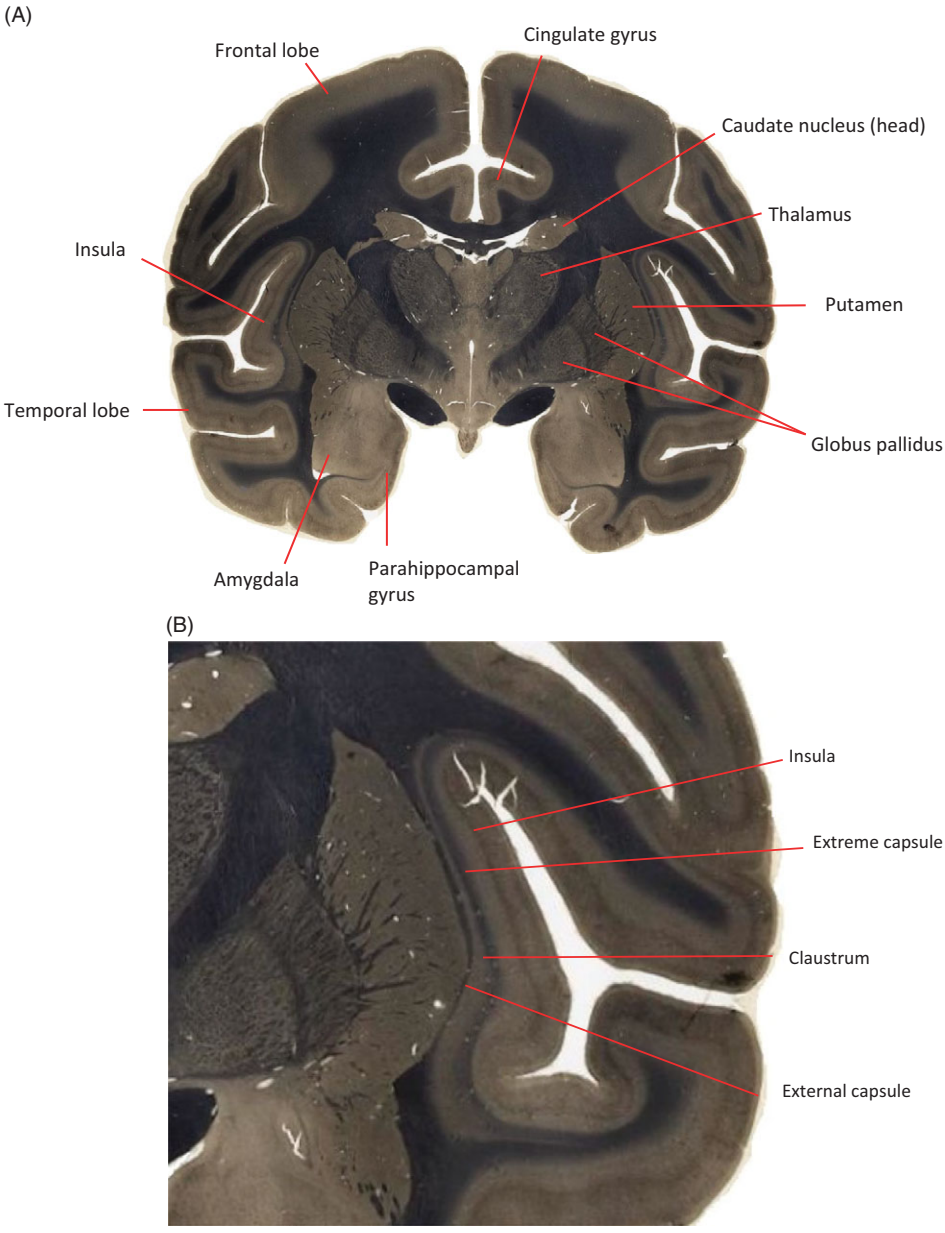

Figure 1.21 (A–B) Coronal section of a Rhesus monkey brain. Both images show a Weil-Myelin stain in which white matter appears black and the cerebral cortex and subcortical nuclei appear grey. The claustrum can be seen between the external and extreme capsules. (Images courtesy of NeuroScience Associates, Knoxville, TN.)

1.8 Orbitomedial Prefrontal Cortex

The **orbitomedial prefrontal cortex** (**omPFC**) is the part of the prefrontal region that is of most relevance to neuropsychiatric disorders. The **prefrontal cortex** as a whole is the extensive portion of the frontal lobe that lies anterior to the motor and premotor areas and is involved in personality, social interactions and cognitive-executive functions (Figure 1.22).

1.8.1 Overview of the Prefrontal Region

The prefrontal cortex incorporates 11 Brodmann areas (**BA8–14** and **BA44–47**)[250] and is extensive in

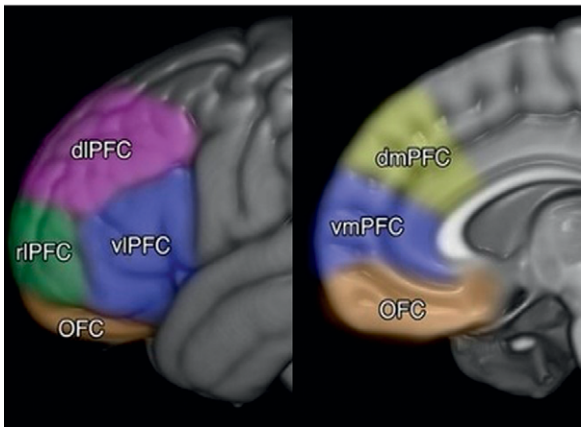

Figure 1.22 The prefrontal cortex. (A) The lateral prefrontal region includes the dorsolateral and ventrolateral prefrontal cortex (dlPFC, vlPFC), together with part of the rostrolateral prefrontal cortex (rlPFC) at the anterior pole of the frontal lobe. The orbitofrontal cortex (OFC) can also be seen in this view. (B) The medial prefrontal region includes the dorsomedial and ventromedial prefrontal cortex (dmPFC, vmPFC), lying above the orbital cortex on the medial aspect of the frontal lobe. Image modified from Clark I and Dumas G (2016) The Regulation of Task Performance: A Trans-Disciplinary Review. *Front. Psychol.* 6:1862. doi: 10.3389/fpsyg.2015.01862 under a CC-BY licence.

the human brain, accounting for 30% of the cortical surface area. It has no specific gyral or sulcal boundaries but can be defined by its connectivity with the **mediodorsal nucleus** of the thalamus, which is useful for identifying the homologous area in experimental animals.

The prefrontal region is described as the **frontal granular cortex**. This refers to the fact that, in contrast to the motor/premotor areas, it has a well-defined internal granule cell layer (layer IV). In electrical stimulation studies, it is the part of the frontal lobe that does not elicit movement. The prefrontal cortex is divided into orbital, medial and lateral regions, corresponding to the three surfaces of the frontal lobe.

1.8.1.1 Orbitomedial and Lateral Prefrontal Regions

The orbitomedial prefrontal cortex consists of the **orbitofrontal cortex** (**OFC**) together with the **medial prefrontal cortex** (**mPFC**). The orbital and medial prefrontal cortices are strongly connected with limbic brain regions (e.g. anterior cingulate cortex, amygdala) and are concerned more with behavioural and emotional responses rather than cognition.

The lateral prefrontal region occupies the hemispheric convexity. It is divided into the **dorsolateral prefrontal cortex** (**DLPFC**) and **ventrolateral prefrontal cortex** (**VLPFC**). The latter corresponds to the inferior frontal gyrus and includes Broca's expressive language area. The lateral prefrontal region is concerned with organising and planning behaviour in pursuit of short-, medium- and long-term goals.

1.8.1.2 Functions of the Prefrontal Region

The overall role of the prefrontal cortex can be summarised as **goal-directed behaviour**. This has cognitive, behavioural, social and emotional aspects.

Personality and Behaviour

The contributions of the prefrontal region to **personality** and **behaviour** are illustrated by the famous case history of railroad construction worker Phineas Gage who in 1848 suffered permanent personality change following the passage of an iron bar through the front of his skull.[251] Characteristic features of anterior frontal lobe injury include **behavioural disinhibition**, with impulsivity and risk-taking behaviour, together with disturbance of **executive functions** including working memory, attention, planning, judgement, problem-solving and decision-making. There may also be mood-related changes such as **apathy**, **depression** or **behavioural inertia**.

Attention and Divided Attention

All parts of the prefrontal region contribute to **attention**. The object or **focus** of attention is determined by the dorsolateral prefrontal cortex. This region includes the **frontal eye fields** (**BA8**) which control voluntary gaze and are also concerned with both overt and covert attention. The frontal eye fields communicate with the **posterior parietal cortex** (**BA7**) via the superior longitudinal fasciculus, constituting the core of the **dorsal attention network**. The orbital cortex helps to sustain focus by **inhibiting distractions**, whilst the medial prefrontal cortex provides the **motivational drive** to pay attention to something in the first place. Prefrontal cortex dysfunction may therefore be associated with poor focus, distractibility or lack of motivation, and may underlie some forms of **attention deficit hyperactivity disorder** (**ADHD**).[252]

The **rostrolateral prefrontal cortex** (**BA10**) is the largest component of the prefrontal cortex and the most extensive cytoarchitectonic zone in the human brain. It corresponds to the **frontal polar region** at the anterior extreme of the frontal lobe. The

rostrolateral prefrontal cortex forms reciprocal connections with **multimodal association cortices** (mainly within the frontal lobe) that receive and integrate information from disparate brain regions. Its precise functions are obscure, but it appears to be involved in **executive control** including aspects of **attention** and **working memory**.

A core function of BA10 appears to be the **flexible allocation** of **cognitive resources** (e.g. dividing attention when multitasking or engaging in a complex activity with several elements). It includes the ability to switch back and forth between mental processes and to hold in mind as 'pending' those that are not the current focus of attention. This capacity has been referred to as **cognitive branching**.[253]

Social Cognition

An important aspect of goal-directed behaviour is **social cognition**. This is the ability to interact effectively with other people within a social group: to form friendships and alliances, to understand the intentions of others and to predict their actions. In some cases it may involve manipulating, deceiving or lying to other people in order to achieve a desired outcome. The importance of the prefrontal cortex in social cognition is evidenced by its role in **autism** (Box 1.13), in which frontal and prefrontal abnormalities have consistently been described.[254]

1.8.2 Orbitofrontal Cortex

The **orbitofrontal** (or **orbital**) **cortex** corresponds to the ventral or inferior surface of the frontal lobe, which overlies the orbital cavities. In clinical practice, damage or disease affecting the orbital region is often associated with **behavioural disinhibition** (e.g. inappropriate behaviour, lack of restraint).

1.8.2.1 Topography of the Orbital Region

The **orbital cortex** (Figure 1.23) is divided into two parts by the **olfactory sulcus**. This is a deep furrow that runs in an anteroposterior direction along the orbital region, close to the midline. It contains the olfactory bulb and tract. The **gyrus rectus** (Latin:

Box 1.13 Autism Spectrum Disorder

Autism or **autism spectrum disorder** (**ASD**) is a heterogenous group of neurodevelopmental conditions characterised by a persistent disturbance of **social communication** and **interactions**.[255] There are typically stereotyped behaviours, restricted activities and interests,[256] rigidity and obsessive traits. The overall prevalence is around 1–3% and is three to four times more common in males.[257]

The first systematic description of childhood autism was provided by the Ukrainian psychiatrist Leo Kanner in 1943.[258] The name 'autism' (Greek: *autós*, self) reflects a fundamentally **egocentric disposition**, such that an autistic child may appear disconnected from their social environment and show little interest in those around him or her. A core feature is the inability to understand the thoughts and feelings of other people or to imagine the world from someone else's perspective. This capacity is known as **theory of mind** (**ToM**).

The most severe cases are profoundly debilitating, with little or no meaningful communication. **Intellectual disability** (defined as an IQ below 70) is found in around a third of those affected. At the other end of the spectrum, so-called **high-functioning autism** or **Asperger's syndrome**, individuals have a normal or above-average IQ and may function well in society if they are able to compensate for their social and communication difficulties.[259]

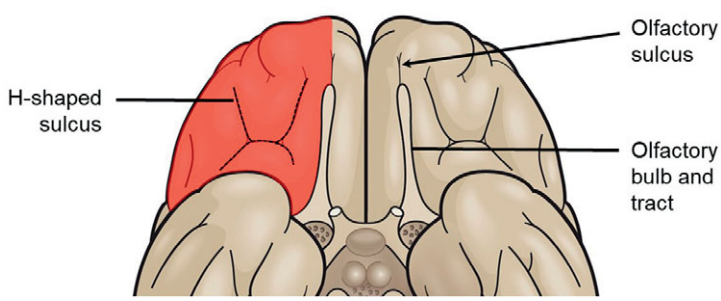

Figure 1.23 The orbital region. The majority of the orbitofrontal cortex is represented by the lateral orbital cortex (*red*), which contains an H-shaped sulcus. The small portion that lies medial to the olfactory sulcus is the gyrus rectus.

