Development of the Nervous System
by Dr Maggie Lowre

It is important to know about the development of the nervous system so we can understand the mature CNS better. Also, some neurological disorders have a developmental origin, and knowledge of some of these mechanisms may be useful in treatment.

The early development of the nervous system is shown in the diagram on the right, as the formation of the neural tube. A strip in the ectoderm of the trilaminar disc differentiates and proliferates to form the neural plate. This then folds to form the neural groove, and this folds to form the neural tube. The wall of the neural tube (neuroepithelium) becomes the CNS, and the neural crest cells become the PNS.

Differentiation

The neuroepithelium differentiates into several types of principal cells. Neuroblasts are all neurons with cell bodies in the CNS. Glioblasts include astrocytes and oligodendrocytes, and also microglia from the mesoderm, which are modified macrophages that migrate into the nervous system. Ependymal cells are the cells that line the ventricles and the central canal. The diagram below shows the formation of ependymal, grey and white matter layers.

The neural crest cells also differentiate into several types of principal cells to contribute to the peripheral nervous system. For example, sensory neurons of the dorsal root ganglia and cranial ganglia, postganglionic autonomic neurons, Schwann cells of the PNS, and non-neuronal derivatives such as melanocytes.

This is a cross section through the whole neural tube. The space in the middle is the neural canal, and there are three layers. Control of differentiation is down to signalling molecule. These molecules affect that target differentiating cells by affecting their phenotype and sending them in certain directions of differentiation. It is an extremely complex process. As the cells produce the signalling molecules, this sets a concentration gradient so the closer the target cells are to the source, the more likely they are to be affected by the signalling molecules. Timing is important because the target cells have to have reached a certain stage of development in order to respond to the signalling molecules.

The signalling molecules are important for influencing cell migration and axonal growth guided by attraction or repulsion.
Development of the spinal cord
In the basic layout of the neural tube, there are three layers (ependymal, grey and white). As you get more towards the development of the spinal cord, there is increased proliferation. The space in the middle is smaller and there is division of the grey matter into plates. There are two alar plates dorsally, and two basal plates ventrally. In the alar plates, the neuroblasts develop into interneurons with sensory function. Some of the neurons in the basal plate will also develop into interneurons, but some will also develop into motor neurones and will send their axons out through the ventral roots to peripheral nerves. At the same time, the neural crest tissue on either side will develop into sensory neurons as the dorsal root ganglia. In the mature spinal cord, the alar plates are called the dorsal horns and the basal plates are the ventral horns.

Signalling molecules come into play when there is the division of function. This is called dorso-ventral patterning. There are several signalling molecules derived from the notochord (one of which is called Sonic Hedgehog) and these particular signalling molecules spread out and induce neuroblasts in the ventral part to differentiate as motor neurons. There is also a set of signalling molecules from the ectoderm which induce the dorsal neuroblasts to develop into sensory cells. There are also other molecules from the mesoderm (e.g. retinoic acid).

Development of the brain
The brain develops from the most anterior tip of the neural tube. The first thing is that there is differential growth of that part of the tube to form three bulges - the primary vesicles. The most anterior vesicle develops into the forebrain, the middle one into the midbrain, and the third one into the hindbrain. This differentiation is at approximately 4 weeks of gestation. The remaining part of the neural tube will develop into the spinal cord.

During the next few days, the first vesicle and the third one divide into two, so there are five secondary vesicles. In the forebrain there is an expanded area, and behind it a less expanded area. The midbrain stays the same. The hindbrain divides into two.

Over the next few weeks there is further development. The wall gets thicker, the space inside gets relatively smaller and you see the development of the ventricular system. There are two lateral ventricles in the developing hemispheres, the third ventricle in the middle of the diencephalon, the aqueduct going through the midbrain, and the fourth ventricle in the hindbrain.

Rather late on you get the development of the cerebellum, which is an outpouching from the wall of the pons.

These diagrams on the right show the same development of the neural tube, but from the side. So firstly during the early development with the three primary vesicles there is folding. There are three folds, and are known as flexures: the cephalic, pontine and cervical flexures. During the next few weeks there is an exaggeration of that folding. This is important in order to get the brain packed inside the developing cranium.

At five weeks there is more differentiation and folding, and at eight weeks the cerebral hemispheres spread backwards to partially hide the diencephalon.

At term, there is a brain that is recognisable at a mature brain with a ventricular system inside it.

This is not the end of the development of the brain, however, as a lot happens post-natally. In fact, myelination doesn’t finish until late teens.
Development of the brainstem

The brainstem is a tubular structure like the spinal cord. There is one big difference - the **fourth ventricle** opens up in the brainstem. This space means that the structures in the grey matter alter their relationship with each other. In the bit of the neural tube that develops into the brainstem, there is a sudden proliferation in a part called the **roof plate**, where previously there hasn’t yet been much proliferation. This proliferation rapidly occurs, and there is natural expansion of the roof plate. This pushes the alar plates more laterally, and so their relationship to the basal plates is that they are lateral to them rather than dorsal to them.

Cranial nerves are associated with various cranial nerve nuclei, which lie in the floor of the fourth ventricle in the brainstem. Some of them are motor, some have a sensory function. The sensory nuclei are more lateral, and the motor nuclei are more medial.

Development of the cortex

There is a layer of **grey matter cortex** over the whole cerebral hemispheres. To get the grey matter cells there, they have to undergo a large amount of **migration** from the germinal layer. The diagram on the right shows the basic five vesicle stage of development. There is continual **proliferation** of neurones, some of which migrate all the way out to the outer membrane. To do this, the cells attach themselves to the processes of special **radial glial cells**, which have their cell bodies at the inner membrane, but have long processes that reach to the outer membrane.

There is a **wave of proliferation**, and the cells resulting from this wave attach to the radial glia and move up. There is then another wave of proliferation, and these cells move up to another level. This continues until there is the traditional six-layered structure of the cortex.

The **timing** of this migration and proliferation is very important. If something goes wrong here, you are likely to have severe cognitive problems.

Developmental disorders of the nervous system

Neural development involves several complex and timed processes. For successful development there has to be correct proliferation, differentiation, axonal development and growth, migration, synapse formation, correct myelination, refining processes post-natally, etc. All of these processes must be at the right place at the right time. These may be disrupted by **genetic** or **environmental** abnormalities. Genetic mutations include Down’s syndrome and Fragile X syndrome. Environmentally, the most important thing is the mother and her lifestyle - smoking, alcohol, diet (folic acid, vitamin A → retinoic acid), drugs, etc. The nervous system **develops fairly early in gestation** - even before women realise they are pregnant. So antenatal and pre-conception advice is important to provide the best environment for developing the baby.

There is ongoing research in its early stages about using stem cell differentiation to replace lost neurons, and about guidance mechanisms for axons to induce CNS regeneration.
**Spinal Cord Function and Dysfunction**
by Dr Maggie Lowrie

The spinal cord consists of a core of grey matter surrounded by white matter. Grey matter in the centre of the cord consists of cell bodies of interneurons and motor neurons. It also consists of neuroglia cells and unmyelinated axons. The dorsal horns receive sensory information from the body via spinal nerves and dorsal roots. This information is used in spinal reflexes or projected to the brain for further processing.

The ventral horns contain motoneurones whose axons control the muscles of the body via the ventral roots and spinal nerves. In the thoracic and upper lumbar region, the intermediate horns contain the sympathetic preganglionic motoneurones whose axons control visceral function via the ventral roots and spinal nerves.

The white matter of the spinal cord contains short pathways which interconnect adjacent segments of the spinal cord, and longer tracts which convey information to and from the brain. White matter consists almost totally of myelinated motor and sensory axons.

The spinal cord is clothed in 3 layers of meninges similar to the brain, but with certain differences. There is an extradural (epidural) space containing fat and a venous plexus, and the pia mater has lateral projections called dentate ligaments which extend to the dura and help to stabilise the spinal cord. The lower end of the spinal cord (ending at L2 as the conus medullaris) is anchored to the coccygeal vertebrae by a pial thread called the filum terminale. The subarachnoid space below the end of the spinal cord, the lumbar cistern, contains the lumbar and sacral spinal roots (cauda equina).

The human spinal cord is divided into 31 different segments. At every segment, right and left pairs of spinal nerves form. Spinal nerves, with the exception of C1 and C2, form inside the intervertebral foramen. Each segment of the spinal cord is associated with a pair of ganglia, called dorsal root ganglia, which are situated just outside of the spinal cord. These ganglia contain the cell bodies of sensory neurons. Ventral roots consist of axons from motor neurons.

C1-C6 = Neck flexors
C3,4,5 = Diaphragm
C6,7 = Elbow, wrist extensors
C7, T1 = Small hand muscles
T7-L1 = Abdominal muscles
L2-L4 = Thigh adductors
L5-S2 = Hip extensors
L4-S2 = Knee flexors
L4-S1 = Extension of toes
L1-L4 = Thigh flexors
L4-S1 = Dorsiflexion of foot
L5-S2 = Plantar flexion of foot, toe flexion

The cervical enlargement corresponds roughly to the brachial plexus nerves, which innervate the upper limb. It includes spinal cord segments C4 to T1. The lumbosacral enlargement corresponds to the lumbosacral plexus nerves, which innervate the lower limb. It comprises segments L2 to S3, and is found about the vertebral levels of T9 to T12.

Somatosensory organisation is divided into the dorsal columns pathway (touch, proprioception, vibration) which involves the cuneate and gracil pathways, and there is also spinothalamic pathway (pain, temperature). Both sensory pathways use primary, secondary, and tertiary neurons to get information from sensory receptors at the periphery to the cerebral cortex.
In the dorsal columns pathway, if the primary axon enters below spinal level T6, the axon travels in the fasciculus gracilis, the medial part of the column. If the axon enters above T6, then it travels in the fasciculus cuneatus, which is lateral to the gracilis pathway. In the medulla, the primary axons synapse with a secondary neuron (internal arcuate fibres), and these fibres cross over at the decussation of the lemniscus, and continue ascending on the contralateral side. Secondary axons terminate in the ventral posterolateral nucleus (VPL) of the thalamus, where they synapse with tertiary neurons. These ascend via the posterior limb of the internal capsule and end in the primary sensory cortex.

The spinothalamic pathway (aka the anterolateral system) works differently. Its primary neurons enter the spinal cord and then ascend one to two levels before synapsing in the substantia gelatinosa. The tract that ascends before synapsing is known as Lissauer’s tract. The secondary axons decussate and ascend in the anterior lateral portion of the spinal cord as the spinothalamic tract. The tract ascends all the way to the VPL of the thalamus, where it synapses with tertiary neurons. These ascend via the posterior limb of the internal capsule to the primary sensory cortex.

Motor organisation is in the form of the corticospinal tract. Cortical upper motor neurons descend in the posterior limb of the internal capsule through the crus cerebri, down through the pons, and to the medullary pyramids, where 95% of the axons cross to the contralateral side at the pyramidal decussation. They then descend as the lateral corticospinal tract.

Dysfunction
The degree of the deficit following a spinal cord lesion depends mainly on three factors. Firstly, the loss of neural tissue - usually small if due to trauma but could be more extensive e.g. metastases, degenerative disease. Secondly, the vertical level of the lesion - generally the higher the lesion the more severe the disability. And finally the transverse plane - which and how many tracts are affected.

Damage to the ascending and descending spinal tracts may produce motor and/or sensory loss (e.g. paralysis, anaesthesia). Hyperreflexia and/or spasticity may develop after the initial spinal shock subsides. Severed CNS tracts do not regenerate but there may be some functional improvement after resolution of local damage if the tracts are only compressed. Syringomyelia refers to a disorder in which a cyst or cavity forms within the spinal cord. This is usually seen in the cervical region, so upper limbs are affected. Spinal gliomas may also cause problems in the same way as other lesions.
**Organisation of Brainstem and Cranial Nerves**

by Dr Steve Gentleman

The **brainstem** is the part of the CNS, exclusive of the cerebellum, that lies between the cerebrum and the spinal cord. The major divisions of the brainstem are the **medulla oblongata**, the **pons** and the **midbrain**.

The general somatic afferent (GSA) fibres provide sensation from the skin and mucous membranes. The general visceral afferent (GVA) sensory fibres are from the GI tract, heart, vessels and lungs. The general somatic efferent (GSE) supply is to the muscles of the eye and tongue movements. The general visceral efferent (GVE) is to the preganglionic parasympathetic.

**Special somatic afferent** fibres are from vision, hearing and equilibrium. **Special visceral afferents** are from smell and taste. **Special visceral efferents** are to muscles involved in chewing, facial expression, swallowing, vocal sounds and turning the head.