Box 1.14 Cytoarchitectonics of the Orbital Region

In Brodmann's 1909 cytoarchitectonic map, the orbital region was divided into two parts: **anterior** (**BA11**) and **posterior** (**BA47**).[62] However, the original BA47 was a large heterogenous cortical zone occupying the posterior orbital region and extending to the orbital part of the **inferior frontal gyrus**. Although it was known to be heterogeneous, it was not further subdivided.

The posterior orbital region was subsequently parcellated by the Canadian neurosurgeon Earl Walker in the macaque. Walker identified three orbital regions, from lateral to medial (**BA12, 13, 14**). The lateral orbital area BA12 has a prominent granule cell layer and is therefore neocortical, whilst BA13 and BA14 are non-neocortical.

BA12 in the orbital region of the macaque corresponds to a portion of Brodmann's original area 47 in the human. In particular, the part that occupies the lateral orbital cortex and extends to the pars orbitalis of the inferior frontal gyrus. Accordingly, this region is referred to as **BA47/12** in the human brain.[262] The remainder of the orbital region is labelled as in the macaque (i.e. BA13, BA14), which facilitates comparison between humans and non-human primates.

rectus, straight) is a thin strip of cortex that is medial to the olfactory sulcus, whilst the remainder of the orbital region is known as the **lateral orbital cortex**.

The lateral orbital cortex contains an H-shaped **orbital sulcus** that divides it into **anterior**, **posterior**, **medial** and **lateral orbital gyri**. It is formed by the **medial** and **lateral orbital sulci**, connected by a **transverse orbital sulcus**, which completes the H-shape. The orbital sulcal pattern is highly variable and may resemble a capital letter K or X, often with detachment of one or more sulcal branches. A classic H-shaped configuration is found in about 30% of hemispheres,[260] and certain variants have been associated with particular neuropsychiatric disorders such as schizophrenia.[261] The cytoarchitectonic divisions of the orbital region are discussed in Box 1.14.

1.8.2.2 Functions of the Orbital Region

The **orbital cortex** receives afferents concerned with the chemical senses of smell (**olfaction**) and taste (**gustation**). It contains a **secondary olfactory cortex** which receives projections from the **piriform cortex** (PirF, PirT) and the other primary olfactory areas. It helps to regulate **appetitive drives** and **reward-seeking behaviours** (e.g. for food, water and sex) which, in animals with smaller and less complex brains, are heavily dependent on the sense of smell.

The **posterior orbital cortex** receives multimodal projections from disparate cortical areas concerning various aspects of a stimulus (e.g. the smell, taste and appearance of food) and integrates this information to determine its **hedonic value** (anticipated reward).[263, 264] However, the reward value of a stimulus is context dependent. For instance, a large meal may have substantial hedonic value to someone who is hungry but low hedonic value to an individual who has just eaten.

Imaging studies have shown that the transition from hunger, to satiety, to excess, is associated with a progressive shift in activity from the left to the right orbital cortex. This is attended by a gradually increasing 'cloying' sensation that prevents overindulgence, and is ultimately replaced by nausea and disgust.[265] This may explain the observation that patients with severe orbital atrophy due to the behavioural variant of **frontotemporal dementia** often have a 'sweet tooth' and tend to eat excessively.[266]

The orbital cortex also contributes to normal **social interactions** by facilitating tact, restraint and consideration for others (what might be referred to as 'good manners'). Of note, it is particularly sensitive to alcohol. **Frontal disinhibition** due to orbital pathology therefore has many features in common with states of intoxication. These may include sexual inappropriateness, selfishness, poor judgement, impulsivity, aggression and inability to delay gratification.

1.8.3 Medial Prefrontal Cortex

The **medial prefrontal region** is the medial part of the frontal lobe that lies anterior to the motor and premotor areas and excludes the cingulate gyrus (of the limbic lobe). It incorporates parts of Brodmann areas 9–11. The medial frontal region receives projections from the orbital cortex and provides efferents to **autonomic effector structures** such as the hypothalamus and midbrain.[267] Functional neuroimaging

studies suggest that the medial prefrontal cortex can be divided into a dorsal **cognitive-executive** region and a ventral **emotional-affective** zone.[268]

The medial frontal region is active during **self-referential tasks** and is particularly associated with **inwardly directed** (or **egocentric**) mental states. It forms part of the **default mode network** of the brain (together with the posterior cingulate cortex, precuneus and inferior parietal lobe) which includes areas that show high baseline metabolic activity.[268] The default mode network is most active when subjects are absorbed in thought, daydreaming or concentrating on a cognitive task, rather than engaging with the outside world.

The posterior part of the medial prefrontal cortex is known as the **pre-SMA** because it lies just in front of the **supplementary motor area** or **SMA**. The pre-SMA also contributes to voluntary motor control (including speech production) but has a more abstract or cognitive role. Unlike the SMA proper, it is not directly involved in movement initiation, but is instead engaged when a choice must be made between conflicting courses of action.[269]

1.8.4 Ventromedial Prefrontal Cortex

The term **ventromedial prefrontal cortex** (or **VMPFC**) is used to describe the inferior portion of the medial prefrontal cortex, together with the medial part of the orbitofrontal cortex. This region forms strong reciprocal connections with the amygdala, septal area and parahippocampal gyrus and also provides afferents to the ventral striatum.

Taken as a whole, the ventromedial prefrontal cortex appears to be important for **decision-making**[270–272] and **moral judgements**.[273, 274] This reflects the view that decisions are often based on 'gut feeling' rather than objective, rational assessment of the available options, which has been referred to as the **somatic marker hypothesis**.[275, 276]

The ability to make decisions based on emotional responses to imagined or hypothetical courses of action is often disturbed in patients with frontal brain lesions. For instance, it has been shown that individuals with ventromedial prefrontal damage tend to have a more **utilitarian** approach to **ethical decision-making** and demonstrate a greater readiness to sacrifice the needs of others to serve the greater good.[277, 278]

The prefrontal region shows **delayed maturation** (including myelination) and undergoes an extended period of **synaptic pruning**, such that it is not fully developed until at least the mid-20s.[279] This may explain some of the challenging behaviours seen in children and adolescents. It might also account for the capacity of certain environmental factors (e.g. cannabis) to modify the risk for psychiatric disorders such as schizophrenia, by acting at a vulnerable period in frontal brain development.[280]

A summary of clinical features associated with dysfunction of the main parts of the prefrontal cortex is provided in Table 1.3.

Table 1.3 Clinical features of prefrontal cortex syndromes

Cognitive deficits (dorsolateral prefrontal cortex, DLPFC)
- loss of abstract categorical thought (e.g. concrete interpretation of analogies, proverbs, metaphors)
- indecisiveness, poor concentration, forgetfulness
- inability to plan ahead or cope with multiple tasks at once
- repetition of thoughts or actions (perseveration)
- attentional deficit due to lack of focus
Behavioural changes (orbitofrontal cortex, OFC)
- behavioural disinhibition (e.g. inappropriate jocularity or sexual behaviour)
- impulsiveness, rash and aggressive behaviour
- inability to delay gratification
- lack of insight and foresight, apparent unconcern
- attentional deficit due to distractibility
Emotional effects (medial prefrontal cortex, mPFC)
- apathy, depression, anhedonia (dominant hemisphere)
- pleasant indifference, elation or hypomania (non-dominant hemisphere)
- reduced empathy and compassion (callous, unemotional behaviour)
- loss of initiative, motivation and spontaneous speech (abulia)
- attentional deficit due to lack of motivation

1.9 Amygdala and Septal Area

The **amygdala** is the main subcortical structure associated with emotion. It has strong reciprocal connections with the **septal area**, which is sometimes referred to as the 'pleasure centre' of the brain.

The amygdala is an almond-shaped nuclear group in the anterior part of the medial temporal lobe (Greek: *amygdalē*, almond). It lies just in front of the hippocampus, close to the temporal pole.

1.9.1 Parts of the Amygdala (Figure 1.24)

The amygdala blends with the medial temporal cortex and is described as **corticoid** because many of its nuclei have a laminated, cortical-type architecture. The amygdala consists of 13 subnuclei, arranged in three groups:

- The **basolateral division** is the largest region in the human brain and includes the lateral, basal and accessory basal nuclei. It receives strong projections from audiovisual association areas.
- The **cortical nucleus** receives afferents from the olfactory tract and is particularly important in animals with an acute sense of smell.
- The **centromedial division** consists of the central and medial nuclei and is the main efferent station of the amygdala. Targets include the hypothalamus, septal area and rostral midbrain.

Although the amygdala is involved in all types of emotional response, it is particularly important in situations that elicit anxiety, fear or rage. It has strong projections to the **hypothalamus**, by which it elicits emotional reactions such as the 'fight or flight' response (including behavioural, autonomic and endocrine components). The nuclear divisions of the amygdala are discussed in Box 1.15.

1.9.2 Amygdala Afferents and Efferents

The connections of the amygdala are markedly asymmetric. It receives afferents from a relatively small number of brain regions but provides efferent projections to the majority of cortical and subcortical structures.

1.9.2.1 Cortical Afferents

The predominant input streams to the amygdala are **olfactory** and **fronto-temporal**. The olfactory tract projects to the **cortical nucleus** and **periamygdaloid cortex**, which both consist of olfactory paleocortex. In the human brain, the major non-olfactory afferents come from **auditory** and **visual association areas** and from the **orbitomedial prefrontal cortex**. These project chiefly to the basolateral nuclear group. There are also inputs from the cingulate gyrus, anterior insula, parahippocampal regions, thalamus and diffuse neuromodulatory systems.

The **lateral nucleus** is the main input station in the human brain. The most prominent projections derive from the **ventral visual stream** (or 'what' pathway) and the **lateral temporal neocortex**, which are concerned with object recognition and semantic categorisation (for instance, signalling the presence of a venomous spider or armed assailant). Input from the **prefrontal cortex** provides a 'top-down' influence that is able to suppress inappropriate emotional reactions: for instance, inhibiting a fight-or-flight response when encountering a snake in a safe environment such as a pet shop or zoo.

1.9.2.2 Efferent Pathways

The amygdala has two named outflow pathways: the stria terminalis and ventral amygdalofugal pathway. The **stria terminalis** (Figure 1.25) is a slender bundle that arises from the posterior amygdala and runs in company with the tail of the caudate nucleus in the lateral ventricle. It comes to lie in the groove between the caudate nucleus and thalamus, before terminating in the septal area, preoptic region, anterior hypothalamus, ventral striatum and rostral midbrain.

The **ventral amygdalofugal pathway** emerges from the anterior amygdala and passes medially through the basal forebrain (below the basal ganglia) to reach similar targets as the stria terminalis. However, the majority of amygdala connections travel through neither bundle, but instead pass diffusely through the hemispheric white matter.

The efferent projections of the amygdala are much more extensive, targeting the majority of cortical and subcortical regions. As observed by the English behavioural neurologist Michael Trimble, 'when the amygdala speaks, the entire brain listens'.[79] This presumably reflects the powerful capacity for emotional states to influence cognition, behaviour, attention and perception.

1.9.3 The Extended Amygdala

The **centro-medial amygdala** is in anatomical continuity with the **bed nucleus of the stria terminalis** via discontinuous cell groups in the basal forebrain.[79] Furthermore, the centromedial and bed nuclei share a common microscopic structure and neurochemistry. This differs from the rest of the amygdala and instead resembles the **striatum**, characterised by the presence of GABAergic medium spiny neurons.