Most things you see on the back of the brainstem are bilateral structures, except for the **pineal gland**, which secretes melatonin (circadian rhythm). The **superior colliculi** are very important in head and neck reflexes related to vision. The **inferior colliculi** are involved in auditory reflexes. A **peduncle** is a fibre tract with a structural function. There is only one cranial nerve that emerges from the dorsal part of the brainstem - the **trochlear nerve** (IV).

The **rhomboid fossa** is also known as the **fourth ventricle**. The cerebellum is held onto the back of the brainstem by the **cerebellar peduncles**. There are the superior, middle and inferior cerebellar peduncles, which connect the cerebellum to the midbrain, pons and medulla respectively. The **dorsal columns** are the main sensory tracts, carrying fine touch and proprioceptive information to the brain.

All except two cranial nerves arise from the brainstem - the olfactory bulbs are at the base of the frontal lobe, and the optic nerves. The oculomotor nerve arises from the **interpeduncular fossa** at the midbrain level, and it supplies most of the extrinsic muscles of the eye. The trigeminal nerve emerges from the pons. The trigeminal nerve is the sensory nerve of the head and neck, but it also is responsible for the muscles of mastication. The abducens nerve, the facial nerve and the vestibulocochlear nerve arise at the **pontine-medullary junction**.

Key features on the medulla are the motor pathways - the **pyramids**. Motor fibres run down the corticospinal tract through the cerebral peduncle, and disappear from view in the pons. They then reappear as the pyramids.
of the medulla. At the base of the medulla there is the **pyramidal decussation**, where 95% of the fibres cross over to the other side.

**Brainstem development**

This is the embryonic spinal cord. Dorsally, there are sensory areas. In the ventral root there are motor fibres.

When the brainstem develops, the **alar plate opens** up.

The result is that the functional columns spread out in a particular distribution.

**Sensory nuclei are more lateral** in the brainstem, and the motor nuclei are much nearer the midline in the brainstem.

There are three divisions of the brainstem: midbrain, pons and medulla. It is important to remember that everything in the brainstem (apart from the pineal gland) are **bilateral** structures.

In the diagram below, the **sensory nuclei** are in **red**, and the **motor nuclei** are in **blue**.

The two **GSE** nuclei in the midbrain are the **oculomotor** nucleus and the **trochlear** nucleus. In the pons, there is the **abducens** nucleus. In the medulla, the only GSE function is the **hypoglossal** nucleus.

Moving out more laterally, there are the **GVE** nuclei (parasympathetic nuclei). The first of these in the midbrain is the **Edinger-Westphal** nucleus, which are associated with the parasympathetic fibres going to the eye (III). At the junction between the pons and the medulla are the **salivatory** nuclei (VII and IX). Moving down further into the medulla, there is a large nucleus called the **dorsal motor** nucleus (X).

Finally there are **SVE** in between the GSE column and the GVE column. In the pons, there is the **trigeminal motor** nucleus (V), and further down there is the **facial** nucleus (VII). In the medulla there is the **nucleus ambiguus**, which is important in vocalisation (IX, X, XI). Finally in the cervical spinal cord, there is the **spinal accessory** nucleus (XI), innervating the sternocleidomastoid and the trapezius muscles.

The sensory nuclei are more lateral. The **trigeminal nerve** dominates sensory innervation of the head and neck. Spread all the way down the GSA column are the various **trigeminal nuclei**. The first at the top in the
midbrain is the **mesencephalic trigeminal** nucleus. There is then the small **pontine trigeminal** in the pons, and the **spinal trigeminal** nucleus runs from the pons, through the medulla, to the spinal cord. Most laterally is the **SSA** column. There are the **vestibulocochlear** nuclei in the pons and medulla. Most medially is the **solitarius** nucleus in the **GVA/SVA** column at the pontine/medullary level, which is involved in taste perception (VII, IX, X).

**Internal structure of the brainstem**

**Midbrain level:** the Mickey Mouse shaped section.

The key structures that define this Mickey Mouse shape are the **cerebral peduncles**. Sometimes called the “crux cerebri”, these are the main fibres coming down from the cortex, going down to the spinal cord, forming the corticospinal tract.

The space between the two peduncles is the **interpeduncular fossa**, which is where the oculomotor nerve arises from.

The **cerebral aqueduct** is another clue that the level you are looking at is the midbrain, and also at this level are the **inferior colliculi**. The last thing that distinguishes the midbrain is the **substantia nigra** on either side. These areas are black because these cells are full of neuromelanin, which is a by-product of dopamine metabolism. The older you get, the more of this you lay down (unless there is Parkinson’s disease).

**Pons level:**

There are a number of distinguishing features to point out in the pons. First of all, **transverse fibres** are unique to the pons. These fibres run between the two **middle cerebellar peduncles**. You can’t see the corticospinal tract is because it is below the level of the pons.

The **fourth ventricle** is another clue that you are at the level of the pons, as the pons forms the floor of the fourth ventricle. The **trigeminal nerve** emerges laterally from the pons.

**Upper Medulla level:**

The wiggly structure is the **inferior olivary nucleus**, which is very important in motor function. This structure is unique to the upper medulla.

There is also the re-emergence of the corticospinal tract in the form of **pyramids**. There is still the **fourth ventricle** in the upper medulla.

The **hypoglossal nerve** nucleus is also present here.
**Lower Medulla level:**

Coming down to the junction of the spinal cord, the cross section is a distinctive round shape.

The **dorsal columns** can be seen here (touch and proprioception). The little one is called **gracilis** (sensory information from the lower limb), and more laterally there is **cuneatus** (sensory information from the upper limb).

In terms of the ventricular system, there is the **central canal**.

Also in the lower medulla is the **pyramidal decussation** (the crossing over of the corticospinal fibres).

**Lateral medullary syndrome** is a set of symptoms seen when there is **thrombosis** of the vertebral artery or the posterior inferior cerebellar artery. The patient will present with **vertigo**, ipsilateral cerebellar **ataxia**, and also ipsilateral **loss of pain/thermal sense** in the face. There are also signs of **Horner’s syndrome**, which is droopy eyelids (ptosis), lack of sweating and miosis related to disruption of sympathetic innervation to the face. The patient will have **hoarseness**, and difficulty in **swallowing**, and there will be a contralateral loss of pain/thermal **sense** in the trunk and limbs.

The **posterior inferior cerebellar artery** has branches which supply the lateral medulla. A lesion could take out the entire lateral part of the medulla. There will therefore be problems with the **vestibular nucleus** (explains the vertigo), the **inferior cerebellar peduncle** (explains the ataxia), the **trigeminal nucleus** (explains the ipsilateral loss of innervation to the face), the **sympathetic tract** (explains Horner’s syndrome), the **nucleus ambiguus** (explains the hoarseness and difficulty swallowing) and the **spinothalamic tract** (explains the loss of sensory information from the body). This is a very rare syndrome.
Blood Supply to the Central Nervous System
by Dr Steve Gentleman

The brain makes up 2% of our body weight, but uses 10 to 20% of our cardiac output, 20% of the body’s oxygen consumption, and 66% of liver glucose. The brain is therefore very vulnerable if its blood supply is impaired.

There are two main sources of blood to the brain - the internal carotid arteries, and also the vertebral arteries, which travel up the cervical vertebrae, come through the foramen magnum at the base of the skull and provide the posterior circulation to the brain. These two sets of arteries come together at the base of the brain to form an anastamotic circuit called the Circle of Willis. From the Circle of Willis, there are three main pairs of cerebral arteries supplying the anterior, middle and posterior cerebrum.

The common carotid artery goes up in the neck and then bifurcates at about the level of the laryngeal prominence. It splits into an internal and external carotid artery. The internal carotid artery has no branches outside the cranial cavity. The external artery supplies all the structures of the face, and therefore has multiple branches. A branch from each subclavian artery is the vertebral artery. It passes up through the transverse foramen of the cervical vertebrae to go to the base of the skull.

When you remove the brain from the skull, the blood vessels remain attached to the base. They form an arrangement called the Circle of Willis. The advantage of this structure is that e.g. if there is damage in one carotid artery, the blood supply from the other one may provide some compensation. The main supply arteries anteriorly are the internal carotid arteries, which pass through the base of the skull and arrive towards the front of the brain. Posteriorly are the two vertebral arteries which come together to form the basilar artery. It is the basilar artery that can be seen on scans, sitting on the anterior surface of the pons. These are the two main feed systems into the Circle of Willis.

The basilar artery splits into two posterior cerebral arteries. The main branch of each internal carotid artery is the middle cerebral artery. Another branch of the internal carotid is the anterior cerebral artery, which supplies the frontal lobes, and also a large amount of the medial longitudinal fissure of the brain all the way back to the parieto-occipital sulcus. To complete the circle there are two posterior communicating arteries, and at the front there is just one anterior communicating artery.

Venous blood in the cranial cavity circulated in venous sinuses rather than veins.

Venous sinuses are made up of the folds of the dura mater (the outermost of the meninges).

There is a large cerebral vein which drains most of the brain itself into a sinus. The sinuses drain to the back of the head, then out through the internal jugular vein.

The diagram shows the folds of the dura forming the sinuses. The biggest venous sinus is the superior sagittal sinus. The venous blood circulates to the back of the head, and then moves laterally through lateral sinus and sigmoid sinus to become continuous with the internal jugular vein.
Stroke is a cerebrovascular accident (CVA). This is defined as a rapidly developing focal disturbance of brain function of presumed vascular origin which lasts for more than 24 hours. A stroke due to a blockage is infarction (85%), and a stroke due to a bleed is a haemorrhage (15%).

Transient Ischaemic Attack (TIA) is a rapidly developing focal disturbance of brain function of presumed vascular origin that resolves completely within 24 hours.

Infarction refers to the degenerative changes which occur in tissue following occlusion of an artery. Ischaemia is a lack of sufficient blood supply to nervous tissue, resulting in permanent damage if blood flow is not restored quickly. This term is often misused when talking about hypoxia or anoxia. Ischaemia is the loss of blood supply which includes glucose as well as oxygen.

Common causes of these occlusions are thrombosis and embolism. A thrombus is a blood clot. An embolism is the plugging of a small vessel by material carried from a larger vessel e.g. thrombi from the heart or atherosclerotic debris from the internal carotid.

Stroke is the third commonest cause of death in the UK, with about 100,000 deaths per annum. 50% of the survivors are permanently disabled, and 70% show an obvious neurological deficit. Risk factors for stroke include age, hypertension, cardiac disease, smoking, and diabetes mellitus.

The cerebral arteries supply three distinct regions of the brain. The perfusion field of the anterior cerebral artery is massive. Damage in the different perfusion fields will present with different symptoms.

Interruption of flow to the anterior cerebral artery will present with paralysis of the contralateral leg more than the arm, and also the face. Frontal lobe function is affected, so there is a disturbance of intellect, executive function and judgement (abulia).

Interruption of flow to the middle cerebral artery is a “classic stroke”. It presents with contralateral hemiplegia in the arm more than in the leg, contralateral hemisensory deficits, hemianopia, and aphasia (left sided lesion).

Interruption of flow to the posterior cerebral artery will present with visual deficits, like homonymous hemianopia and visual agnosia. There is also receptive aphasia, where you can’t understand speech.

Lacunar infarcts are often associated with hypertension (a lacune is a small cavity). They appear in deep structures of the brain (subcortical, particularly in the basal ganglia) as a result of small vessel occlusion. The deficit is dependent on the anatomical location of the blockage.

Haemorrhagic stroke can be extradural (trauma, immediate effects, surgical emergency as risk of pressure build-up and brainstem coning); subdural (trauma, lower pressure so delayed effects, rupture of bridging veins between venous sinuses of the brain); subarachnoid (ruptured aneurysm of basal vessels); or intracerebral (spontaneous hypertensive, within the brain itself).
Cerebral Blood Flow Regulation and the Blood Brain Barrier
by Professor John Laycock

Oxygen and glucose supply to the brain
Blood flow to the brain is high, at approximately 55ml/100g of tissue per minute! This is 16% of the total cardiac output. Whenever blood flow to the brain is reduced by more than 50%, insufficient oxygen is delivered to the tissues and function is increasingly impaired. If the total cerebral blood flow is interrupted for as little as 4 seconds, unconsciousness will result. After a few minutes, irreversible damage occurs to the brain.