The centromedial and bed nuclei are therefore grouped together as the **extended amygdala** which forms a distinct structural-functional unit (Figure 1.26). The extended amygdala is a striatal-

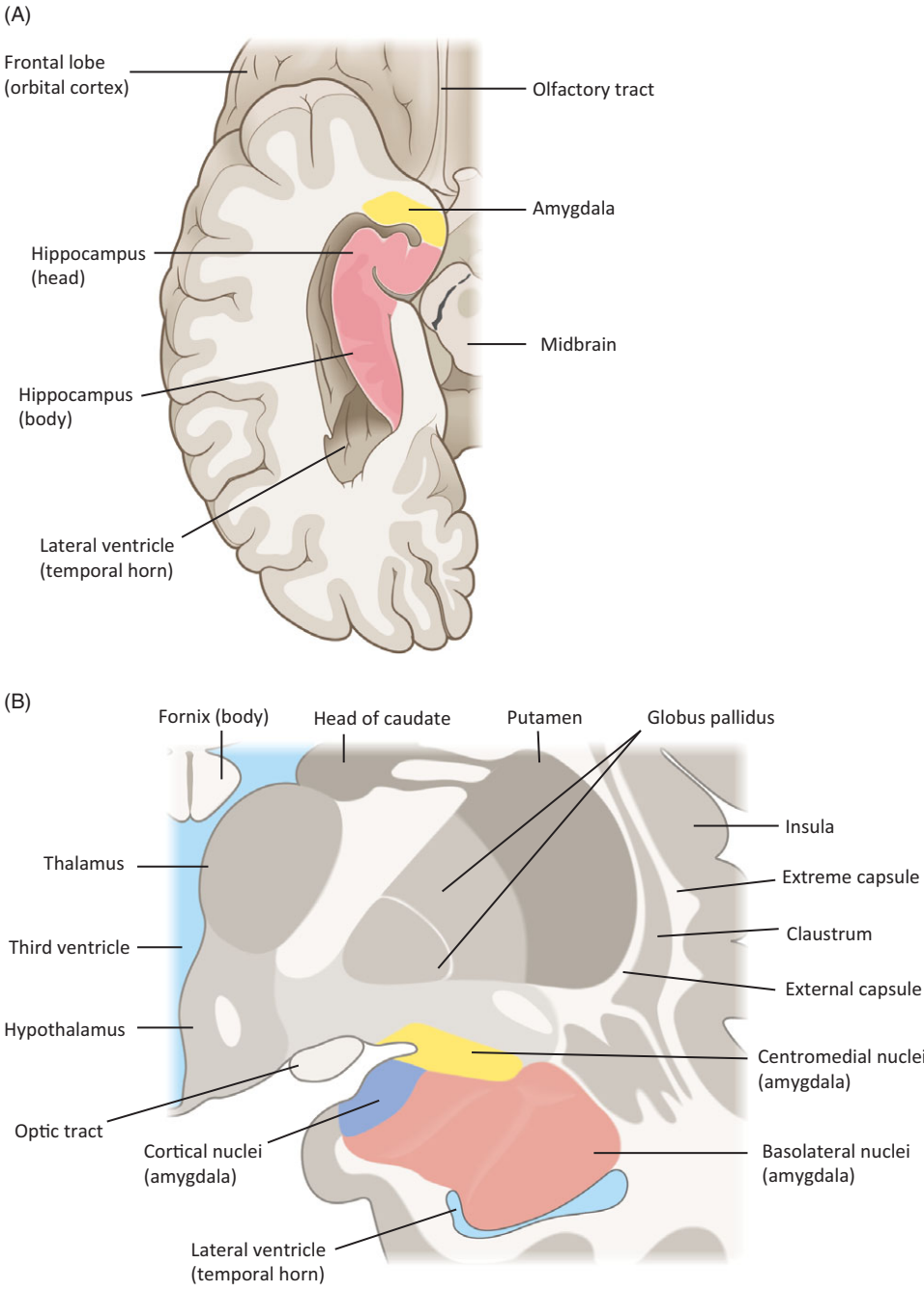

Figure 1.24 The amygdala. (A) This is an axial section of the cerebral hemisphere showing the position of the amygdala (*yellow*) in the medial temporal region, just anterior to the hippocampus (*red*). (B) Diagram showing the amygdala and its main subnuclei, in coronal section. Note its position, just inferior to the basal ganglia, in the medial temporal lobe.

like basal forebrain mechanism for inhibiting and releasing **emotional behaviours** orchestrated by the hypothalamus. The remainder of the amygdala is cortex-like, rather than striatal, and can be regarded as belonging to the limbic lobe.[79] The amygdala therefore has three functional domains: **olfactory** (cortical nucleus), **neocortical/fronto-temporal** (basolateral complex) and **striatal** (extended amygdala).[284]

Box 1.15 Nuclear groups of the Amygdala

The term 'amygdala' was first used by the German physiologist and anatomist Karl Burdach in 1819 who referred to it as the **corpus amygdaloideum** or almond-like body.[281] However, he was describing what would now be called the **basolateral nuclear group**; in other words, the portion that is most conspicuous in the human brain.

In the 1920s, the American neuroanatomist John Black Johnson undertook a comparative anatomical study of the amygdala and divided it into three regions: **basolateral**, **cortical** and **centromedial**.[282] He noted that the centromedial group is continuous with the **bed nucleus of the stria terminalis** and has the same structure and neurochemistry. The bed nucleus lies close to the midline overlying the anterior commissure, just below and medial to the head of the caudate nucleus. It belongs to what is now called the **extended amygdala**, which also includes the centromedial nuclei.

The German anatomist Harold Brockhaus parcellated the amygdala into more than 30 areas but recognised a major division into deep and superficial portions.[283] He referred to the deep part as the **amygdaleum proprium** ('amygdala proper') which corresponded to Burdach's corpus amygdaloideum and Johnson's basolateral complex. This was distinguished from the superficial part, which he called the **supraamygdaleum.** This consists of the centromedial and cortical nuclei, which lie above the basolateral nucleus (Latin: *supra*, above).

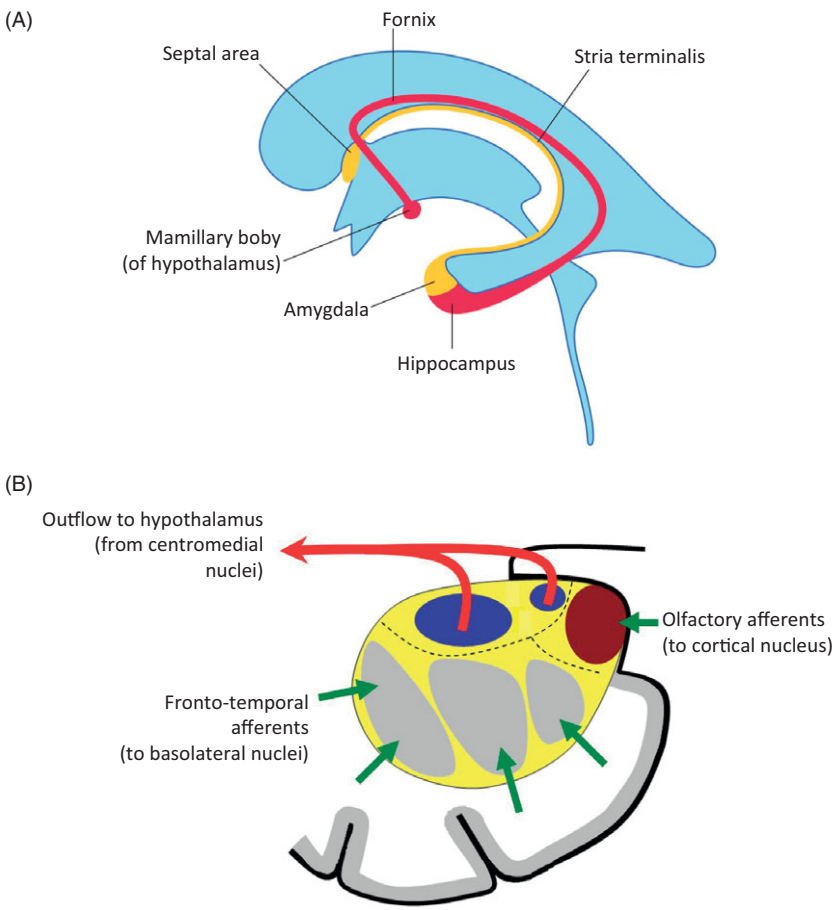

Figure 1.25 Amygdala and hippocampus. (A) The stria terminalis (of the amygdala) and the fornix (of the hippocampus) both follow a C-shaped pathway through the cerebral hemisphere and have similar targets. (B) The main outflow of the amygdala arises from the centromedial nuclei (*blue*) and projects strongly to the hypothalamus and septal area, via the stria terminalis.

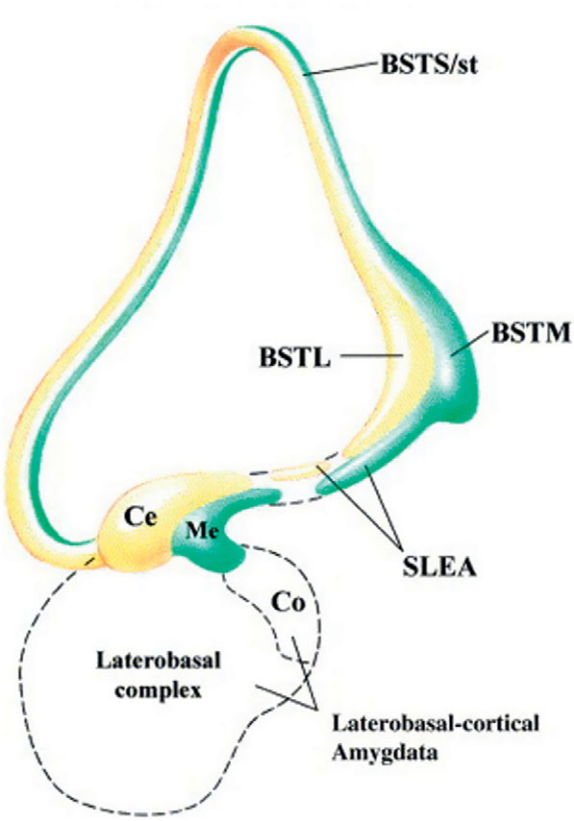

Figure 1.26 The extended amygdala. The centromedial nuclei of the amygdala (Ce, Me) are in anatomical continuity with the bed nucleus of the stria terminalis (BSTL, BSTM) via the sublenticular extended amygdala (SLEA) which passes beneath the basal **ganglia**, and have similar anatomical connections and functions. (Courtesy of Professor Michael Trimble.)

It was initially thought that the **centromedial nuclei** provide a rapid, short-term or phasic response to threat, characterised by **acute fear**, whilst the **bed nucleus** was responsible for slower but longer-lasting tonic **anxiety states**. Subsequent imaging studies with superior spatial resolution suggest that both components of the extended amygdala are responsible for **acute fear** and **long-term anxiety**.[285]

1.9.4 Functions of the Amygdala

The amygdala is responsible for evaluating the **emotional significance** of events, especially those that are potentially harmful. As such, it has been described as a **danger detector** that elicits emotional responses to perceived threat. It is also important for normal **social interactions** and emotion-related **implicit learning**.

1.9.4.1 Response to Threat

The role of the amygdala in the response to **overt threat** is illuminated by studies in people with **Urbach-Wiethe disease**.[286] This is a very rare autosomal dominant condition in which there is marked degeneration of the amygdala in two-thirds of cases. Features include **reduced emotionality**, **fearlessness** and **reckless behaviour**. Patients also lack the normal sense of **personal space**, reporting that close proximity to other people does not make them feel uneasy.[287]

Despite the absence of a functioning amygdala and no previous experience of fear, it is nevertheless possible to induce panic attacks in these patients. This has been achieved experimentally by administering air enriched with carbon dioxide, mimicking suffocation.[288] These results imply that the amygdala responds specifically to **environmental threat** (primarily via auditory and visual modalities) and is not simply the anatomical locus for all fear responses.

The role of the amygdala in the assessment and reaction to overt threat contrasts with that of the **lateral orbital loop** of the basal ganglia. This passes through the head of the **caudate nucleus** and is hyperactive in **obsessive-compulsive disorder**. It appears to be concerned with the identification of **hidden dangers** and **potential risks** (e.g. invisible contaminants, undiagnosed disease). Hyperactivity in the lateral orbital loop is associated with habitual checking for the presence of **covert threat**.[289]

1.9.4.2 Facilitating Social Interactions

The role of the amygdala in **social interactions** is highlighted by lesion studies in non-human primates. These have shown rapid loss of position in the social hierarchy (e.g. alpha status) following ablation of the amygdala. This is presumably due to difficulties reading the behaviour and intentions of other troop members.[290, 291]

The amygdala responds to **emotional facial expressions** and **body language**. This contributes to the ability to 'read' other people and work out their intentions (e.g. friendly, sexually receptive, dishonest, aggressive). Amygdala dysfunction may therefore lead to problems recognising emotions and understanding what other people are thinking or feeling, which has obvious implications for individuals with autism spectrum disorder (Box 1.16).

The amygdala is also implicated in **anger** and **rage**. Aggressive behaviours may be initiated by the amygdala in response to provocation but can be suppressed by the prefrontal cortex. This pathway is

regulated by **serotonin**, and reduced serotonin levels have been implicated in **inappropriate aggression**, **rage** and **impulsivity**. This may occur in isolation or in the context of other neuropsychiatric or personality disorders.[292]

Box 1.16 Neuroanatomy of Autism

Autism is regarded as a neurodevelopmental disorder with a complex aetiology that involves both genetic and environmental elements. The latter may include vascular, viral or autoimmune insults during critical phases of brain development. It is a heterogenous group of disorders with overlapping clinical features, which helps to explain the conflicting reports of structural brain changes. However, abnormalities have consistently been described in the cerebellum, amygdala and prefrontal cortex.

The **cerebellum** and its connections with the cerebral cortex are particularly implicated, evidenced by the near-universal presence of ASD in patients with **agenesis of the cerebellum**.[293] There are also numerous reports of cerebellar **Purkinje cell loss** in autism,[294, 295] and features of ASD have been documented following cerebellar injury.[38]

A number of studies have reported structural abnormalities of the **amygdala**[296–299] and abnormal responses to **emotional facial expressions**.[300–303] These findings are in keeping with the observation that individuals with ASD find it difficult to understand what other people are thinking and feeling.

Evidence of abnormal **frontal lobe growth trajectory** is another consistent finding. There have been numerous reports (including longitudinal MRI and post-mortem studies) of an initial increase in the growth and thickness of the frontal cortex, followed by a subsequent reduction in frontal lobe size.[304] There is also evidence of abnormal cortical lamination, suggesting defects in the process of neurogenesis, migration and cortical development.[305]

1.9.4.3 Implicit Learning

The amygdala is one of several brain regions (including the hippocampus) that shows significant **synaptic plasticity** in adulthood and contributes to memory and learning. The amygdala is particularly implicated in emotion-related **implicit learning**. An example is **fear conditioning**, in which a neutral stimulus is paired with an aversive stimulus.[306]

For instance, provided that the amygdala is intact, patients with dense temporal lobe amnesia can be conditioned to avoid shaking hands by repeatedly administering electric shocks via a concealed hand buzzer. They have no explicit memory of the electric shocks and are unable to account for the aversion, but may confabulate a plausible explanation.[307]

Another example is seen in people who develop anterograde amnesia in early life and survive into old age (for instance, the well-known patients HM and Clive Wearing).[308–310] Having no recollection of the past 30 or 40 years, they are unsurprisingly horrified when confronted with the elderly appearance of their reflections. The experience itself is quickly forgotten but over time may lead to the development of a **mirror phobia** that the patient is unable to explain.[311]

Strong projections from the amygdala to the hippocampus facilitate **emotionally salient** episodic memories. This is particularly evident for events that are potentially harmful (e.g. mugging, sexual assault, combat situations) so that the individual remembers exactly where and when the threat occurred, in vivid detail. This may partially account for the phenomenon of **flashbulb memory** that is sometimes seen in **post-traumatic stress disorder (PTSD)**.[312, 313]

1.9.5 Septal Area

In animals such as the domestic dog, the **septal area** consists of a substantial column of nuclei on either side of the midline in the frontal region, between the lateral ventricles (Figure 1.27). In the human brain, the equivalent area is occupied by a semi-transparent membrane, the **septum pellucidum**, whilst the septal area itself is displaced downwards and forwards, in front of the anterior commissure. It is thus referred to as the **precommissural septum**.

On a midsagittal section of the human brain, the septal area is represented by a very small region just in front of the **lamina terminalis**, a thin sheet of tissue forming the anterior wall of the **third ventricle**. It occupies the crescent-shaped **paraterminal gyrus**. This is a tiny region that is immediately inferior to the genu of the corpus callosum and posterior to the subgenual area of the cingulate gyrus. The septal area consists of the cholinergic **medial** and **lateral septal nuclei**.

In humans and experimental animals, electrical stimulation or self-stimulation of the septal area produces feelings of pleasure, contentment or sexual arousal,

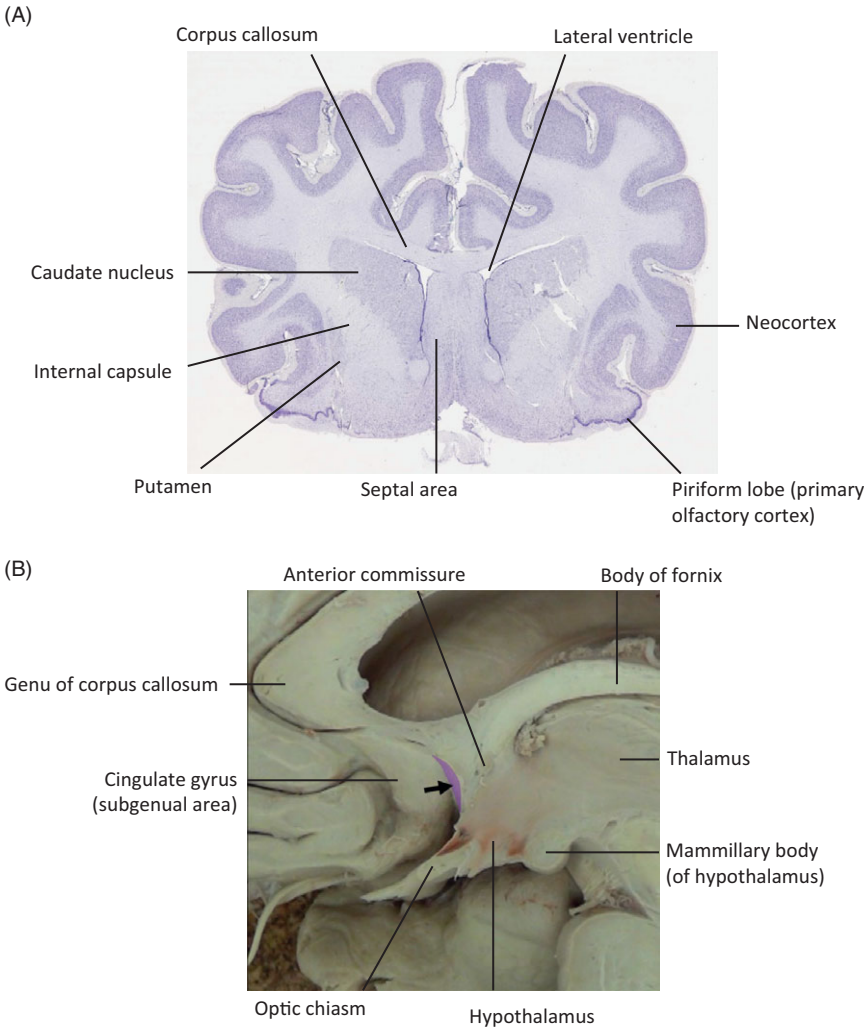

Figure 1.27 The septal area. (A) This is a Nissl-stained coronal section through the cerebral hemispheres of a domestic dog. The septal area can be seen as a substantial column of cholinergic neurons (on each side) lying between the lateral ventricles. Note also the thin, three-layered olfactory cortex of the piriform lobe which contrasts with the much thicker neocortex. (Image courtesy of NeuroScience Associates, Knoxville, TN.) (B) In the human brain, the septal area is represented only by a very slender crescent of tissue lying in front of the anterior commissure on the medial hemispheric surface. The position of the septal area is highlighted in magenta (indicated by the arrow)

and it has been observed that rodents may choose to self-stimulate the septum in preference to food, water or sex.[149, 314, 315] This is associated with increased activity in the **ventral tegmental area** and **limbic striatum**. In contrast, experimental ablation of the septal region leads to an acute dysphoric state characterised by violent outbursts, known as **septal rage**.[316–318]

1.9.5.1 Connections of the Septal Area

The septal area has reciprocal links with the olfactory bulb, hippocampus, amygdala and cingulate gyrus. It is also connected to autonomic effector structures such as the hypothalamus, rostral midbrain and nuclei of the diffuse neurochemical systems.

Connections between the septal area and amygdala run obliquely along the ventral surface of the brain, just lateral to the optic tract, in a pathway known as the **diagonal band of Broca**. This is also a route of communication between the septum and hippocampus.

There is reciprocal activity between the septal area and **habenula**. The latter is a tiny nuclear group just in

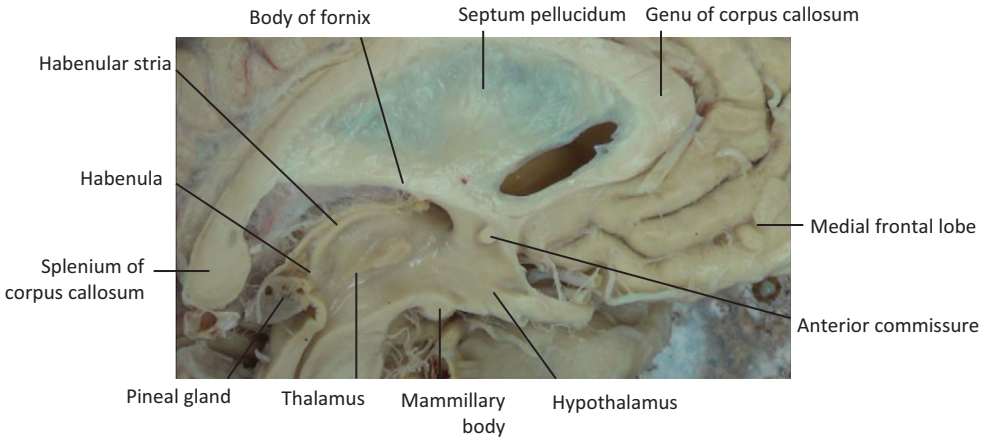

Figure 1.28 Pineal gland and habenula. This is a midsagittal section of the cerebral hemiphere showing the pineal gland, habenula and stria medullaris thalami (or habenular stria).

front of the pineal gland (Figure 1.28) that is involved in negative reward states and depression. The septum and habenula communicate via the **habenula stria** (or **stria medullaris thalami**). This is a slender bundle that runs in an anteroposterior direction along the medial thalamus, in the roof of the third ventricle.

The septal area projects to the hippocampus (via the fornix) as the **septo-hippocampal projection**. This induces **synchronisation** of hippocampal pyramidal cells associated with low-frequency bursting activity (4–12 Hz) known as the **theta rhythm**. In experimental maze-learning tasks in rodents, theta rhythm is seen during **exploratory food-seeking behaviour**[319] and coincides with discovery of a hidden reward. Theta rhythm facilitates **synaptic plasticity** in the hippocampus, which presumably encodes the spatial location of the reward.

The septal area is stimulated by **oxytocin** and has been implicated in social, sexual and parental bonding.[320] Links with the extended amygdala and basal forebrain mechanisms controlling fear and anxiety may be of relevance to **social anxiety disorder** which is characterised by biased attention to **social threat**.[321] A potential link has also been suggested between developmental abnormalities of the septum and **antisocial behaviour**.[322]

1.10 Basal Ganglia Loops and Ventral Striatum

The basal ganglia are traditionally regarded as belonging to the motor system. However, the majority of the basal ganglia connections are in fact **non-motor** (cf. the cerebellum) and contribute to cognitive-executive and limbic-affective functions, including reward-based learning.

1.10.1 Parts of the Basal Ganglia

The **corpus striatum** is the main part of the basal ganglia and is composed of the caudate and lentiform nuclei. Whilst these two nuclear groups are fused anteriorly, they are separated by white matter for most of their antero-posterior extent (Figure 1.29).

The **caudate nucleus** is C-shaped and nestles into the inner curvature of the lateral ventricle. It has a head, body and tail (Latin: *cauda*, tail). On coronal sections, the head and body of the caudate nucleus can be seen in the side wall of the lateral ventricle, whilst the slender tail occupies the roof of the temporal horn.

The **lentiform nucleus** lies beneath the insula. It is said to resemble a lens (Latin: *lentiform*, lens-shaped) but is best regarded as a cone. Its base underlies the insula whilst the apex points towards the midline. The lentiform nucleus is composed of the putamen and globus pallidus.