Normally, there is a vast surplus provision of glucose (the principal energy source) to the brain via the blood. This supply of glucose is extremely important because the brain cannot synthesise or utilise any other source of energy, although ketones can be metabolised to a very limited extent. If the supply of glucose to the brain is interrupted, or the blood glucose concentration is low (i.e. hypoglycaemia), then brain function is impaired. If the glucose concentration falls below 2mM, it can result in unconsciousness, coma, and ultimately death.

Because of the constant need by the brain for oxygen and glucose, it is vital that the cerebral blood flow be maintained which means that an efficient regulatory system must be operational. It is regulated by mechanisms affecting total cerebral blood flow and by mechanisms which relate activity or requirement in specific brain regions to altered localised blood flow.

Regulation of cerebral blood flow
Total cerebral blood flow is autoregulated between mean arterial blood pressures (MABP) of approximately 60 and 160mmHg. Furthermore, the local delivery of oxygen to brain tissue is related to the needs of that tissue by the process of local autoregulation.

Neural factors that control cerebral blood flow include sympathetic nerve stimulation producing vasoconstriction, which probably only operates when arterial blood pressure is high. There is also parasympathetic (facial nerve) stimulation producing slight vasodilation if necessary. There are also central cortical neurones releasing a variety of vasoconstrictor neurotransmitters, such as catecholamines including dopaminergic neurons which produce vasoconstriction (localised effect related to increased brain activity).

Dopaminergic neurones innervate penetrating arterioles and pericytes around capillaries. Pericytes are a form of brain macrophages with diverse activities (e.g. immune function, transport properties, contractile, etc). Dopaminergic neurones may participate in the diversion of cerebral blood to areas of high activity. Dopamine may cause contraction of pericytes via aminergic and serotoninergic receptors.

Chemical factors also control cerebral blood flow. Vasodilators include CO₂, pH, nitric oxide, K⁺, adenosine, and anoxia. Other chemical factors include kinins, prostaglandins, histamine, and endothelins.

Cerebral arterial vasodilation by CO₂:
This diagram illustrates a blood vessel. The vessel is surrounded by endothelial cells, and around that are smooth muscle cells. Below that there is neural tissue (nerve cells).

Hydrogen ions (vasodilator) in the blood are unlikely to have an effect on cerebral blood flow, maybe just a slight effect. The main reason is that the BBB remains relatively impermeable to hydrogen ions. Hydrogen ions are mediated by the effects of CO₂ which can cross the BBB without any problems (it is a lipophilic molecule). Once it gets through the BBB, it gets to the smooth muscle cells and the ECF outside it. Both of these places contain carbonic anhydrase. Immediately there
is CO$_2$ reacting with water to form carbonic acid, and then hydrogen ions and bicarbonate. The hydrogen ions then cause vasodilation. This is how the CO$_2$ works.

CO$_2$ is effective as a vasodilator, but this appears to be an indirect effect by producing hydrogen ions on the brain side of the blood-brain barrier.

**Nitric oxide** is produced in the smooth muscle cells by the conversion of arginine to citrulline with the release of NO (facilitated by the presence of NO synthase). The way it works is by guanylyl cyclase being produced, and this converts GTP to cGMP, which causes calcium ions to move into endocytes and various other storage sites, and therefore allowing the smooth muscle to relax and cause vasodilation.

**Brain compartments**

Neurones are surrounded by an extra-cellular fluid. There are also the ventricles, containing cerebrospinal fluid. There is also a third fluid in the brain, the blood. There is a blood flow to the choroid plexus to produce CSF.

There are certain parts of the brain, which lie outside the BBB. This means they are subject to meeting the molecules of the general circulation, and they connect to other parts of the brain. These organs are called circumventricular organs (CVOs), which are areas of the brain which lie outside the blood brain barrier.

**Formation of CSF**

CSF is formed by the choroid plexus, which is capillaries surrounded by ependymal cells (tight junctions). These cells secrete CSF into the ventricles - the lateral ventricles, then to the third ventricle via the interventricular foramina, down the cerebral aqueduct into the fourth ventricle and into the subarachnoid space via the medial and lateral apertures. The volume of CSF is about 80-150ml. Its main functions are in protection (physical and chemical), and also in nutrition of neurones, and the transport of molecules.

**The Blood Brain Barrier**

The main function of the BBB is to protect the brain from potentially harmful substances in the blood (e.g. certain toxins and circulating transmitters such as catecholamines) and from wide variations in ion concentrations. The barrier is mainly due to the presence of tight junctions between endothelial cells of the microvasculature (making the capillaries “non-fenestrated”) and astrocyte end-feet close to the capillary walls. The BBB allows some lipophilic molecules (e.g. alcohol) access to the brain CSF and ECF. However, it only allows certain hydrophilic substances to enter the CSF and brain ECF by means of specific transport mechanisms, examples being:

- water, via aquaporin 1 and 4 channels
- glucose, via GLUT1 proteins
- amino acids, via 3 different transporters
- electrolytes, via specific transporter systems

Some areas of the brain (collectively called the circumventricular organs, CVOs) have “fenestrated” capillaries and therefore lie outside the blood-brain barrier. In other words, molecules can readily pass from blood to the CSF and ECF. For example, in the median eminence region of the hypothalamus, the subfornical organ (SFO), and the organum vasculosum of the lamina terminalis (OVLT).
Thalamus and Hypothalamus
by Dr Maggie Lowrie

The diencephalon, which is divided in two by the narrow third ventricle, is the second compartment of the forebrain. It contains two major parts: the thalamus and the hypothalamus. The thalamus is a collection of several large nuclei that serve as synaptic relay stations and important integrating centres for most inputs to the cortex. It also plays a key role in general arousal and focused attention.

The thalamus occupies most of the diencephalon. It is divided into the left and right thalamus by the third ventricle. The right and left thalamus are connected by the intermediate mass. Each thalamus is a collection of individual nuclei with separate functions and connections with ipsilateral forebrain structures. The nuclei are all interconnected.

The thalamus functions as a relay centre between the cerebral cortex and the rest of the CNS. It integrates information, and is involved in virtually all functional systems.

Specific thalamic nuclei have reciprocal connections with a primary cortical area (i.e. with a clearly defined function). For the visual system, the inputs are sent to the lateral geniculate nucleus of the thalamus, which in turn projects to the primary visual cortex in the occipital lobe. The medial geniculate nucleus acts as a key auditory relay between the inferior colliculus of the midbrain and the primary auditory cortex. The ventral posterior nuclei are a key somatosensory relay, which sends touch and proprioceptive information to the primary somatosensory cortex. The ventral posterolateral nucleus is somatosensory for the body, and the ventral posteromedial is somatosensory for the head. The ventral anterior nucleus helps to function in coordination and planning of movement, and in learning movement. The ventral anterior nucleus helps to function in planning movement, and initiates wanted movement and inhibits unwanted movement. The thalamus also plays an important role in regulating states of sleep and wakefulness.

Association nuclei have more diffuse reciprocal connections with the association cortex. The anterior, lateral dorsal, and dorsal medial nuclei connect with parts of the limbic system (cingulate and prefrontal cortex). The lateral posterior and pulvinar nuclei connect with the association cortex at the junction of the parietal, temporal and occipital lobes and the prefrontal cortex.

The intralaminar nuclei receive inputs from the reticular formation of the brainstem, and project diffusely to all cortical areas. The reticular nucleus also receives inputs from the reticular formation but projects to the other thalamic nuclei only, regulating the flow of information through these to the cortex. Thus the reticular formation, intralaminar nuclei, and reticular nuclei form the reticular activating system, which controls the level of arousal of the brain by modulating the level of activity of the cerebral cortex.

Cerebrovascular events (strokes) can cause thalamic syndrome, which results in a contralateral hemianaesthesia, burning or aching sensation on one half of the body (painful anaesthesia) often accompanied by mood swings. Sensation is reduced, exaggerated or altered, the patient feels pain, and there is emotional disturbance.

The hypothalamus lies below the thalamus and is on the undersurface of the brain. Although it is a tiny region that accounts for less than 1 percent of the brain’s weight, it contains different cell groups and pathways that form the master command centre for neural and endocrine co-ordination. Indeed, the hypothalamus is the...
single most important control area for homeostatic regulation of the internal environment. Behaviours having to do with preservation of the individual and species (e.g. eating, drinking, reproducing) are among the many functions of the hypothalamus. The hypothalamus lies directly above and modulates the function of the pituitary gland, an important endocrine structure, which is attached to the hypothalamus by the infundibulum.

The hypothalamus is also divided in two by the third ventricle. It is a collection of individual nuclei with separate functions. It mainly has ipsilateral connections with the forebrain.

The paraventricular nucleus and the supraoptic nucleus contain oxytocin and vasopressin neurons which project to the posterior pituitary, but also contain neurons that regulate ACTH and TSH secretion from the anterior pituitary, as well as gastric reflexes, maternal behaviour, blood pressure, feeding, immune responses, and temperature.

Hypothalamic control is important in behavioural control of eating, drinking, sexual behaviour, circadian rhythm and memory. It responds to many different signals, some of which are generated externally and some internally. It is thus richly connected with many parts of the CNS. The hypothalamus co-ordinates homeostatic mechanisms by the autonomic nervous system (via connections with the brainstem and spinal cord), the endocrine system (via the pituitary), and by controlling behaviour (via connections with forebrain structures). Forebrain structures associated with the hypothalamus include the olfactory system and the limbic system (hippocampus, amygdala, cingulate cortex, septal nuclei).

The hypothalamus is responsive to light, olfactory stimuli, steroids, neural information, autonomic inputs, blood borne stimuli (like leptin, ghrelin, angiotensin, insulin, pituitary hormones, cytokines, etc), and stress.

A patient with a hypothalamic tumour will present with polydipsia, polyuria, and absent menses. Later they will have labile emotions, experience rage, perhaps show inappropriate sexual behaviour, have memory lapses, have temperature fluctuations, have decreased thyroid, adrenal cortex and gonadal function, and also have hyperphagia.

Extra:
Medial Preoptic nucleus = urinary bladder contraction, HR↓, BP↓
Supraoptic nucleus = oxytocin and vasopressin release
Paraventricular nucleus = oxytocin and vasopressin release
Anterior hypothalamic nucleus = thermoregulation, panting, sweating, thyrotrophin inhibition
Suprachiasmatic nucleus = vasopressin release, circadian rhythm
Lateral Preoptic nucleus = thermoregulation in skin, mucous membranes, and hypothalamus itself
Lateral nucleus = thirst and hunger
Dorsomedial hypothalamic nucleus = GI stimulation
Ventromedial nucleus = satiety, neuroendocrine control
Arcuate nucleus = LH releasing hormone, FSH releasing factor, feeding, dopamine, GHRH
Mammillary nuclei = memory
Posterior nucleus = BP↑, pupillary dilation, shivering
**Touch, Proprioception and Nociception**

by Dr Maggie Lowrie

The somatosensory system is concerned with sensory information coming from the skin, muscles, joints and ligaments. **Touch and proprioception** are carried via the dorsal columns pathway to the somatosensory cortex. **Touch** includes fine touch, pressure and vibration. **Proprioception** provides position sense and includes joint position, muscle length and muscle tension.

**Receptors:**

All receptors for touch and proprioception are **mechanoreceptors**. They transduce a mechanical stimulus (deformation) into electrical signals. They are the modified terminals of the peripheral axons of primary sensory neurons. Receptors for temperature are **thermoceptors**, and receptors for pain are **nociceptors**.

The function of mechanoreceptors depends on several factors. Firstly, the **degree of specialisation** from free nerve endings to elaborate accessory structures. Secondly, the **location** of the receptors, for example in various layers of skin or around the hair shaft. The muscle spindle detects changes in muscle length, and the Golgi tendon organ detects changes in muscle tension. Thirdly, **physiological properties** such as activation threshold will determine sensitivity (all touch and proprioception receptors are low threshold). These may be slow or fast adapting.

**Adaptation:**

**Adaptation** is a property of certain receptors through which they become less responsive or cease to respond to repeated or continued stimuli of constant intensity.

It is the decline in the frequency of firing of a neuron, particularly of a receptor, under conditions of constant stimulation. Adaptation occurs in most sense receptors. It is useful because it prevents the nervous system from being bombarded with information about insignificant matters like the touch and pressure of our clothing.

**Sensory neurons:**

The cell bodies of sensory neurons are in the peripheral nervous system, in the dorsal root ganglia or in the trigeminal ganglia.

There are various classifications of axons. Type I axons are muscle spindles and Golgi tendon organs. Type II axons / Aβ axons are for most other mechanoreceptors, like Meissner corpuscles, Merkel endings, etc. All are fast conducting.

Type III axons are for some nociceptors, cold receptors, most hair receptors, some visceral receptors and preganglionic autonomic efferents.