The **putamen** (Latin: *putamen*, husk or shell) is the outermost portion of the lentiform nucleus. The inner part is the **globus pallidus**, which has internal and external segments. It is named because of its pallid appearance in comparison to the caudate putamen. This is due to the presence of myelinated fibres forming the internal connections of the basal ganglia.

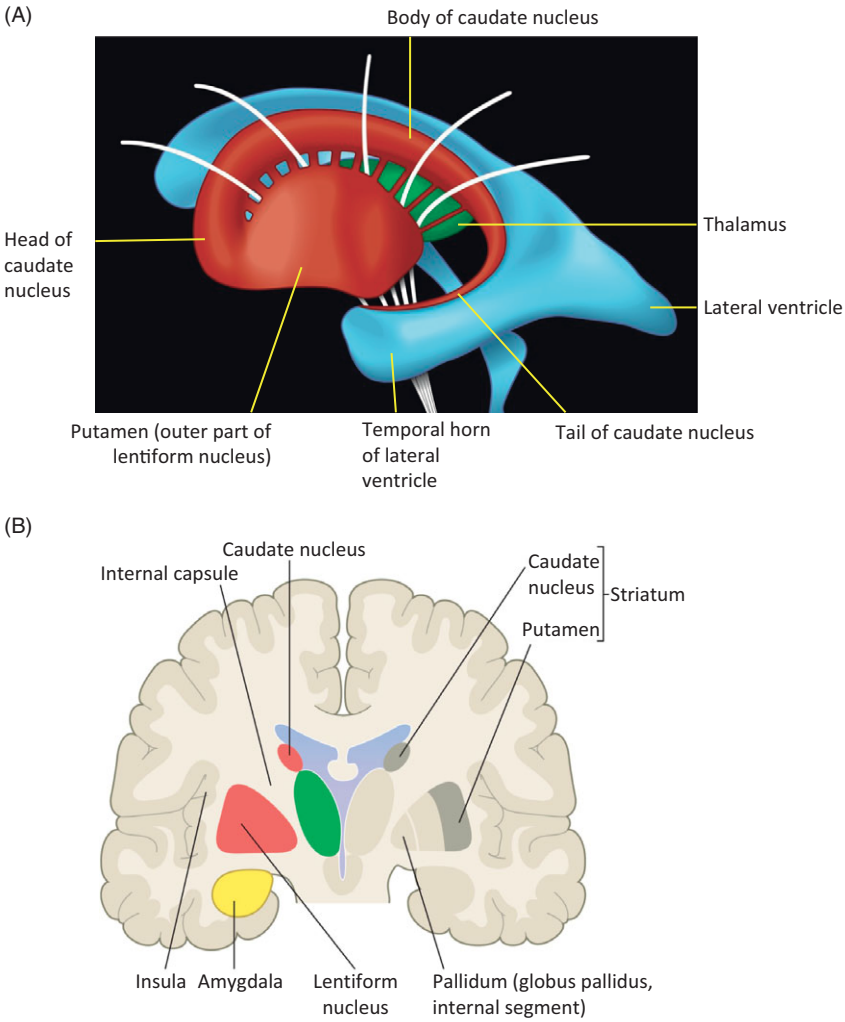

Figure 1.29 The basal ganglia. (A) The corpus striatum (*red*) consists of the C-shaped caudate nucleus and cone-shaped lentiform nucleus, which are almost completely separated by the internal capsule (a V-shaped sheet of white matter, represented here by *white lines*). (B) A diagram showing the basal ganglia and thalamus in coronal section. The amygdala is also indicated. From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014).

1.10.1.1 Striatum and Pallidum

Topographical division of the corpus striatum into the caudate and lentiform nuclei reflects the fact that these structures are almost completely separated by the **internal capsule**. However, it is also possible to identify two functional zones, based on afferent and efferent connections:

- The **striatum** (caudate nucleus, putamen) is the 'input' region of the basal ganglia, which receives projections from the overlying cerebral cortex.
- The **pallidum** (globus pallidus) is the 'output' portion of the basal ganglia. In particular, the internal segment of the globus pallidus is the principal outflow station.

Terminology used to describe the corpus striatum is potentially confusing. It is important to emphasise that the structural term **corpus striatum** (meaning the caudate and lentiform nuclei) is not the same as the term **striatum** (meaning caudate-putamen or 'input region').

Two other components of the basal ganglia are the substantia nigra and subthalamic nucleus. The **substantia nigra** is found in the midbrain and gives rise to the **nigro-striatal tract**, which supplies the dorsal

striatum with dopamine. The **subthalamic nucleus** belongs to the diencephalon. It is a small, lens-shaped nucleus lying just below the thalamus that has an excitatory effect on the internal pallidum.

1.10.2 Basal Ganglia Loops

The striatum and pallidum participate in **basal ganglia loops** that arise and terminate in the cerebral cortex. Projections enter the striatum ('input region'), and this gives rise to intrinsic connections which converge on the internal pallidum ('output region'). The pallidum, in turn, projects to the thalamus. The loop is completed by a **thalamo-cortical pathway** that returns to the point of origin.

Activity in the basal ganglia loops is controlled by the neurotransmitter **dopamine**, supplied by the midbrain. There are three major types of loop which each project to a specific portion of the striatum:

- The **putamen** (motor striatum) is concerned with the selection, initiation and execution of voluntary movements.
- The **caudate nucleus** (cognitive striatum) takes part in cognitive-executive loops that contribute to functions including attention, gaze control and working memory.
- The **ventral striatum** (limbic striatum) contributes to the control of emotion and behaviour and belongs to the positive reward pathway of the brain.

The **dorsal striatum** includes the caudate nucleus and putamen, whilst the **ventral striatum** is not further subdivided. The latter occupies the most anterior and ventral aspect of the basal ganglia, where the caudate nucleus and putamen are fused beneath the anterior limb of the internal capsule. The ventral striatum is also known as the **nucleus accumbens septi** (Latin: nucleus that leans against the septum) due to its proximity to the septal area.

The anatomy of the **voluntary motor loop** is the best-understood component of the basal ganglia, due to its involvement in movement disorders such as **Parkinson's disease** and **Huntington's disease**. However, the basic arrangement of the motor and non-motor loops is the same.

1.10.3 Direct and Indirect Pathways

In each basal ganglia loop, the striatum gives rise to **direct** and **indirect pathways** that converge on the pallidum. These are composed of medium spiny neurons which use the neurotransmitter GABA and are therefore inhibitory. Neurons belonging to the direct pathway express **excitatory** (**D1**) dopamine receptors, whilst those of the indirect pathway express **inhibitory** (**D2**) receptors.

Dopamine therefore simultaneously stimulates the direct pathway and inhibits the indirect pathway, shifting the balance of activity in favour of the direct pathway. The dopamine supply to the striatum derives from the midbrain via the **nigrostriatal tract** (dorsal striatum) and **mesolimbic pathway** (ventral striatum). These arise from the substantia nigra and ventral tegmental area respectively.

1.10.3.1 Voluntary Motor Loop (Figure 1.30)

In the motor loop, cortical projections derive from the **supplementary motor area** (**SMA**) in the medial frontal lobe and project to the **putamen** ('motor striatum'). The putamen gives rise to direct and indirect pathways that converge on the motor portion of the pallidum. The pallidum provides efferents to the thalamus, and the loop is completed via a **thalamo-cortical projection** to the SMA.

Dopamine lowers the threshold for movement initiation by increasing activity in the direct pathway. Lack of striatal dopamine (as in Parkinson's disease) therefore leads to **akinesia** due to a relative excess of indirect pathway activity and reduced recruitment of the SMA. Conversely, dopamine excess is associated with unwanted involuntary movements or **dyskinesias** as a result of excessive direct pathway activity.

The internal pallidum is the principal outflow of the basal ganglia, which has an inhibitory influence on movement. The **subthalamic nucleus** provides tonic stimulation to the internal pallidum, reinforcing its inhibitory outflow and promoting stillness. This explains why infarction of the subthalamic nucleus leads to **hemiballismus**, characterised by explosive involuntary movements on the opposite side of the body. The subthalamic nucleus is an effective target for deep brain stimulation in the treatment of idiopathic Parkinson's disease.[323]

1.10.3.2 Cognitive-Executive Loops

Three cognitive-executive loops project to the caudate nucleus. The **oculomotor loop** arises and terminates in the **frontal eye fields** and is involved in the control of **voluntary saccades** and **attention**. This includes both overt attention (as reflected in the direction of gaze)

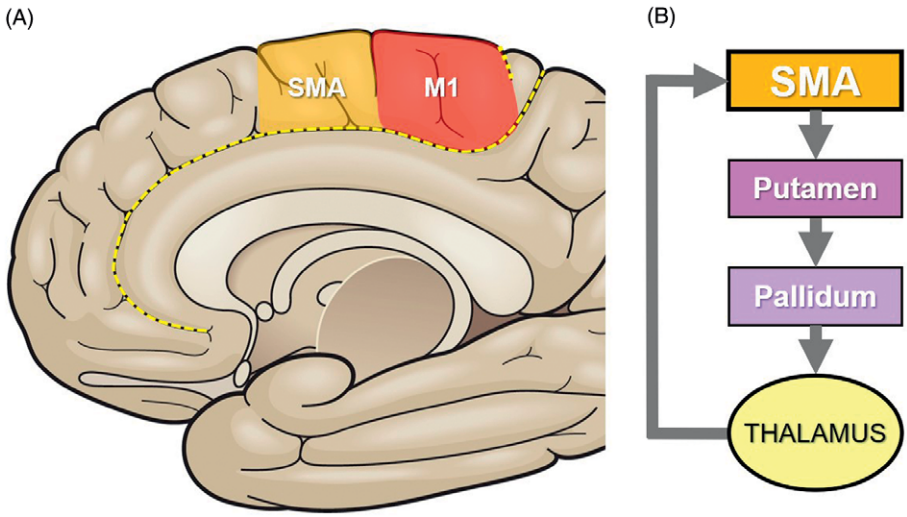

Figure 1.30 The voluntary motor loop of the basal ganglia. (A) Diagram of the medial hemispheric surface showing the primary motor cortex (M1) and supplementary motor area (SMA). (B) Connections of the basal ganglia motor loop, which arises and terminates in the SMA.

and covert attention (the ability to focus on something whilst appearing to attend to something else).

A second loop centres on the **dorsolateral prefrontal cortex**. This also receives converging afferents from the lateral premotor area and parietal association cortex, and appears to be important for higher-order **cognitive-executive functions** such as organising, planning and multitasking. It centres on the **middle frontal area** (**BA46**), which is particularly implicated in **working memory**.

Finally, the **lateral orbital loop** arises and terminates in the **orbitofrontal cortex** and projects to the head of the caudate nucleus. The caudate nucleus also receives afferents from the anterior cingulate gyrus and the auditory and visual association areas of the lateral temporal lobe. The lateral orbital loop appears to be concerned with the assessment of **covert threat** and is hyperactive in patients with **obsessive-compulsive disorder** (Box 1.17).

1.10.3.3 Ventral Striatum and Limbic Loop

The limbic loop of the basal ganglia passes through the **ventral striatum** (Figure 1.31), which, in turn, projects to the **ventral pallidum**. It centres on the anterior cingulate and orbitomedial prefrontal cortices, but there are also contributions from the hippocampus and amygdala. The limbic-associated portions of the basal ganglia are known as the **ventral striatopallidal complex** and extend into to the amorphous **basal forebrain** region or 'substantia innominata' (Latin: 'substance with no name') which lies below the basal ganglia and anterior commissure, just lateral to the hypothalamus.[328]

The terms 'ventral striatum' and 'nucleus accumbens' are essentially synonymous. The **accumbens** is divided into an inner **core region** that blends with the overlying caudate-putamen, together with a more distinct **shell** that is medial and ventral to the core. The shell is rich in receptors for dopamine, nicotine, opiates and cannabinoids and has been implicated in **addiction** (e.g. smoking, alcohol) and **drug abuse** (e.g. cannabis, heroin).[79]

This explains **dopamine dysregulation syndrome** in which patients with Parkinson's disease become addicted to their dopamine replacement therapy and take unnecessary escalating doses.[329] There are often impulse control problems such as **hypersexuality** or **pathological gambling**, and some patients develop a repetitive pattern of obsessive behaviour called **punding**, characterised by purposeless alignment or ordering of objects.

The ventral striatum and ventral tegmental area belong to the **positive reward pathway**. This reinforces **adaptive behaviours** that lead to a favourable outcome, which is correlated with dopamine release in the ventral striatum. Activity in the reward pathway increases the likelihood that the successful behaviour will be repeated.