Type IV axons are most nociceptors (dull, aching pain), warmth receptors, some visceral receptors, few mechanoreceptors, and postganglionic autonomic efferents.
The **receptive field** is the number of receptors innervated by one sensory neuron. The larger the receptive field size, the lower the acuity. Density of receptive fields varies over the body. The **intensity of the stimulus** is coded by frequency of firing of the neuron. The amplitude of the action potential does not change. Usually firing frequency is related to \( \log \) [stimulus intensity], i.e. if the stimulus increases 10 fold, then the firing frequency doubles.

**Central Pathway:**

The **posterior column-medial lemniscus pathway** is the sensory pathway responsible for transmitting *fine touch, vibration and conscious proprioceptive* information from the body to the cerebral cortex.

The name comes from the two structures that the sensation travels up: the posterior (or dorsal) columns of the spinal cord, and the medial lemniscus in the brainstem.

**Discriminative sensation** is well developed in the fingers of humans, and allows us to feel fine textures and determine what an unknown object in our hands is without looking at it. This fine sensation is detected by **Meissner's corpuscles** that lie in the dermis of the skin close to the epidermis. When these structures are stimulated by slight pressure, an **action potential** is started. Alternatively, proprioceptive muscle spindles and other skin surface touch receptors such as Merkel cells, Ruffini endings, Pacinian corpuscles, and hair follicle receptors (Peritrichial endings) may involve the first neuron in this pathway.

The action potential travels up an axon (the cell body of the neuron will be in a **dorsal root ganglion**). (The neurons are classified as **pseudo-unipolar**, so they are regarded as having just one long process, which includes both a peripheral branch dendrite and central branch axon.) So the sensation travels from the skin, along the axon, past the neuronal cell body, and into the dorsal column of the spinal cord.

The axons continue inside the **spinal cord**, running up the dorsal column. Axons from the lower body are most medial, and run in the **gracile** tract of the spinal column. Sensory axons from the upper body enter the spinal cord later, specifically from T6 on up, so are more lateral and travel up the **cuneate** tract.

At the level of the closed medulla oblongata, these axons synapse with neurons in the **gracile nucleus** and **cuneate nucleus**. The secondary neurons (that start in the nuclei) cross over to the other side of the medulla (as internal arcuate fibres) to form the **medial lemniscus**. This crossing over is commonly referred to as the sensory **deccussion**. At the medulla, the medial lemniscus is orientated perpendicular to the way the fibres travelled in the posterior columns. For example, in the columns, lower limb is medial, upper limb is more lateral. At the medial lemniscus, axons from the leg are more ventral, arm fibres more dorsal. Fibres from the trigeminal nerve (supplying the head) come in dorsal to the arm fibres, and travel up the lemniscus too.

The axons travel up the rest of the **brainstem**, and synapse at the **thalamus** (at the ventral posterolateral nucleus for sensation from the neck, trunk, and extremities, and at the ventral posteromedial nucleus for
Neurons starting in the thalamus travel up the posterior limb of the *internal capsule*, and again head and leg swap relative positions. The axons synapse in the *primary sensory cortex*, with lower body sensation most medial (e.g. the paracentral lobule) and upper body more lateral.

A sensory stimulus only becomes a conscious, localised sensation (perceived) when it reaches the cortex. *Somatosensory I* (SI) is where the body map is distorted according to relative density inputs from different parts of the body. The response of neurones in SI varies. Some respond to stimulus properties like pressure and vibration, and some respond to abstracted properties like movement and object shape. *Somatosensory II* (SII) receives intracortical projections from SI. The posterior parietal cortex is necessary for interpretation of spatial relationships.

Injury to the pathway anywhere from the periphery to the cortex may result in *anaesthesia* or *paraesthesia*, which are useful in diagnosis. Some degenerative disorders affect the somatosensory system predominantly, e.g. some peripheral neuropathies.

**Nociception**

This sensation provides information about noxious (unpleasant or harmful) stimuli. When this information is processed by the brain it is perceived as *pain*. A nociceptive stimulus can be measured, but pain is subjective. Pain is much more susceptible to contextual influences than other modalities.

*Visceral pain* is carried peripherally by autonomic nerves and centrally in the spinothalamic and dorsal columns pathways. Localisation of visceral pain is mainly referred to the body wall at the same spinal level. *Somatic pain* and *temperature* (from skin, muscles, joints and ligaments) are carried to the brain by the *spinothalamic tract*.

Nociceptors are *polymodal*, i.e. they are triggered by mechanical, thermal or chemical stimulus. They have *free nerve endings* with *high threshold*. They are *slow adapting*. The cell bodies of the sensory neurons are in the peripheral nervous system (dorsal root ganglia or trigeminal ganglia). There are two axon types for nociception, including Aδ *mechanoceptors* or *thermoceptors* (fast, sharp pain, leads to avoidance) and also C *chemoceptors* e.g. bradykinin or histamine (producing dull aching pain, leads to guarding to allow recovery). Receptive fields for nociception are usually quite *large*, and intensity is coded by frequency of firing.

**Central Pathway:**

The *spinothalamic tract* carries information to several destinations in the brain:

- to the local VPL and VPM nuclei of the thalamus and then on to SI and SII cortex, for analysis of localisation and intensity of the noxious stimulus.
- to the brainstem etc for perception of pain (affective pathway).
- to the periaqueductal grey of the midbrain to inhibit pain (central inhibition pathway).

The pathway *decussates* at the level of the spinal cord, rather than in the brainstem like the posterior column-medial lemniscus pathway and corticospinal tract.

The *lateral* spinothalamic tract transmits pain and temperature. The *anterior* spinothalamic tract transmits crude touch.
The spinothalamic tract uses three neurons to convey sensory information from the periphery to conscious level at the cerebral cortex.

**Pseudounipolar neurons** (those with only one long process) in the dorsal root ganglion have axons that lead from the skin into the dorsal spinal cord where they ascend or descend one or two vertebral levels via Lissauer’s tract and then synapse with secondary neurons in either the substantia gelatinosa or the nucleus proprius. These secondary neurons are called **tract cells**.

The axons of the tract cells cross over (**decussate**) to the other side of the spinal cord via the anterior white commissure, and to the anterolateral corner of the spinal cord (hence the spinothalamic tract being part of the anterolateral system). The axons travel up the length of the spinal cord into the brainstem.

Travelling up the brainstem, the tract moves dorsally. The neurons ultimately synapse with third-order neurons in several nuclei of the **thalamus**, including the medial dorsal, ventral posterior lateral, and ventral medial posterior nuclei. From there, signals go to the **cingulate cortex**, the primary somatosensory cortex, and insular cortex respectively.

Somatotropic organisation is maintained through the entire pathway from dermatomes to cortex. Cortical representation of pain is not well understood. Localisation and intensity of the stimulus only may register there. In the **affective pain pathway**, the axons of the spinothalamic tract send collateral branches to the brainstem (reticular formation), thalamus (intralaminar nuclei), hypothalamus and forebrain (e.g. cingulate gyrus, insula) to trigger an increase in awareness and so we can register the unpleasantness of the stimulus i.e. pain.

**Central (descending) inhibition** is where cerebral activity triggers a descending pathway in the brainstem which inhibits the nociceptive pathway in the dorsal horn. This pathway uses endogenous opioids and other transmitters.

**Peripheral inhibition** takes place in superficial levels of the dorsal horn (substantia gelatinosa). Stimulation through non-nociceptive inputs inhibits projection of a nociceptive stimulus to the spinothalamic tract. This is Gate Theory.

In **nociceptive dysfunction**, disruption of the pathway may reduce pain but predisposes the patient to increased injury. For example, in syringomyelia or Charcot joints. Some changes may exacerbate pain, for example thalamic syndrome, or windup in the dorsal horn, or phantom pain.
Synapse is the Greek word for "contact" or "junction". Synapses allow for contact from neurone to muscle or from neurone to neurone. The basic structure is similar throughout the nervous system, and arrangements can be simple or complex. The contact ratio ranges from 1:1 for muscle to 10,000:1 in the CNS.

The membrane potential of the post-synaptic neurone can be altered in two directions by inputs. It can be made less negative (be brought closer to threshold for firing) which is an excitatory post synaptic potential (EPSP) or it can be made more negative (brought further away from threshold for firing) which is an inhibitory post synaptic potential (IPSP). In an EPSP the probability of firing is enhanced, and in an IPSP the likelihood of the cell producing an action potential is less.

EPSPs and IPSPs can also summate. The degree of summation will determine how readily a neurone can reach threshold to produce an action potential.

The neuromuscular junction is a specialised synapse between the motor neuron and the motor muscle fibre cell membrane.

Activation of the neuromuscular junction occurs when an action potential arrives at the junction. The Ca$^{2+}$ influx into the pre-synaptic terminal causes ACh release, and ACh binds to receptors on the motor end plate. The ion channel opens, and the Na$^+$ influx causes an action potential in the muscle fibre. At rest, individual vesicles release ACh at a very low rate causing miniature end-plate potentials (mEPP).

Alpha motor neurons are lower motor neurons of the brainstem and the spinal cord. They innervate the (extrafusal) muscle fibres of the skeletal muscles. Their activation causes muscle contraction. The motor neuron pool contains all alpha motor neurons innervating a single muscle.

The Motor Unit is the name given to a single motor neuron together with all the muscle fibres that it innervates. It is the smallest functional unit with which to produce force. Humans have approximately 420,000 motor neurons and 250 million skeletal muscle fibres. On average each motor neuron supplies about 600 muscle fibres. Stimulation of one motor unit causes contraction of all the muscle fibres in that unit.

There are three different types of motor unit, classified by the amount of tension generated, speed of contraction and fatiguability of the motor unit. Type I is slow (S type I), and these motor units have the smallest diameter cell bodies, small dendritic trees, the thinnest axons and the slowest conduction velocities. Type IIA is fast and fatigue resistant (FR, type IIA), and these motor units have larger diameter cell bodies, larger dendritic trees, thicker axons and faster conduction velocities. Type IIB is fast but fatiguable (FF, type IIB), with larger diameter cell bodies, larger dendritic trees, thicker axons and faster conduction velocities.

There are two mechanisms by which the brain regulates the force that a single muscle can produce. The first is recruitment. Motor units are not randomly recruited; there is an order to this. Recruitment is governed by the “size principle”. Smaller units are recruited first (these are generally the slow twitch units). As more force is required, more units are recruited. This allows fine control (e.g. when writing), under which low force levels are required. Recruitment order is S, FR, then FF. De-recruitment occurs in the reverse order.
Rate coding is the second mechanism. A motor unit can fire at a range of frequencies. Slow units fire at a lower frequency. As the firing rate increases, the force produced by the unit increases. Summation occurs when units fire at a frequency too fast to allow the muscle to relax between arriving action potentials.

Neurotrophic factors are growth factors which prevent neuronal death and promote growth of neurons after injury. Motor unit and fibre characteristics are dependent on the nerve which innervates them. If a fast twitch muscle and a slow twitch muscle are cross innervated, the soleus becomes fast and the FDL becomes slow. The motor neurone has some effect on the properties of the muscle fibres which it innervates.

Organisation of the spinal cord: motor tracts

Reflex function
A reflex is an automatic and often inborn response to a stimulus that involves a nerve impulse passing inward from a receptor to a nerve centre and then outward to an effector (as a muscle or gland) without reaching the level of consciousness. It is an involuntary co-ordinated pattern of muscle contraction and relaxation elicited by peripheral stimuli, whose magnitude and timing are determined respectively by the intensity and onset of the stimulus. If the biceps is tapped, the reflex occurs quickly and is related in size to how hard the biceps was hit. Reflexes differ from voluntary movements in that once they are released, they can’t be stopped.

In the monosynaptic (stretch) reflex, it begins when stretching stimulates a sensory receptor such as a muscle spindle. The sensory neuron is excited, and within the integrating centre of the spinal cord, the sensory neuron activates the motor neuron. The motor neuron is excited, and the effector (the same muscle) contracts to relieve the stretching. The Hoffman (H) reflex is the electrical equivalent of this tendon jerk mechanism. Other reflexes include flexion withdrawal and flexion withdrawal with crossed extensor.
Traditionally we think of reflexes as being autonomic (knee jerk) and stereotyped behaviours (sneeze, cough) in response to stimulation of peripheral receptors. But can they be influenced? Try clenching teeth or making a fist when having the patellar tendon tapped, and you’ll find the reflex is very strong! This is the Jendrassik manoeuvre.

In terms of supraspinal control of reflexes, higher centres of the CNS exert inhibitory and excitatory regulation upon the stretch reflex. Inhibitory control dominates in normal conditions (N). Decerebration reveals the excitatory control from supraspinal areas (D). Rigidity and spasticity can result from brain damage giving over-active or tonic stretch reflexes.

If the knee is extended and the muscle goes slack, the spindle is shortened to maintain its sensitivity. This is the gamma reflex loop.

Facilitation from higher centres acts on the motoneurone, increasing its sensitivity to afferent input, or indirectly via gamma motoneurones and the muscle spindle, increasing afferent input to the alpha motoneurones.

Higher centres and pathways involved include:
- Cortex: corticospinal (fine control of limb movements, body adjustments)
- Red nucleus: rubrospinal (automatic movements of the arm in response to posture/balance changes)
- Vestibular nuclei: vestibulospinal (altering posture to maintain balance)
- Tectum: tectospinal (head movements in response to visual information)

Hyper-reflexia is sometimes seen due to a stroke (for example). This is because of a loss of descending inhibition. This can be seen at the patellar tendon and at the biceps, as well as in the Babinski sign.

Hypo-reflexia is when reflexes are below normal or absent. This is mostly associated with lower motor neuron diseases.
**The Basal Ganglia and Cerebellum**
by Dr Marios Politis

The balance between the basal ganglia and the cerebellum allows for a smooth, co-ordinated movement, and a disturbance in either system will show up as movement disorders.

The basal ganglia are a group of nuclei situated at the base of the forebrain. They are associated in a variety of functions, including voluntary motor control, procedural learning, eye movements, cognitive function and emotional function.

The main components of the basal ganglia are the **striatum** (composed of caudate and putamen), the internal and external segments of the **globus pallidus** (GPi and GPe), and the **subthalamic nucleus** (STN). There is also the pars reticulate and the pars compacta of the **substantia nigra** (SNr and SNc).

The **striatum** is two distinct masses of grey matter separated by a large tract of white matter called the **internal capsule**. The two masses are called the **caudate nucleus** and the **lentiform nucleus**. The lentiform nucleus is comprised of the **putamen** and the **globus pallidus**. The internal organisation of the striatum is extraordinarily complex, and is 96% GABAergic and 2% cholinergic.

The **globus pallidus** is divided into two functionally distinct parts. Both segments contain primarily GABAergic neurons, which therefore have inhibitory effects on their targets. **GPe** receives input from the striatum, and projects to the subthalamic nucleus. **GPi** receives signals from the striatum via the “direct pathway” and the “indirect pathway”.

The **substantia nigra** is a mesencephalic grey matter portion of the basal ganglia, divided into SNr (reticulate) and SNc (compacta). SNr often works with GPi to inhibit the thalamus (SNr-GPi complex). SNc produces dopamine, which is very significant in maintaining balance in the striatal pathway.

The **subthalamic nucleus** is a diencephalic grey matter portion of the basal ganglia, and the only portion of the ganglia that actually produces an excitatory glutamic acid neurotransmitter. The role of the subthalamic nucleus is to stimulate the SNr-GPi complex and is part of the “indirect pathway”.

The largest component, the striatum, receives input from many brain areas but sends outputs only to other components of the basal ganglia. The pallidum receives its most important input from the striatum, and sends inhibitory output to a number of motor-related areas. One part of the substantia nigra functions similarly to the pallidum, and another part provides the source of the neurotransmitter dopamine’s input to the striatum. The subthalamic nucleus receives input mainly from the striatum and cortex, and projects to the internal segment of the pallidum.

From the cerebral cortex, the supplementary motor area, the premotor area, the primary motor, somatosensory, and parietal cortex project to the caudate and putamen. From the putamen, there are projections to the GPe and SNr (direct pathway), and projections to the GPi (indirect pathway). The GPe and SNr are the only output of the basal ganglia, with their projections to the thalamus, and via the thalamus back to the cortex (SMA and PMA are the two regions involved in movement preparation and planning).
The globus pallidus (GPI) and the substantia nigra (SNr) inhibit the thalamus. The putamen inhibits GPI and SNr which in turn releases the thalamus from inhibition. The thalamus through its projections to the cortex releases the selected movement. The correct balance is maintained by the SNc which provides excitatory inputs to the caudate and putamen. The GPI and SNr are the messengers of all information from the basal ganglia. They perform this role by inhibiting the thalamus. Their code consists in the modulation of the inhibitory input to the thalamus.

Disorders of the basal ganglia

Parkinson's disease is a progressive degenerative disorder of the CNS. It is neuronal degeneration in the substantia nigra / SNc with a dramatic loss of dopamine cells (more than 80%).

The degeneration of dopamine neurons and the loss of nigro-striatal dopaminergic terminals in the caudate and putamen is usually idiopathic. A small proportion of cases, however, can be attributed to known genetic factors.

Early in the course of the disease, the most obvious symptoms are movement-related. Bradykinesia is slowness of movements, and the patient experiences difficulty in small movements such as doing up buttons and handling a knife. The face often becomes hypomimic (absence of movements that normally animate the face, expressionless, mask-like). Patients also experience akinesia, which is the difficulty in the initiation of movements. This needs external sensory triggers to initiate movement e.g. a visual trigger because they cannot initiate movements internally. Tremor at rest ceases with voluntary activity. It usually starts in one hand (asymmetry) and tends to spread with time to other parts of the body. R rigidity is a type of resistance to passive movements. To the physician passively moving the patient’s limb feels like bending a lead pipe, so this is known as “lead pipe rigidity”.

Patients with Parkinson's disease are seen walking in slow, small steps, with shuffling feet and a reduced arm swing. This is described as a Parkinson gait. They sometimes also have a stooped posture - their head and body will be bent forwards and downwards.

Huntington's disease is a neurodegenerative genetic disorder that affects muscle coordination and leads to cognitive decline and dementia. It typically becomes noticeable in middle-age. The disease is caused by an autosomal dominant mutation on either of an individual’s two copies of a specific gene, which means any child of an affected parent has a 50% risk of inheriting the disease. Physical symptoms of Huntington's disease can begin from any age, but usually begin between 35 and 44 years of age.

Huntington’s disease is the most common cause of abnormal involuntary writhing movements called chorea and is much more common in people of Western European descent. Choreic movements are rapid, jerky, involuntary movements of the body. These movements usually affect the hands and the face at first. Early in the course of the disease, patients can mask the spontaneous movements by incorporating them into socially acceptable movements. They gradually increase overtime until the patients become totally incapacitated by them. Later on, there is cognitive decline and dementia. Death usually occurs 10 to 15 years from the onset of symptoms. The symptoms of chorea are also called ‘hyperkinesia’.

Cerebellum

The cerebellum is a region of the brain that plays an important role in motor control. It contributes to coordination, precision and accurate timing. It receives input from sensory systems and from other parts of the brain and spinal cord, and integrates these inputs to fine tune motor activity. It is also involved in some cognitive functions such as attention and language, and probably in some emotional functions such as regulating fear and pleasure responses.

The cerebellum is located at the bottom of the brain, with a large portion of the cerebral cortex above it and the pons of the brainstem in front of it. It is separated from the overlying cerebrum by a layer of leathery dura mater. All of its connections with other parts of the brain travel through the pons (the metencephalon of the hindbrain is the pons and cerebellum).
Anatomically, the cerebellum has a molecular layer (top), a layer of Purkinje cells (middle) and a granular cell layer (bottom). There are two fibre types - mossy fibres (enter at granular level and synapse with Purkinje cells) and climbing fibres (enter at Purkinje cell layer). Climbing fibres compare different inputs and project to the deep nuclei and output to the thalamus and postural and vestibular centres.

There are three highways into and out of the cerebellum - the superior, middle, and inferior cerebellar peduncles.

The cerebellum is divided into two hemispheres, and the narrow midline zone is called the vermis. The unusual surface appearance of the cerebellum conceals the fact that most of its volume is made up of a very tightly folded layer of grey matter (the cerebellar cortex). Underneath the grey matter is the white matter, made up largely of myelinated nerve fibres running to and from the cortex. Embedded within the white matter (sometimes called the arbor vitae [Tree of Life]) are three deep cerebellar nuclei, composed of grey matter.

The three deep nuclei are the fastigial nucleus (involved in balance and has connections with the vestibular system and reticular nuclei), the interposed nucleus and the dentate nucleus, which are both involved with voluntary movement, and have projections to the thalamus and the red nucleus. There are three sources of input - mossy fibres from spinocerebellar pathways, climbing fibres from the inferior olive, and mossy fibres from the pons bringing information from the cerebral cortex (these are called corticopontine connections and cross over after synapsing in the pons).

The cerebellum is divided horizontally into 3 lobes - anterior, posterior and flocculonodular. These lobes divide the cerebellum from top to bottom. In terms of function, however, there is a more important distinction along the medial-to-lateral dimension. Leaving out the flocculonodular part, which has distinct connections and functions, the cerebellum can be parted functionally into a medial sector called the spinocerebellum and a larger lateral sector called the cerebrocerebellum. A narrow strip of protruding tissue along the midline is called the vermis (Latin for "worm"). The smallest region, the flocculonodular lobe, is often called the vestibulocerebellum.

The vermis and the primary connections are with the vestibular nuclei, although it also receives visual and other sensory input. Its function is to tune balance (stance and gait), and it is involved in the vestibulo-ocular reflex. Disorders will cause an ataxic gait (wide based stance), imbalance when eyes are closed (Romberg sign) and nystagmus.

The spinocerebellum is the flocculonodular lobe. It is the oldest part in evolutionary terms and participates mainly in balance and spatial orientation; its primary connections are with the vestibular nuclei, although it also receives visual and other sensory input. Its function is to tune balance (stance and gait), and it is involved in the vestibulo-ocular reflex. Disorders will cause an ataxic gait (wide based stance), imbalance when eyes are closed (Romberg sign) and nystagmus.

The lateral zone is the cerebrocerebellum. It receives input from the cerebral cortex via the pontine nuclei and sends output mainly to the ventrolateral thalamus (then to motor areas) and to the red nucleus. It is thought to be involved in the initiation of skilled movements, and planning movement that is about to occur. The lateral lobe is the newest part of the cerebellum, and projects to the dentate nucleus. It also plays a role in cognitive function, attention, processing of language and emotional control.
Main signs in cerebellar disorders

1) Instability when standing or walking-Wide based stance, staggering and wide based walking (looks drunk) = ataxia.
2) Imbalance when eyes are closed = Romberg sign.
3) Reduced muscle tone (floppy limbs) = hypotonia.
4) Inability to judge distance and when to stop = dysmetria.
5) Slurred speech = dysarthria.
6) Inability to coordinate movements, inability to perform rapid alternating movements = dysdiadochokinesia.
The Neuromuscular Junction
by Dr Wikipedia and Dr David Dexter

A neuromuscular junction is the synapse of the axon terminal of a motoneuron with a motor end plate, the highly excitable region of muscle fibre plasma membrane responsible for initiation of action potentials across the muscle’s surface, ultimately causing the muscle to contract.

The neurotransmitter involved in neurotransmission at the NMJ is acetylcholine. The NMJ is the location where the neurone activates muscle to contract. This is a step in the excitation-contraction coupling of skeletal muscle:

1. Action potential arrives at pre-synaptic nerve terminal, and voltage sensitive calcium channels open. Calcium ions flow from the extracellular fluid into the pre-synaptic terminal cytosol.
2. The influx of calcium ions causes the neurotransmitter-containing vesicles to fuse with the nerve terminal cell membrane through SNARE proteins.
3. Fusion results in the emptying of the acetylcholine into the synaptic cleft (exocytosis).
4. Acetylcholine diffuses into the synapse and binds to the nicotinic acetylcholine receptors bound to the motor end plate.
5. These receptors are ligand-gated ion channels, and when they bind acetylcholine, they open, allowing sodium ions to flow in and potassium ions to flow out of the muscle’s cytosol.
6. Because of the differences in electrochemical gradients across the plasma membrane, more sodium moves in than potassium moves out, producing a local depolarisation of the motor end plate known as end-plate potential (EPP).
7. This depolarisation spreads across the surface of the muscle fibre and continues the excitation-contraction coupling to contract the muscle.
8. The action of acetylcholine is terminated with the enzyme acetylcholinesterase degrades part of the neurotransmitter and the rest of it diffuses away.
9. The choline produced by the action of acetylcholinesterase is recycled - it is transported, through reuptake, back into the pre-synaptic terminal, where it is used to synthesise new ACh molecules.