The dopamine 'reward signal' is strongest when the reward is unexpected (referred to as **prediction**

Box 1.17 Neuroanatomy of OCD

Obsessive-compulsive disorder affects approximately 1–2% of the population and is characterised by intrusive and distressing obsessions and compulsions.[324] Although previously categorised as an anxiety disorder, anxiety is now regarded as secondary.[256]

The brain regions that are hyperactive in OCD belong to the **lateral orbital loop** which passes through the head of the **caudate nucleus**. It appears to be concerned with the identification of **hidden risks** (in contrast to the amygdala, which responds to **overt threat**). Patients with OCD are unable to feel satisfied that the possibility of harm has been eliminated, leading to an endless cycle of **doubt** and **checking**, accompanied by distress and anxiety. Neuroimaging studies in patients with OCD have demonstrated overactivity in the lateral orbital loop and its components (anterior cingulate gyrus, head of the caudate nucleus, lateral orbital cortex).

Activity in the lateral orbital loop is correlated with symptom severity and may normalise after successful treatment, for instance by using **serotonin-selective reuptake inhibitors** (**SSRIs**) or **cognitive-behavioural therapy** (**CBT**).[325–327]

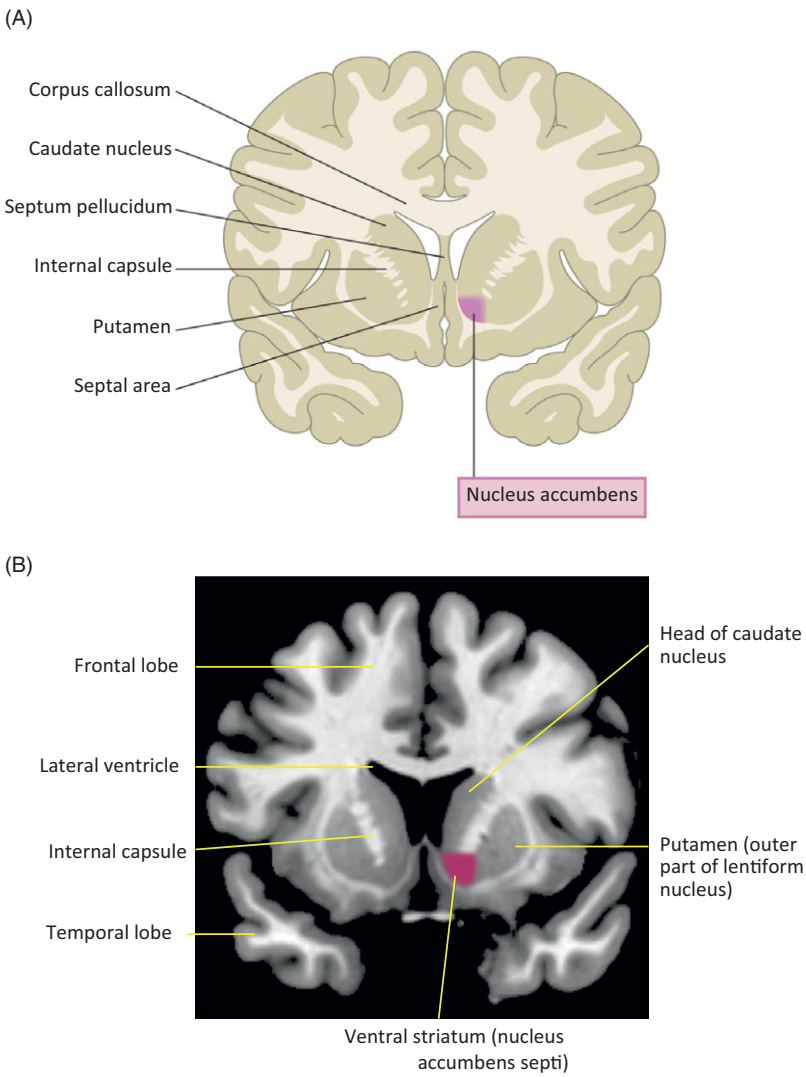

Figure 1.31 The ventral (limbic) striatum. (A) Diagram showing the location of the ventral striatum (or nucleus accumbens) in close proximity to the septal area. From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014). (B) Corresponding image on a coronal MRI scan.

error). This may account for phenomena such as Stockholm syndrome and the tendency for some individuals to remain in abusive relationships, due to the unpredictable nature and timing of occasional kind gestures.

Although the basal ganglia loops are often depicted as **parallel segregated circuits**, with separate motor, cognitive and limbic streams, there is in fact considerable overlap between projections.[79] Broadly speaking, motor areas project to the dorsolateral striatum, cognitive-executive areas occupy the intermediate regions, and limbic lobe and amygdala afferents are received by the ventromedial striatum. Overlap between motor and limbic territories may explain the phenomenon of **paradoxical kinesis** in Parkinson's disease (Box 1.18).

1.11 Thalamic Region, Pineal Gland and Habenula

The **thalamic region** (which includes the hypothalamus) belongs to the **diencephalon**, and its general anatomy has been discussed in previous sections (see Figure 1.28). The **pineal gland** and **habenula** constitute the **epithalamus** which lies above and posterior to the thalamus (Greek: *epi*-, upon). The epithalamus is involved in circadian rhythms, sleep-wake cycles and depression.

1.11.1 Thalamus

The thalamus is composed of numerous subnuclei (Figure 1.32) separated into **anterior**, **medial** and

Box 1.18 Paradoxical Kinesis

The term **paradoxical kinesis** describes transient reversal of akinesia during a fight-or-flight response in patients with Parkinson's disease.[330–332] For instance, a profoundly akinetic parkinsonian patient may be able to run freely from a burning building.[333] Presumably this reflects recruitment of motor pathways via the limbic loop of the basal ganglia, initiated by the amygdala.

Another form of paradoxical kinesis is readily observed in the neurology outpatient clinic. Patients with significant **gait initiation** difficulties (**start hesitation**, **freezing**) may be able to move much more easily if asked to step over a series of objects or when walking on a patterned surface. Some patients are able to overcome akinesia by reacting to a musical rhythm or by using a metronome as an **external cue**.[334, 335] These phenomena are probably due to the fact that the motor loop of the basal ganglia is more concerned with the initiation of **internally generated** (or **egocentric**) voluntary acts rather than those that are **externally cued** (or **allocentric**).[336, 337] For the same reason, a patient with Parkinson's disease may find it much easier to catch a ball than to throw one,[338] which was described by the British neurologist Oliver Sacks as 'borrowing the will of the ball'.[339]

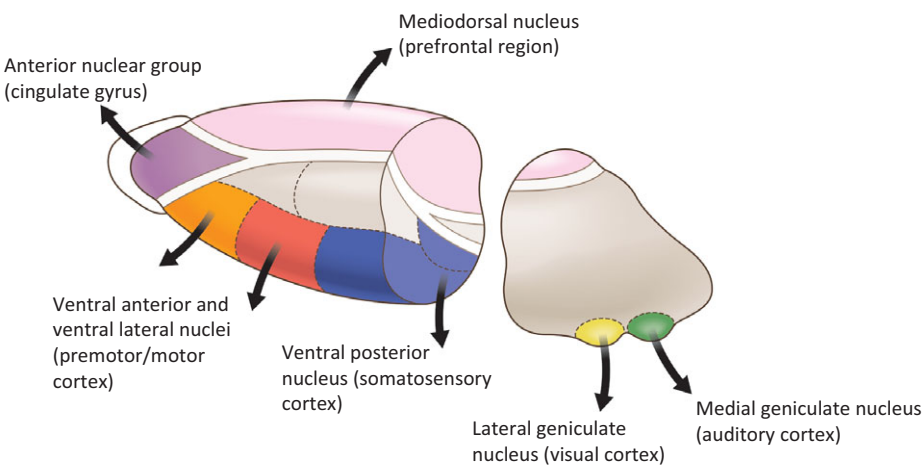

Figure 1.32 Thalamic nuclei. This is an illustration of the left thalamus, which consists of numerous subnuclei, each of which projects to a particular part of the cerebral cortex.

lateral nuclear groups by a Y-shaped **internal medullary lamina**. This thin sheet of white matter contains a few small **intralaminar nuclei** which give rise to diffuse cortical projections that contribute to arousal, wakefulness and pain.

The anterior limbs of the internal medullary lamina clasp the **anterior nuclear group**. The stem of the Y divides the posterior thalamus asymmetrically so that the **lateral nuclear group** is larger than the **mediodorsal nucleus**. A thin shell of grey matter, the **reticular nucleus**, lies just outside the thalamus, separated from it by the **external medullary lamina**. The reticular nucleus receives collateral fibres from incoming projections and inhibits other thalamic nuclei.

Two small knee-shaped eminences in the posterolateral thalamus, the **medial** and **lateral geniculate bodies**, project to, respectively, the primary auditory and visual cortices. The posterior pole of the thalamus is the **pulvinar**. It provides afferents to parietal and occipital association cortices that bypass the primary visual (striate) cortex. The presence of these **extrastriate visual pathways** may account for the phenomenon of **blindsight**, in which people with cortical blindness are able to react to visual stimuli (above the level of chance) despite having no conscious experience of vision.[340]

1.11.1.1 Anterior and Mediodorsal Nuclei

The **anterior** and **mediodorsal nuclei** of the thalamus are of most relevance to neuropsychiatric disorders. The anterior nucleus is part of the Papez circuit and is therefore important for episodic memory. It receives projections from the **mamillary bodies** of the hypothalamus via the **mamilothalamic tract** and in turn projects to the anterior and posterior cingulate cortices.

The **mediodorsal nucleus** faces the cavity of the third ventricle and forms reciprocal connections with the prefrontal region. It has two subnuclei. The **magnocellular division** is composed of neurons with large cell bodies (Latin: *magnus*, great). It projects to the **orbitomedial prefrontal cortex** and is involved in emotion and behaviour. The **parvocellular nucleus** contains smaller neurons (Latin: *parvum*, small) and projects to the **dorsolateral prefrontal cortex**. It therefore contributes to executive functions (e.g. working memory, attention).

Lesions in the anterior and mediodorsal nuclei of the thalamus may therefore interfere with memory and executive functions or interrupt non-motor basal ganglia loops. For this reason, relatively small anteromedial thalamic strokes may cause abrupt cognitive deficits. These are known as **strategic infarcts** or '**single-stroke dementia**'. Post-stroke dementia may also occur following infarction of the basal ganglia, inferior parietal lobe, medial temporal lobe or hippocampus.[341]

1.11.2 Hypothalamus

The **hypothalamus** (see Figure 1.28) is a tiny brain region composed of numerous subnuclei that are involved in homeostasis, reproductive functions and behaviour. It is divided into three regions from anterior to posterior (supraoptic, tuberal and mamillary) and has three parasagittal zones, from medial to lateral (periventricular, medial and lateral).

The hypothalamus helps to maintain **homeostasis** by regulating parameters such as blood sugar, core body temperature and plasma osmolality by influencing behaviour (via basic drives such as hunger and thirst) and by controlling the activity of the **endocrine** and **autonomic nervous systems**. It influences hormone secretion via the **anterior pituitary gland** and contributes to normal circadian rhythms, sleep-wake cycles, sexual behaviour and reproductive functions.

In states of **chronic stress**, the hypothalamus induces release of **adrenocorticotrophic hormone** (**ACTH**) from the anterior pituitary gland, which in turn stimulates the **adrenal gland** to produce **cortisol**. This is known as the **hypothalamic pituitary-adrenal** (**HPA**) **axis.** Increased HPA axis activity is seen in a number of neuropsychiatric conditions including major depression, bipolar affective disorder, panic disorder, generalised anxiety disorder, OCD and schizophrenia.[342–345]

The role of the hypothalamus in **emotional expression** was determined in part by the **brain transection studies** of Walter Cannon and Philip Bard in the late 1920s.[45, 46, 346, 347] It was demonstrated in experimental animals that separation of the cerebral cortex does not abolish emotional responses (e.g. hissing, spitting, arching of the back) provided that the hypothalamus is intact. In contrast, lesions below the level of the hypothalamus (effectively 'disconnecting' it from the periphery) attenuate or abolish emotional behaviours (Figure 1.33).