Hemicholinium-3, also known as Hemicholine, is a drug that blocks the reuptake of choline by the high affinity transporter ChT at the pre-synapse. The reuptake of choline is the rate limiting step in the synthesis of ACh, hence Hemicholinium decreases the synthesis of ACh. It is therefore classified as an indirect ACh antagonist. This drug is frequently used as a research tool in animal and in vitro experiments.

Tubocurarine is a non-depolarising neuromuscular blocker, used as a skeletal muscle relaxant. It is a competitive antagonist of acetylcholine at the post-synaptic nicotinic acetylcholine receptors on muscle fibres. It prevents the depolarisation of the motor end plate, and hence inhibits the initiation of an action potential. 70-80% block is necessary for the desired effects of flaccid paralysis. It can be administered intravenously, with a 2 or 3 minute onset of action, and duration of about 60 minutes. The drug is 70% excreted in urine, and 30% in bile. The drug is contra-indicated in renal / hepatic patients. It cannot cross the placenta or the blood brain barrier. Tubocurarine is used in the relaxation of skeletal muscles; although side effects may include ganglion block (leading to a decrease in total peripheral resistance) and histamine release from mast cells. These two effects cause tachycardia, bronchospasm, and excess secretions. This is why respiration must always be assisted.

Atracurium is another antagonist of ACh at the post-synaptic site at the NMJ. It is a non-depolarising neuromuscular blocker like Tubocurarine, but its effects have a shorter duration. Neuromuscular blockers like these drugs don’t affect pain sensation or consciousness, and respiration must always be assisted. There is usually a classical order in which muscles are affected on administration of neuromuscular blockers. First the extrinsic eye muscles (causing double vision), then the small muscles of the face, limbs and pharynx, then the respiratory muscles. Recovery is in the reverse order. The actions of neuromuscular blockers can be reversed by using an anticholinesterase (like neostigmine) and atropine.

Suxamethonium is a depolarising neuromuscular blocker. It has a structure related to acetylcholine, and is a post-synaptic nAChR agonist, which causes excitation for a long period of time, and so action potentials can no longer be produced as the cell cannot repolarise because the membrane potential is above the threshold and ion channels are inactivated. It is degraded by Butyrylcholinesterase (a plasma enzyme).
**Sound Conduction and Transduction**
by Dr Maggie Lowrie

The **outer ear** consists of the pinna (auricle) and the external acoustic meatus (external auditory meatus / auditory canal), and these structures collect and conduct sound waves towards the tympanic membrane.

The **middle ear** is an air-filled chamber in bone, lying between the tympanic membrane laterally, and the oval and round windows medially.

The **inner ear** is the cochlea and the organs of balance. Hair cells transduce mechanical energy of sound into electrical signals in the cochlear nerve.

Sound is a pressure wave in the air - alternating areas of compressed and non-compressed air. These waves have a **frequency**, which is the cycles per second measured in Hz, and this is perceived as **pitch**. Waves also have an **amplitude**, which is the intensity of the waves, and this is perceived as **loudness**. The **decibel range** is a log scale of loudness.

0dB is the threshold of hearing. 30dB is a whisper, 50dB is normal conversation, 90dB is shouting, 120dB is the loudness of a gunshot, and 140dB is the loudness of a pneumatic drill.

The mechanisms of amplification are fantastic in the ear. Conduction through the middle ear amplifies sound by around 30 dB. This is achieved by a lever system of articulated ossicles, and it is helped by the ratio of the area of the tympanic membrane to the oval window (17:1).

There are also a couple of **protective mechanisms**. For example, reflex contraction of the tensor tympani and stapedius muscles reduces the amplitude of vibrations passing through ossicles. This protects against natural sounds but maybe not against man-made sounds like a gunshot. The auditory tube allows **equilibration of air pressure** on either side of the tympanic membrane.

**Conductive hearing loss** is a condition in which sound is prevented from reaching the cochlea. Causes include wax build-up in the outer ear that stops vibrations; **otitis media** (inflammation and fluid build-up); **otosclerosis of ossicles** (bony extensions grow from ossicles); **perforated tympanic membrane** (trauma or sound of very high intensity); and also **congenital** malformations.
The **cochlea** is essentially a hollow tube in bone, curled into a spiral. It is divided longitudinally into 3 compartments, separated by 2 membranes. The sound wave causes vestibular (Reissener’s) and basilar membranes to vibrate. Cochlear hair cells are attached to the basilar membrane.

Compensatory movements of the oval and round windows protect the cochlea from excessive pressure. Perilymph has concentrations of ions similar to extra-cellular fluid. Endolymph is physiologically unusual, with high concentrations of potassium. Hair cells are found along the basilar membrane.

The **Organ of Corti** (the spiral organ) is the organ of the inner ear that contains the auditory sensory cells. The diagram on the right shows a cross section through the cochlea. It is the structure that transduces pressure waves into **action potentials**.

**Hair cells** are surrounded by supporting cells. The **tectorial membrane** is gelatinous and does not vibrate with sound. The **spiral ganglion** is embedded in modiolus and innervates hair cells. **Stria vascularis** secretes endolymph (high in K\(^+\) and low in Na\(^+\)). The organ of Corti has highly specialised structures that respond to fluid-borne vibrations in the cochlea. The organ of Corti contains between 15,000 to 20,000 auditory nerve receptors. Each receptor has its own hair cell.

The shear force on the hairs opens **ion channels** that are permeable to K\(^+\) and Ca\(^{2+}\), leading to hair cell plasma **membrane depolarisation** and activation of voltage-dependent calcium channels at the synaptic basolateral pole of the cells which triggers exocytosis of glutamate neurotransmitter to the synapse and electrical signalling to the auditory cortex via the spiral ganglion neurons.

The pinna and the middle ear act as mechanical transformers and amplifiers to that by the time sound waves reach the organ of Corti, their pressure amplitude is 22 times that of the air impinging on the pinna. The organ of Corti is damaged by excessive sound levels.

**Hair cells** are the sensory receptors of both the auditory system and the vestibular system. The auditory hair cells are located within the organ of Corti on a thin basilar membrane in the cochlea. They are called hair cells because of the tufts of stereocilia that protrude from the apical surface of the cell into the scala media (the fluid filled tube of the cochlea). There are many stereocilia per cell.

There are two types of hair cell. **Inner hair cells** are cells that convert mechanical sound into an electrical nerve signal. Deflection of the stereocilia opens mechanically gated ion channels to allow K\(^+\) and Ca\(^{2+}\) to enter the cell and cause membrane depolarisation, voltage-gated calcium influx, neurotransmitter release and **action potential** generation in the nerve. The Perilymph in the scala tympani has a very low concentration of positive ions, and this electrochemical gradient allows the repolarisation of the hair cell. Inner hair cells are about 3,500 cells arranged in a single row. They are densely innervated by about 10 sensory axons per cell.
**Outer hair cells** are acoustical pre-amplifiers. The efferent nerve causes the cell to change shape, which in turn amplifies the response to sound of adjacent inner hair cells at the centre of the vibration. The depolarisation of the cell membrane triggers active vibrations of the cell body, which drives oscillations in the cell's length, which occur at the frequency of the incoming sound and provide mechanical feedback amplification. Without outer hair cells, sensitivity decreases by about 50dB. Outer hair cells are about 20,000 cells arranged in 3 rows. They are sparsely innervated, with about one axon per several cells. Both types of hair cell respond to sound but the inner hair cells are the ones which provide information for the brain.

**Transduction mechanism:**
The basilar membrane vibrates in response to sound. Upward movement displaces stereocilia away from the modiolus, and K⁺ channels open. K⁺ enters the cell from the endolymph and the hair cell depolarises. Downward movement displaces stereocilia towards the modiolus, and K⁺ channels close, causing the hair cell to hyperpolarise.

The cells are highly sensitive, and response to threshold sound requires just a 0.3nm deflection. It depends on the maintenance of endolymph at +80mV by the stria vascularis. Depolarisation opens Ca²⁺ channels in the body of the hair cell. Glutamate released from the base depolarises the axon of the spiral ganglion cell, which causes an action potential.

**Differentiation of Pitch:**
Perceived pitch of a sound is determined by frequency. The normal human range is from 20Hz to 20kHz.

We are probably most sensitive at 1-3kHz, which is the usual frequency of sound for human speech. The basilar membrane acts as a frequency analyser. High frequencies vibrate the basilar membrane nearer to the base, and low frequencies vibrate the membrane nearer to the apex.

**Auditory Pathway:**
Sound information travels down the vestibulocochlear nerve, through intermediate stations such as the cochlear nuclei and superior olivary complex of the brainstem and the inferior colliculus of the midbrain, being further processed at each waypoint. The information eventually reaches the thalamus, and from there it is relayed to the cortex. The primary auditory cortex is located in the temporal lobe.

The cochlear nucleus is the first site of the neuronal processing of the newly converted “digital” data from the inner ear. The trapezoid body is a bundle of decussating fibres in the ventral pons that carry information used for binaural computations in the brainstem. The superior olivary complex is located in the pons, and receives projections predominantly from the ventral cochlear nucleus. The lateral superior olive detects interaural level differences, and the medial superior olive distinguishes interaural time difference. The lateral lemniscus is a tract of axons in the brainstem that carries information about sound from the cochlear nucleus to various brainstem nuclei and ultimately the contralateral inferior colliculus of the midbrain. The inferior colliculi are located just below
the visual processing centres (the superior colliculi). The central nucleus of the inferior colliculus is a nearly obligatory relay in the ascending auditory system, and most likely acts to integrate information (specifically regarding sound source localisation from the superior olivary complex and dorsal cochlear nucleus) before sending it to the thalamus and cortex. The medial geniculate nucleus is part of the thalamic relay system.

The primary auditory cortex is the first region of the cerebral cortex to receive auditory input. Perception of sound is associated with the right posterior superior temporal gyrus, the cortical region responsible for the sensation of basic characteristics of sound such as pitch and rhythm. The auditory association area is located within the temporal lobe of the brain, in Wernicke's area, near the lateral cerebral sulcus. This is an important region for the processing of acoustic signals so that they can be distinguished as speech, music or noise.

The auditory pathway consists of bilateral pathways. There are also lateral inhibition mechanisms, with descending feedback loops.

The primary auditory cortex is subdivided according to frequency response. Cells respond to specific features of sound, e.g. on/off, duration, repetition, intensity and some more complex sound patterns e.g. rising/falling frequencies and animal vocalisations. In the secondary cortex, neurones respond to more complex sound patterns.

Sensorineural Deafness:
This is generally defined as a type of hearing loss in which the root cause lies in the vestibulocochlear nerve, the inner ear, or central processing centres of the brain. Sensorineural hearing loss can be mild, moderate, or severe, including total deafness. The great majority of human sensorineural deafness is caused by abnormalities in the hair cells of the organ of Corti in the cochlea. Most sensory hearing loss is due to poor hair cell function. The hair cells may be abnormal at birth, or damaged during the lifetime of an individual.

There are many examples of sensory causes of sensorineural deafness. Presbycusis is progressive bilateral symmetrical age-related sensorineural hearing loss. It is the cumulative effect of aging on hearing. The hearing loss is most marked at higher frequencies. Noise-induced hearing loss occurs because of prolonged exposure to loud noises. Ménière’s Disease is a disorder of the inner ear that can affect hearing and balance to a varying degree. It is characterised by episodes of vertigo and tinnitus and progressive hearing loss, usually in one ear. Ototoxic drugs such as tobramycin, furosemide, methotrexate and aspirin (aminoglycosides, loop diuretics, antimetabolites and salicylates) can also cause hearing loss. Aplasia of the cochlea and chromosomal syndromes are rare, although hearing loss can be inherited.

Neural causes of deafness include acoustic neuroma and viral infection. Measles can damage auditory nerves, and meningitis can damage the nerves or cochlea. Mumps, HIV and Chlamydia can cause hearing loss, and syphilis transmitted to a foetus can result in deafness.

Central causes are rare, but can include demyelination in multiple sclerosis and injury to the central auditory pathway.
The Vestibular System
by Professor Michael Gresty

The vestibular system contributes to balance and sense of spatial orientation. Together with the cochlea, it constitutes the labyrinth of the inner ear. It is the only sensory organ specialised to transduce absolute motion in space. Angular (rotator) motion (of the head) is sensed by the semicircular canals, and acceleration of the head and strength and direction of gravity are sensed by the otolith organs.

There are various normal functions of the vestibular system. It subserves perception of movement in space and tilt with respect to gravity, and also provides reflex balance reactions to sudden instability of gait or posture. These are known as vestibulo-spinal reflexes. Another function is to stabilise the eyes on fixed targets, which preserves visual acuity during head movements. These are known as vestibulo-ocular reflexes. The vestibular system also assists in the control of blood pressure and heart rate during rapid up-down tilts. It assists in the synchronisation of respiration with body reorientations. The vestibular system also provokes motion sickness when stimulated in unusual motion environments. It functions to provide a reference of absolute motion in space, which helps interpret the relativistic signals of the other senses in creating a perception of spatial orientation.

Disorders of the vestibular system cause (in corresponding order):
- False perception of movement in space - vertigo
- Instability of gait and posture - vestibular ataxia
- Inability to stabilise the eyes - vestibular nystagmus in unilateral lesions, oscillopsia during head movement in bilateral vestibular lesions
- Slight impairment of orthostatic control in the acute phase of vestibular loss
- Severe nausea and vomiting in the acute phase of unilateral vestibular loss
- Loss of co-ordination on directional reorientation; motion intolerance, oversensitivity to visual motion in the environment

Anatomy and Physiology

The basic mechanism in the vestibular system is the hair cell. The hair cells synapse with primary neurone dendrites (cell bodies in the Scarpas ganglion), and these project to the vestibular nuclei in the brainstem. Hair cells are stimulated by deflections by forces of inertial resistance to acceleration (otoliths) and endolymphatic fluid rotation (canals). The hair cell receptor potential depolarises towards the kinocilium, and hyperpolarises away from the kinocilium. The ganglion cell discharge has an increased firing frequency towards the kinocilium, and a decreased frequency away from the kinocilium.

Our vestibular system contains three semi-circular canals in each labyrinth. They are approximately at right angles to each other, and are called the horizontal (lateral), anterior (superior) and posterior (inferior) semicircular canals. The semicircular canals are three half circular interconnected tubes. Each canal is filled with a fluid called endolymph. Little hair cells project from the ampulla in the wall of the canal and are unidirectionally oriented so that the acceleration phase of head rotation to a particular side or direction preferentially stimulates the canals on that side. For example, rotation to the right stimulates the right canal, and rotation in the opposite direction inhibits that canal activity.

As the skull twists in any direction, the endolymph is thrown into different sections of the canals. The hair cells detect when the endolymph rushes past and a signal is sent to the brain.

When head rotation decelerates to stop, the canal on the opposite side is stimulated. For example, stopping a rightwards rotation stimulates the left canal. Each canal has a tonic firing rate so that when the head is still, the tonuses from the right and left canals balance out. A canal is stimulated preferentially by rotation in its
plane. The pattern of stimulation from all canals on both sides signals rotation in all 3D directions. Loss of canal function on one side gives a permanent partial impairment of sensitivity to rotation in the ‘on’ direction of the defunct canal. This is not so with otoliths, which are omnidirectional.

While the semicircular canals respond to rotations, the otolith organs sense linear accelerations. We have two on each side, one called utricle, and the other saccule. Otoconia crystals rest on a viscous gel layer, and are heavier than their surroundings, so they get displaced during linear acceleration, which in turn deflects ciliary bundles of hair cells and thus produce a sensory signal. The saccule is orientated in an approximately vertical plane. Hair cells with their overlaying layer of otoconia project normal to the plane with directional sensitivities in all combinations of vertical and antero-posterior directions. The plane of the utricle is oriented approximately horizontally. Hair cells project vertically with directional sensitivities in all combinations of lateral and antero-posterior directions.

Otolith hair cells are stimulated by inertial resistance of the otoconial mass to linear head acceleration (it tends to stay still when the head moves, like people swaying on the bus when it accelerates or brakes). The vector sum of utricular and saccular stimulation patterns give signals of linear acceleration in all 3D directions.

The lateral vestibulo-spinal tract descends ipsilaterally in the ventral funiculus of the spinal cord. Axons terminate in the lateral part of the ventral horn and influence motor neurons to limb (especially extensor antigravity) muscles. The medial vestibulo-spinal tracts descend bilaterally in the medial longitudinal fasciculus (MLF) to the cervical and upper thoracic spinal cord. The axons terminate in the medial part of the ventral horn and influence motor neurons to the neck and back muscles.

The Vestibulo-Ocular Reflex
The VOR is a reflex eye movement that stabilises images on the retina during head movement by producing an eye movement in the direction opposite to head movement, thus preserving the image on the centre of the visual field.

The superior and medial vestibular neurons project to the motor nuclei supplying the extraocular muscles. Axons of the medial vestibular nucleus cross the midline and project to the contralateral abducens nucleus to abduct the eye (in the opposite direction to head rotation). Axons from the abducens nucleus cross and ascend in the medial longitudinal fasciculus (MLF), and excite the contralateral oculomotor nucleus to adduct the other eye (in the opposite direction to head rotation).

When the head rotates, say to the left, the eyes rotate in compensation to the right with a velocity that matches head velocity. The eye and head rotations cancel each other so that the direction of fixation of the eyes remains stabilised on the visual targets by this vestibulo-ocular reflex. With continuing head rotation, frequent saccades (fast eye movements) reposition the eyes more centrally to form an overall pattern of normal or physiological vestibular nystagmus.

Superior vestibular neurones from the vertical canals project ipsilaterally to the third and fourth nuclei to generate vertical vestibular-ocular reflexes.

Consequences of Vestibular Lesions
Vertigo
Vestibular projections via the thalamus to the temporal/parietal spatial cortex subserve perception of motion in space. In the case of a unilateral canal lesion the tonus of the intact canal gives a signal as if the head is rotating to the intact side. Accordingly the patient may experience symptoms of intense spinning (an
illusionary rotation to the intact side) or feelings as if on a boat or that the ground is unsteady. Such illusory motion is the symptom of vertigo.

**Vestibular nystagmus**
In acute unilateral vestibular disorder the unopposed tonus of the intact canal causes the eyes to be driven to the lesioned side. This is a vestibulo-ocular reflex as if the head were turning to the intact side. This drifting movement is detected by the brainstem which intermittently resets eye position with fast saccades generating the overall pattern of a vestibular nystagmus which beats to the intact side. Such nystagmus is florid only in the acute phase of loss and is minimised by visual suppression mechanisms. Vestibular nystagmus may sometimes be torsional and very occasionally vertical.

**Oscillopsia**
Marked loss of vestibular function impairs eye stabilisation during rapid head movements because the vestibulo-ocular reflex is the only mechanism which can drive fast compensatory eye movements. The subject may complain that the visual world is seen to bounce or lag behind during active or passive head movements because of the impaired eye stabilisation. This gives rise to the head shaking tests. Normally if a subject is asked to look at a target and the head is oscillated rapidly the eyes will be seen to remain fixed on target. If the subject has bilateral loss of vestibular function the eyes will be taken off by the head swing and multiple catch up saccades will be made to regain the target. Loss of function on one side may be detected by discrete fast swings of the head. During a fast swing to the good side the eyes will remain on target, whilst during a swing to the lesioned side, the eyes will be taken off target and will execute saccades to re-attain target fixation.

**Vestibular Ataxia**
Bilateral vestibular disorder causes a mild gait ataxia which is worse at speed, when negotiating rough ground or when vision is reduced. Unilateral vestibular disorder causes a tendency for the body and head to lean or fall to the lesioned side (determined by the ipsilaterality of vestibular-spinal projection), which becomes pronounced in difficult balancing situations.

**Hypotension and Respiratory Dysrhythmia**
Vestibular projections affect heart rate, peripheral vasculature and respiratory muscles. Loss of vestibular tone can provoke hypotensive episodes so that the patient feels faint as well as dizzy. Vestibular stimulation may also affect respiratory rhythm.

**Nausea and Vomiting**
Vestibular nuclei project to a wide range of autonomic structures in both the brainstem and the hypothalamus. In the acute phase of a unilateral vestibular disorder, the unusual pattern of stimulation also provokes symptoms like motion sickness, which is nausea and vomiting.

**Impaired Sensory Integration**
There is often a loss of co-ordination on directional reorientation because of motor intolerance and oversensitivity to visual motion in the environment. Patients often experience impairments of local navigation, e.g. difficulties with navigating one’s bedroom in darkness, veering then walking.
**Structure and Function of the Eye**

by Dr Merrick Moseley

Protection of the eye is afforded by the bony margin of the **orbit**, which is formed superiorly by the frontal bone and inferiorly by the zygomatic bone, with aspects of the sphenoid greater wing, ethmoid bone, lacrimal bone and the maxillary bone. This anatomical arrangement imposes limits on the visual field, for example compared with a rabbit that has protruding eyes to detect predators. Risks to humans these days include playing squash without goggles, as squash balls fit very snugly into the orbit and as such are a potential source of serious eye injury.

The eye is a slightly asymmetrical sphere with a diameter of about 24 to 25mm and a volume of 6.5cc. It is a three layered structure. The external layer is formed by the **sclera** and **cornea**. The intermediate layer is divided into two parts – anterior and posterior. The anterior part comprises the **iris** and **ciliary body**, and the posterior part is the **choroid**. The internal layer (sensory part of the eye) is the **retina**.

**Tears**

The main functions of tears are maintaining an optically smooth surface, hydration, oxygen source (by being a surface for gas exchange) and removal of debris (bactericidal). Tears comprise lacrimal gland fluid supplemented by conjunctival and lid-margin secretions. Tear secretion increases by a factor of 40 to 50% volume under strong physical or emotional stimulus. The tear film (pre-corneal layer) is made of three layers:

1) **Outermost lipid layer** with oils secreted by meibomain glands provides hydrophobic barrier
2) **Aqueous layer** with water and proteins secreted by lacrimal gland promotes spreading of the tear film, control of infectious agents and promotes osmotic regulation
3) **Inner mucous layer** with mucin secreted by the conjunctival goblet cells coats the cornea and provides a hydrophilic layer that allows for the even distribution of the tear film.

The thin pre-corneal layer of tears acts as a nutritional route and for gas exchange with the avascular outer corneal epithelium, as well as providing an optically smooth surface which is maintained by blinking which is the first element of the image formation system of the eye. The visco-elastic nature of the tears helps to lubricate and cushion the gliding surfaces during blinking.

There are three main types of tears. **Basal tears** are the normal tears that keep the cornea wet and nourished. **Reflex tears** result from irritation of the eye by foreign particles, or from the presence of irritant substances such as onion vapours in the eye’s environment. The trigeminal V1 nerve bears the sensory pathway of the tear reflexes. When the trigeminal nerve is cut, tears from reflexes will stop, but not emotional tears. Psychic tears are the third category, generally referred to as crying or weeping. It is increased lacrimation due to strong emotional stress, suffering, mourning or physical pain.

Elimination of tears is 25% by evaporation and 75% by active pumping into the nasal cavity via the lacrimal drainage system.

**Dry eye syndrome** arises from any disease is associated with deficiency of the tear film components. Dry spots appear on the cornea and conjunctival epithelium. Early changes are reversible and treatment is commonly with artificial tears.

**Cornea**

The cornea forms the anterior sixth of the eye and is the major refracting surface. The cornea will ‘rebound’ if indented or flattened thus maintaining a constant refractive power. It is an avascular structure consisting of five anatomical layers: epithelium, Bowman’s membrane, stroma, Descemet’s membrane and endothelium. 90% of the thickness of the cornea is taken up by the **stroma** consisting of regularly arranged collagen fibrils.
**Descemet's membrane** provides a barrier to infection generally remaining intact during corneal ulceration. The *endothelium* cannot regenerate if damaged hence the requirement for corneal transplantation if this layer becomes diseased.

The main functions of the cornea are therefore transparency, bending light, providing strength and acting as an infection barrier. The cornea transmits greater than 95% of incident light but absorbs UV radiation. Thus the cornea is the site of injury in solar keratitis (snow-blindness), as snow is highly reflective of UV radiation.

**Sclera**
The ‘white of the eye’ is the sclera. It is roughly spherical and forms the posterior five sixths of the globe. It functions to provide a tough outer protective coat affording a barrier to light, infection and trauma and the stresses and strains induced by the contractions of the extraocular muscles. It also maintains the shape of the eye by resisting the force of the internal intraocular pressure.

**Aqueous Humour**
The plasmalike fluid which fills the anterior chamber at the front of the eye is the aqueous humour. The key principle here is the flow pathway of the aqueous. Aqueous is actively secreted and diffuses out from the epithelial cells of the *ciliary body*. It then flows forward between the *iris* and the *lens* and then leaves the eye through the *trabecular meshwork* and *Canal of Schlemm*. The aqueous humour is replaced every 100 minutes. Blockage of the trabecular meshwork leads to an increase in the intraocular pressure above the normal mean of 16mmHg. This pressure increase may lead to damage of the optic nerve head, a condition known as primary open angle glaucoma (a leading cause of blindness).