This concept was further supported by **electrical stimulation studies** carried out by Stephen Hanson and Walter Hess in the 1930s and 1940s.[348] These

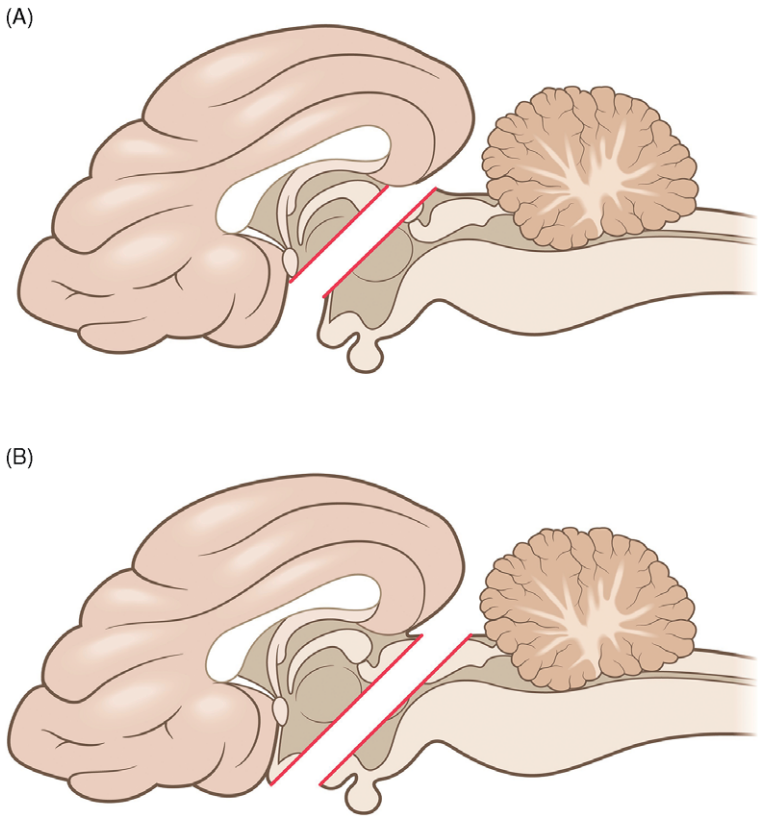

Figure 1.33 Brain transection studies (Philip Bard, 1928). (A) Emotional expression is preserved in experimental animals with high transections (above the level of the hypothalamus). (B) Emotional behaviours are attenuated or abolished following low transections, which separate the hypothalamus from the periphery.

experiments showed that complex emotional behaviours could be elicited in experimental animals by direct electrical stimulation of the hypothalamus.[349] It has also been shown that emotional expression is preserved following bilateral ablation of the cerebral cortex.[350]

Aggressive emotional displays in animals with no functioning cerebral cortex, or produced as a result of hypothalamic stimulation, were referred to as **pseudoaffective reflexive states** or **sham rage**. This reflects the view that conscious experience is localised to the cerebral cortex, and the concept that subjective emotional experiences (**feelings**) can be dissociated from their behavioural manifestations (**emotional expression**).

1.11.3 Pineal Gland

The **pineal gland** is a small endocrine gland that is shaped like a pine cone (Latin: *pinea*, pine cone) (see Figure 1.28). It lies above and behind the thalamus in the roof of the third ventricle and secretes the sleep-inducing hormone **melatonin** in low-light conditions (Greek: *melas*, black). This helps to control **sleep-wake cycles** and maintain normal **circadian rhythms**. It also influences **seasonal activities** such as migration in birds, controls the **onset of puberty** and influences reproductive and **sexual functions**.[351–353]

Melatonin release is modulated by a projection from the **suprachiasmatic nucleus** (**SCN**) of the hypothalamus, which in turn receives afferent fibres from the retina via the **retinohypothalamic tract**. The suprachiasmatic nucleus acts as a 'biological clock' that is regulated by the amount of light falling on the retina. This is of relevance to neuropsychiatric disorders, in which disturbance of sleeping patterns and circadian rhythms is common. Reduced exposure to sunlight is also associated with a number of mood disorders including **bipolar affective disorder**, **major depression** and **seasonal affective disorder** (**SAD**). Paradoxically, the peak risk for suicide is in the early summer.[354, 355]

1.11.4 Habenula

The **habenula** is a small, bilaterally symmetric structure that lies in front of the pineal gland in the roof of

the third ventricle (see Figure 1.28).[356] Its name derives from the diminutive form of the Latin word *habena*, meaning rein (cf. the reins of a horse). This refers to the strap-like appearance of the pineal stalk which forms a V-shape on either side of the triangle-shaped **habenular trigone**. The habenula consists of the **medial** and **lateral habenular nuclei** (MHb, LHb).

The habenula receives afferent fibres via the **habenular stria** and gives rise to efferent projections to the rostral midbrain. The latter travel via the **fasciculus retroflexus** and terminate in the **interpeduncular nucleus** (the **habenulo-interpeduncular pathway**) together with the nuclei of the diffuse neuromodulatory systems (e.g. the raphē nuclei and locus coeruleus).

The **medial habenula** mainly receives projections from the septal area and other basal forebrain cholinergic nuclei. It is involved in stress responses, depression, memory and withdrawal from nicotine, cocaine, methamphetamine and alcohol.[356] The **lateral habenula** has much more extensive inputs, including afferents from the medial prefrontal cortex, hypothalamus, amygdala and basal ganglia in addition to the septum. The lateral habenula is involved in reward-based learning, spatial memory, stress and anxiety, depression and addiction. It exerts its effects by influencing the diffuse neuromodulatory systems.[357]

Activity in the lateral habenula is particularly associated with **negative reward states** and downregulation of brain stem neurochemical pathways that are associated with positive affect. It shows reciprocal activity with the **septal area**. The lateral habenula therefore represents the counterpart of the ventral striatal positive reward pathway: the 'stick' of carrot-and-stick learning. Increased habenular activity is found in experimental models of depression (Box 1.19).

1.12 Diffuse Neurochemical Systems

The **diffuse neurochemical** (or **neuromodulatory**) systems of the brain (Figure 1.34) influence wakefulness, pain perception, arousal, attention, vigilance, impulse control and memory.[363] This is achieved by modulating the excitability of large distributed neuronal networks and by influencing transmission of information from the thalamus to the cerebral cortex.

1.12.1 General Organisation

The six main neuromodulatory systems are those for **serotonin**, **noradrenaline**, **acetylcholine**, **dopamine**, **orexin** and **histamine**. The nuclei of origin are in the brain stem, hypothalamus and basal forebrain, and despite being composed of only a few thousand neurons, they give rise to extensive projections that ramify throughout the central nervous system, including the spinal cord.

The diffuse neurochemical systems provide strong afferents to the olfactory bulb, amygdala, ventral striatum and limbic cortices. As such, they are important targets in clinical neuropsychiatric practice and are modulated by psychotropic agents including **antidepressants** (serotonin, noradrenaline), **antipsychotics** (dopamine, serotonin) and **neurotropic agents** used in dementia (acetylcholine).

1.12.1.1 Nuclei of Origin

Most of the diffuse neurochemical systems originate from the **tegmentum** (central core) of the brain stem. In order to reach the cerebral hemispheres, their axons pass through the **medial forebrain bundle**, a compact white matter conduit that traverses the lateral hypothalamus. The diffuse systems influence target structures via **metabotropic** (**G-protein**

Box 1.19 The Learned Helplessness Model of Depression

The term **learned helplessness** is used to describe a state of **passive futility** in response to aversive events over which we have no control. It derives from studies in experimental animals subjected to inescapable electric shocks. It was originally thought that **active avoidance** is the default behavioural pattern, and that **passive acceptance** is a learned response, but it turns out that the reverse is true. In other words, animals respond passively to aversive stimuli by default and can only overcome this by **learning to take control**.[358]

The original experiments were carried out by the American psychologist Martin Seligman in the 1960s in dogs.[359, 360] A similar state of **learned helplessness** has been observed experimentally in humans.[361] It has been shown to be associated with changes in the diffuse **neuromodulatory systems** that control mood and is used as an experimental paradigm for depression. Behaviour consistent with learned helplessness is seen in **depression**, **PTSD** and in people who remain in **abusive relationships**.[362]

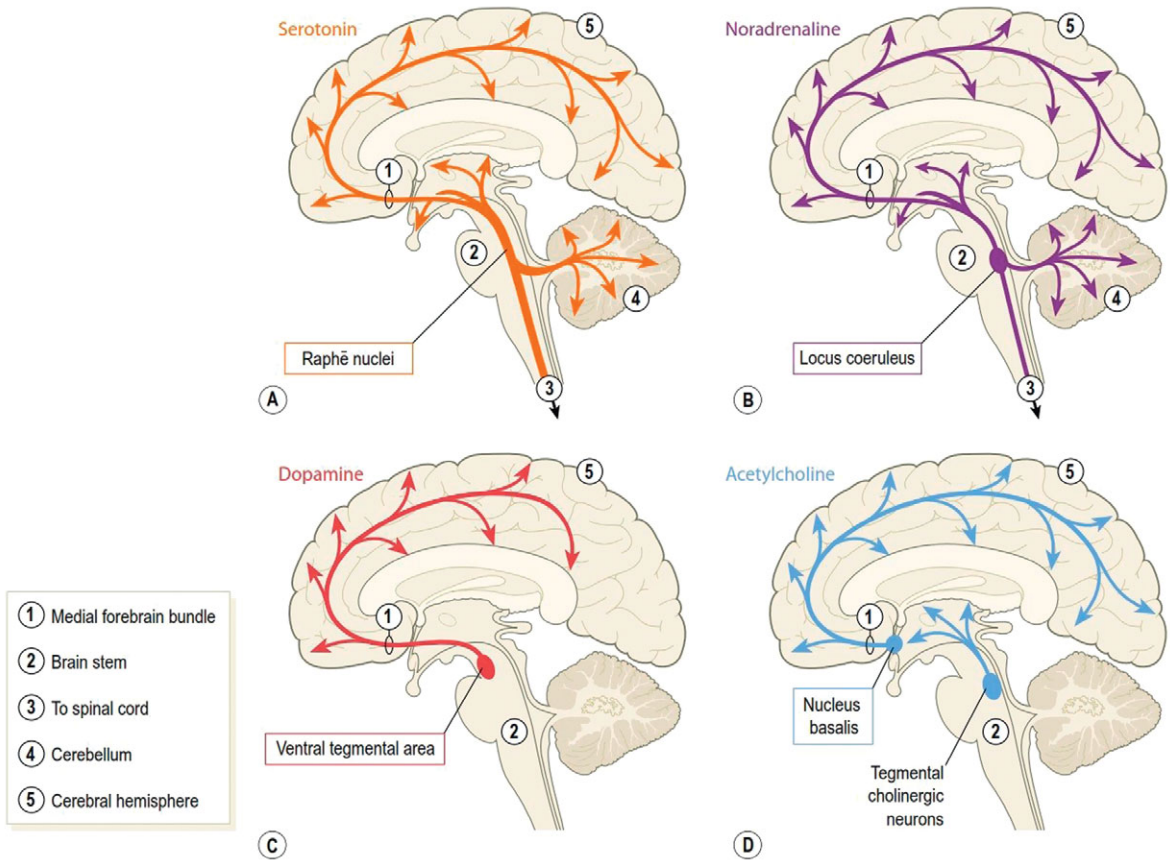

Figure 1.34 Diffuse neuromodulatory systems. Illustration of the main diffuse neurochemical pathways for serotonin (A), noradrenaline (B), dopamine (C) and acetylcholine (D), which all traverse the medial forebrain bundle in the lateral part of the hypothalamus. From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014).

coupled) receptors rather than **ionotropic** (rapid, **ion-channel-linked**) receptors and thus have a slower but longer-lasting **neuromodulatory** effect compared to classical neurotransmitters such as glutamate and GABA.

Contact with target neurons occurs at **varicosities** rather than conventional synapses, which are distributed along the length of axons like grapes on a vine (***boutons en passant***). Neurotransmitters may also be released directly into the extracellular compartment and CSF. In this way, a single neuron may influence up to 250,000 target cells.[364]

1.12.1.2 Overall Functions

The neuromodulatory systems produce **global changes** in the excitability of neural networks in different physiological states. For instance, **active waking** is characterised by prominent cholinergic, serotonergic and noradrenergic tone. In **quiet waking** the same pattern is seen, but activity is reduced. In **REM sleep** there is marked activity in the cholinergic system whilst the serotonergic and noradrenergic projections fall silent. In contrast, during **slow-wave sleep** there is reduced cholinergic tone and increased release of both serotonin and noradrenaline.[365–367]

1.12.2 Monoamine Nuclei of the Brain Stem

The **monoamine nuclei** of the brain stem are divided into the **catecholamines** (**group A**) and **indoleamines** (**group B**).[368, 369] The catecholamines contain a single **catechol ring** and are referred to as **monocyclic**. The indoleamines contain an **indole group** with two rings and are described as **bicyclic**. The two catecholamines are **noradrenaline** (**NA**) and **dopamine** (**DA**), whilst

the single indoleamine is **serotonin** or **5-hydroxytryptamine** (**5-HT**). Noradrenaline is also known as **norepinephrine** (**NE**).

1.12.2.1 Noradrenergic Nuclei

The catecholamine nuclei are labelled **A1–A16**. The first seven (**A1–A7**) are noradrenergic and are found in the pons and medulla. The **locus coeruleus** (plural: loci coerulei) corresponds to **A6**. This is a longitudinal column of approximately 10,000 neurons located in the dorsolateral part of the rostral pons. It is a pigmented nucleus that contains **neuromelanin** (a by-product of catecholamine metabolism) and is readily identified with the naked eye. It lies just beneath the floor of the fourth ventricle and resembles a pencil lead in axial sections. The name derives from its supposedly bluish colour (Latin: *coerulean*, violet). The noradrenergic projection has been implicated in attention, arousal, mood, anxiety, memory and control of sleep-wake cycles.

During wakefulness, noradrenergic activity is associated with **focussed attention** and **vigilance**, particularly with respect to interesting or **novel stimuli**.[370–372] However, excessive noradrenergic tone may lead to **hypervigilance** and **anxiety**[373–375] and has been implicated in **PTSD**.[376, 377] States of hypervigilance also impair cognitive performance, as reflected in the J-shaped relationship between physiological arousal and learning, the **Yerkes-Dodson curve**.[378] Alterations in brain stem monoamine projections (e.g. noradrenaline, serotonin) are also implicated in **depression**.[379–384]

1.12.2.2 Dopaminergic Nuclei

The remaining nine monoamine nuclei (**A8–A16**) are dopaminergic and are located in the midbrain, hypothalamus and olfactory bulb. The substantia nigra corresponds to A9, but this a large nucleus that projects only to the dorsal striatum (via the nigro-striatal tract), so it cannot be regarded as a diffuse neuromodulatory system.

The **ventral tegmental area** or **VTA** (**A10**)[385] is just medial to the substantia nigra (Figure 1.35). The projection field of the VTA is less extensive than that of the serotonergic and adrenergic projections but nevertheless supplies all limbic brain regions via the **meso-cortico-limbic** dopamine pathway. This has two components. A **mesocortical** projection arises in the VTA and terminates in the limbic lobe and orbitomedial prefrontal cortex, whilst the **mesolimbic** pathway is destined for subcortical limbic brain structures (e.g. amygdala, ventral striatum). A fourth dopamine pathway, the tuberoinfundibular tract, projects from the hypothalamus to the pituitary gland and influences prolactin release, but it is not regarded as a diffuse neurochemical system.

Excessive dopamine release via the diffuse neuromodulatory pathways may contribute to the **positive symptoms** of **schizophrenia** (i.e. delusions, hallucinations).[386,387] This explains the rationale for

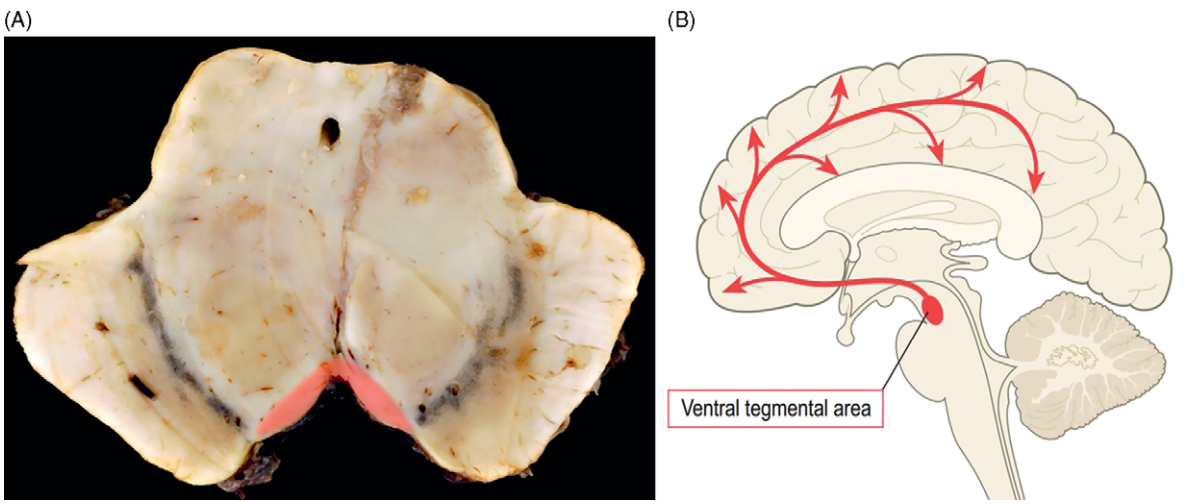

Figure 1.35 Dopamine supply to the ventral striatum. (A) Axial section of the midbrain showing the location of the ventral tegmental area or VTA (*red*) just medial to the deeply pigmented substantia nigra. (B) Diagram illustrating the projection field of the VTA, which includes the ventral striatum, amygdala, hippocampus and orbitomedial prefrontal cortex. From Johns, *Clinical Neuroscience: An Illustrated Colour Text* (Elsevier, 2014).

Box 1.20 Serotonin, Impulse Control and Aggression

Impulse control and aggression are regulated by a pathway linking the **amygdala** and **orbitomedial prefrontal cortex**, which is modulated by the neurotransmitter **serotonin**.[395] In normal individuals, increased amygdala activity is seen in states of **provoked anger**,[396] but this can be suppressed by the **prefrontal cortex**.[397] Evidence from structural and functional imaging studies suggests that dysfunction of this frontolimbic control pathway may be associated with **inappropriate aggression**.[398]

In keeping with these observations, reduced functional connectivity between the amygdala and prefrontal cortex has been shown to be a risk factor for aggressive behaviour in patients with **schizophrenia**.[399] Aggressive tendencies and impulsivity can also be manipulated experimentally in normal controls via dietary depletion of tryptophan, the amino acid precursor of serotonin.[400]

Evidence for a potential genetic contribution is provided by Brunner syndrome, a rare single-gene disorder characterised by intellectual disability coupled with **increased aggression** and **antisocial behaviours** such as arson, attempted rape and exhibitionism.[401] The cause is a knock-out mutation in the *MAOA* gene, which encodes **monoamine oxidase A** (**MAO-A**). This leads to an excess of monoamine neurotransmitters, including serotonin, which presumably has downstream effects that interfere with the normal mechanisms regulating impulsivity and aggression.

dopamine receptor antagonists in the management of psychosis[388], which ultimately led to the **dopamine hypothesis of schizophrenia**. However, this has subsequently been modified in the light of evidence suggesting that mesolimbic dopamine excess is coupled with a **reduction of dopamine** in the **prefrontal cortex**.[386]

1.12.2.3 Serotonergic Brain Stem Nuclei

The **indolamine system** consists of a series of serotonergic nuclei running along the midline of the brain stem. These are the **raphē nuclei** (Greek: *raphē*, seam),[368, 369] and each has a descriptive name (e.g. nucleus raphē obscurus, magnus, pallidus). There are seven raphe nuclei in the human brain, but up to nine are recognised in other species. The **caudal group** (**B1–B4**) is located in the hindbrain and spinal cord, a **rostral group** (**B6–B9**) is found in the midbrain and diencephalon, whilst a single nucleus lies in the midpons (**B5**).

The raphē nuclei supply widespread CNS targets including the spinal cord, brain stem, cerebellum, diencephalon, cerebral cortex and all limbic brain structures (e.g. olfactory bulb, cingulate gyrus, hippocampus, ventral striatum, amygdala). This extensive projection system has been implicated in the modulation of arousal, mood, memory, sleep and wakefulness.

A projection from the **nucleus raphē magnus** of the medulla (the **raphespinal tract**) descends within the spinal cord to modify ascending **nociceptive impulses** as part of a spinal gating mechanism for pain. This partially explains why some antidepressants have an **analgesic** effect.[389]

Reduced serotonergic activity has been associated with **aggressive-impulsive** behaviour[390, 391] which is exacerbated by increased dopamine levels.[392] Dysfunction of the serotonergic system has been documented in both **antisocial personality disorder**[393] and **borderline personality disorder**.[394] The role of the serotonin-regulated frontolimbic pathway in the control of impulsivity and aggression is discussed further in Box 1.20.

1.12.2.4 Acetylcholine, Histamine and Orexin

The diffuse **cholinergic system** originates primarily from the basal forebrain and contributes to memory, arousal and the control of sleep-wake cycles. Projections for **orexin** and **histamine** arise from small nuclei in the hypothalamus but have widespread targets including the thalamus, cerebral cortex, limbic lobe and the nuclei of other diffuse neurochemical systems.

Cholinergic Basal Forebrain Nuclei

There are eight cholinergic nuclei in the human brain (**Ch1–Ch8**), most of which are found in the **basal forebrain**.[402] Their projections are topographically organised. For instance, the principal cholinergic innervation to the hippocampus is from Ch1/Ch2, a projection to the olfactory bulb arises from Ch3, whilst Ch4 provides input to the neocortex,

hippocampus and thalamus. The projection from Ch1 to the hippocampus constitutes the **septohippocampal projection** from the medial septal nucleus (discussed above in relation to hippocampal theta rhythm).

The largest cholinergic nucleus is the **nucleus basalis of Meynert** (**Ch4**). This lies in the substantia innominata, below the lentiform nucleus and lateral to the thalamus, in proximity to the ventral striatopallidal complex. Ch4 projects widely to the cerebral cortex including the hippocampus, where it acts to promote **cortical excitability** and **synaptic plasticity**. Degeneration of the basal nucleus in **Alzheimer's disease** contributes to memory loss, explaining the utility of cholinergic potentiating agents in mild to moderate dementia.

The **pedunculopontine nucleus** or **PPN** (**Ch5**) occupies the tegmentum of the brain stem at the junction of the midbrain and pons. It forms part of the **mesencephalic locomotor centre** which is important for gait initiation. It degenerates in Parkinson's disease and is a potential therapeutic target for deep brain stimulation in this condition.[403]

Orexinergic Projection

The orexin system originates from neuronal cell bodies in the lateral and posterior **hypothalamus.** Orexins (orexin-A, orexin-B) are **neuropeptides** that promote **hippocampal neurogenesis** and facilitate **spatial learning**.[404] The name 'orexin' derives from the Greek word for appetite, reflecting their positive influence on **food-seeking behaviours** and energy metabolism (e.g. promoting deposition of brown fat). These roles help to maintain a state of motivated wakefulness and vigilance in hungry animals.

Orexins (or **hypocretins**) also have a positive impact on mood, such that low levels of orexin may result in **depression**, in addition to memory deficits and altered feeding behaviour. A role in the control of sleep-wake cycles is evidenced by the finding that hypothalamic orexin deficiency underlies **narcolepsy**.[405]

Histaminergic Projection

The histaminergic projection arises from the **tuberomammillary nucleus** of the hypothalamus and contributes to wakefulness. It is most active during states of **high vigilance** and falls silent during sleep (cf. noradrenaline). This explains why older **antihistamines** that cross the blood–brain barrier cause somnolence and can be used as sleeping tablets (e.g. promethazine, diphenhydramine).

The hypothalamic histaminergic projection is part of the **ascending arousal system**, which also includes the locus coeruleus, raphē nuclei and pedunculopontine nucleus. These projections promote general cortical excitability and wakefulness and are disturbed in **brain stem coma**. The histamine projection exerts an excitatory influence on **thalamocortical relay neurons** whilst at the same time suppressing inhibitory interneurons. This has a thalamic gating role, facilitating transmission of information to the cerebral cortex.

The alert waking state is associated with **desynchronisation** of cortical neurons, corresponding to low-amplitude, high-frequency activity on **electroencephalography** (**EEG**). A reduction in afferents from the ascending arousal system leads to hyperpolarisation of thalamocortical neurons which switch to a **rhythmic bursting** pattern. This results in synchronisation of cortical neurons and a high-amplitude, slow-wave pattern on EEG.

For the full list of references, please refer to the book-hosting website at www.cambridge.org/9781911623076.

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