**Lens**
The major constituents of the lens are *water* (66%) and *protein* (33%). It is biconvex, elliptical and avascular. It functions to form an image on the retina secondary to that produced by the major refracting structure of the eye (the cornea). The lens plays a major role in accommodation. The *capsule* completely envelopes the lens and is the basement membrane (the thickest in the body) of the lens epithelium. The epithelium consists of a single sheet of cuboidal cells spread over the front of the lens. No corresponding posterior layer exists. The bulk of lens consists of hexagonal lens fibres formed throughout life from the epithelial cells which elongate as they move towards the poles.

**Opacification** of the lens leads to a loss of visual acuity. It may be congenital, age-related or metabolic. This is treated by removing the lens and (in the past 30 years) replacing it with a synthetic lens. The invention of an artificial intraocular lens is credited to a medical student who observing the removal of a cataractous lens ‘naively’ enquired of the surgeon why no replacement lens was being put back. Half of all global blindness (25 million people) is due to cataracts.

**Ciliary Body**
The ciliary body comprises smooth muscle and the ciliary processes, the epithelial surfaces of which, as already described, are responsible for the production of aqueous. The ciliary body has two additional functions: the support of the zonule fibres which hold the lens in position and its role in accommodation. Contraction of the ciliary body leads to a relaxation of the zonule and the lens becomes more spherical leading to an increase in its power.

**Vitreous**
The vitreous is a transparent colourless gel which fills the posterior four fifth's of the eye. It is no longer referred to as a 'humour'. It is 90% water, with few cells such as hyalocytes, and structural proteins like collagen. Hyaluronic acid gives vitreous gel properties, and it is slightly thicker than egg white. The functions of vitreous are in transparency, mechanical buffering, and passive transport and removal of metabolites.

Changes that occur with age or in young myopic eyes include the appearance of empty spaces. The outer surface of the vitreous may collapse and pull away from the internal coats of the eye resulting in a vitreous detachment. This is a normal consequence of ageing but can lead to retinal detachment.
The pupil regulates light input to the eye. In light conditions, the pupil constricts to cause a decrease in aberrations and glare, an increased depth of focus and it reduces bleaching of photopigments. In dark conditions, the pupil dilates to enlarge the visual field and to lower the threshold for light perception. The response to light is not a simple reflex, but it is rather a regulatory process - a servomechanism.

In the centre of the retina is the optic nerve, a circular to oval white area measuring about 2 x 1.5 mm across. From the centre of the optic nerve radiate the major blood vessels of the retina. Approximately 17 degrees (4.5-5 mm), or two and half disc diameters to the left of the disc, can be seen the slightly oval-shaped, blood vessel-free reddish spot, the fovea, which is at the centre of the area known as the macula by ophthalmologists.

A circular field of approximately 6 mm around the fovea is considered the central retina while beyond this is peripheral retina stretching to the ora serrata, 21 mm from the centre of the optic disc.

The retina is approximately 0.5 mm thick and lines the back of the eye. The optic nerve contains the ganglion cell axons running to the brain and, additionally, incoming blood vessels that open into the retina to vascularise the retinal layers and neurons.

A radial section of a portion of the retina reveals that the ganglion cells (the output neurons of the retina) lie innermost in the retina closest to the lens and front of the eye, and the photosensors (the rods and cones) lie outermost in the retina against the pigment epithelium and choroid.

Light must, therefore, travel through the thickness of the retina before striking and activating the rods and cones. Subsequently the absorption of photons by the visual pigment of the photoreceptors is translated into first a biochemical message and then an electrical message that can stimulate all the succeeding neurons of the retina.

The retinal message concerning the photic input and some preliminary organization of the visual image into several forms of sensation are transmitted to the brain from the spiking discharge pattern of the ganglion cells.

All vertebrate retinas are composed of three layers of nerve cell bodies and two layers of synapses. The outer nuclear layer contains cell bodies of the rods and cones, the inner nuclear layer contains cell bodies of the bipolar, horizontal and amacrine cells and the ganglion cell layer contains cell bodies of ganglion cells and displaced amacrine cells. Dividing these nerve cell layers are two neuropils where synaptic contacts occur.

The first area of neuropil is the outer plexiform layer (OPL) where connections between rod and cones, and vertically running bipolar cells and horizontally oriented horizontal cells occur.

The second neuropil of the retina is the inner plexiform layer (IPL), and it functions as a relay station for the vertical-information-carrying nerve cells, the bipolar cells, to connect to ganglion cells. In addition, different varieties of horizontally- and vertically-directed amacrine cells, somehow interact in further networks to influence and integrate the ganglion cell signals. It is at the culmination of all this neural processing in the inner plexiform layer that the message concerning the visual image is transmitted to the brain along the optic nerve.

Viewed under an electron microscope, the photoreceptor consists of an outer segment, filled with stacks of membranes (like a stack of poker chips) containing the visual pigment molecules such as rhodopsins. There is also an inner segment containing mitochondria, ribosomes and membranes where opsin molecules are assembled and passed to be part of the outer segment discs. There is also a cell body containing the nucleus of the photoreceptor cell, and a synaptic terminal where neurotransmission to second order neurons occurs.
These expanding membrane plates become detached as free floating discs inside the outer segment membrane in the case of the rods. In the case of the cones though, the outer segment discs remain attached to the outer segment membrane. So the outer segment is a structure filled entirely with discs of folded double membranes in which are embedded the light sensitive visual pigment molecules.

**Vertical pathway** involves photoreceptors, bipolar cells and ganglion cells.

**Horizontal pathway** involves horizontal cells and amacrine cells.

The **fovea** is an avascular zone with the maximum density of photoreceptors, and it has a high spatial resolution. The whole foveal area including foveal pit, foveal slope, parafovea and perifovea is considered the **macula** of the human eye.

Familiar to ophthalmologists is a **yellow pigmentation** to the macular area known as the **macula lutea**. This pigmentation is the reflection from yellow screening pigments, the xanthophyll carotenoids zeaxanthin and lutein present in the cone axons of the Henle fibre layer. The macula lutea is thought to act as a **short wavelength filter**, additional to that provided by the lens. As the fovea is the most essential part of the retina for human vision, protective mechanisms for avoiding bright light and especially ultraviolet irradiation damage are essential. For if the delicate cones of our fovea are destroyed we become blind.

It is important for our understanding of the organisation of the visual connections for us to know the **spatial distribution of the different cell types** in the retina. **Photoreceptors**, we know, are organised in a fairly exact mosaic. In the fovea, the mosaic is a hexagonal packing of cones. Outside the fovea, the rods break up the close hexagonal packing of the cones but still allow an organised architecture with cones rather evenly spaced surrounded by rings of rods. Thus in terms of densities of the different photoreceptor populations in the human retina, it is clear that the cone density is highest in the **foveal pit** and falls rapidly outside the fovea to a fairly even density into the peripheral retina. There is a peak of the rod photoreceptors in a ring around the fovea at about 4.5 mm or 18 degrees from the foveal pit. The optic nerve (blind spot) is of course photoreceptor free.

**Visual Acuity**

The most commonly measured subjective visual attribute is visual acuity: the ability to see **fine detail**. This is a measurement of the **spatial resolving power of the eye**. It is determined in the clinic using **Snellen’s chart** named after the 19th century German ophthalmologist who implemented this standardised form of testing.

Test results are expressed as a **fraction** where the numerator refers to the test distance (standardised to 6 meters) and the denominator refers to the line with letters whose size corresponds to a distance at which the limbs which make up the letter subtend 1 minute of arc. One minute of arc is taken to be the limit of acuity (at least for letters) of a normal person. For example a patient with an acuity of 6/60 is able to read (at the 6 meter test distance) what a normal person would be able to read at 60 metres. The resolving power of the eye is thus 10 times poorer than normal i.e. 10 min arc.
Photoreceptors and Colour Perception

Two basic types of photoreceptor, rods and cones, exist in the vertebrate retina. The rods are photoreceptors that contain the visual pigment - rhodopsin and are sensitive to blue-green light with a peak sensitivity around 500 nm wavelength of light. Rods are highly sensitive photoreceptors and are used for vision under dark-dim conditions at night. Cones contain cone opsins as their visual pigments and, depending on the exact structure of the opsin molecule, are maximally sensitive to either long wavelengths of light (red light), medium wavelengths of light (green light) or short wavelengths of light (blue light). Cones of different wavelength sensitivity and the consequent pathways of connectivity to the brain are, of course, the basis of colour perception in our visual image.

Most mammalian species are dichromatic containing as well as rods only middle and short wavelength sensitive cones in their retinas. Primates and humans, birds, reptiles and fish are trichromatic, tetrachromatic and some even pentachromatic (the latter three vertebrate phyla). Thus long, medium and short wavelength cones have been demonstrated to exist in human retina by photometric and psychophysical methods: L-cones (red) are known to be maximally sensitive to wavelengths peaking at 564nm, M-cones (green) at 533nm and S-cones (blue) at 437nm respectively.

Congenital colour deficiencies affect around 8% of males and 0.5% of females. There are also conditions such as anomalous trichromacy (protanomaly, deutanomaly, tritanomaly), dichromacy (protanopia, deuteranopia, tritanopia), and monochromacy.

All these congenital defects in colour vision can be assessed using simple pseudoisochromatic tests such as the Ishihara colour plates. Observers are simply asked to find the hidden numbers or more simply trace a path across a coloured background in an organised series of tests. The results from which can diagnose the nature of the abnormality.
Image formation by the eye is done by **refraction** of light, the extent of which depends on the radius of the curvature and the refractive index. Structures involved in this include the cornea, aqueous, lens and the vitreous. The degree to which these structures refract light is known as **dioptic power**. A dioptre \(= \frac{1}{f} \), where \(f\) is the focal length of the lens in metres.

**Emmetropia** is the normal state in which parallel light rays (from a distant source) are brought to focus on the retina. Accommodation is relaxed. **Ametropia** is refractive error, and this can manifest itself as **myopia** (short sight), **hypermetropia** (long sight), or as **astigmatism**.

**Myopia** is short-sightedness. In this condition, light rays from a distant object are brought to focus in front of the retina. Myopia is corrected by use of concave (diverging) negative lenses. Myopia most commonly arises because the eyeball is disproportionately long given the power of the cornea and lens.

**Hypermetropia** is long-sightedness, also known as hyperopia. In this condition, parallel light rays are brought to focus behind the retina. This is corrected by the use of convex (converging) positive lenses. Hyperopia most commonly arises because the eyeball is disproportionately short given the optical power of the lens and cornea.

The third kind of ametropia is known as **astigmatism** which can occur in combination with either hypermetropia or myopia. In this condition there is a **variation in the focussing power** of the eye as a function of orientation of the image. Consider light rays emerging from an image of a cross. The horizontal axis or meridian is correctly focussed on the retina whilst the vertical meridian is focussed in front of the retina.

Astigmatic refractive errors are corrected by lenses with a cylindrical component - those in which the power varies as a function of the axis.

**Presbyopia** refers to the naturally occurring loss of the ability of the eye to accommodate due to a hardening of the crystalline lens. This results in a loss of visual acuity for near objects such as reading material. The eye may still remain emmetropic for images viewed at a distance. It affects increasing numbers of individuals from the age of 40 onwards, and 100% by the age of 50. It is corrected by the use of converging, positive lenses “reading glasses”.

**Primary Visual Pathway**

The picture on the right shows the **retinogeniculostriate pathway**. The optical radiations fan out over some considerable area in comparison to the optic nerve or the optic tract.

An **opsin** in a **photoreceptor** cell absorbs a photon and transmits a signal to the cell through a signal transduction pathway, resulting in hyperpolarisation of the photoreceptor. Photoreceptors synapse directly onto **bipolar cells**, which in turn synapse onto **ganglion cells** of the outermost layer, which will then conduct action potentials to the brain. A lot of visual processing arises from the patterns of communication between neurons in the retina. In addition, **horizontal** and **amacrine** cells transmit information laterally, resulting in more complex receptive fields.

Information is transmitted from the eye to the brain along the **optic nerve**. About 90% of the axons in the optic nerve go to the **lateral geniculate nucleus** in the thalamus. This parallel processing is important for reconstructing the visual world. Another population of ganglion cells sends information to the **superior colliculus** in the midbrain, which assists in controlling eye movements (saccades) and other motor responses.
Another population of ganglion cells are **photosensitive retinal ganglion cells**, containing melanopsin, and they send information via the **retinohypothalamic tract** to the **prectum** (pupillary reflex), to several structures involved in the control of circadian rhythms and sleep such as the **suprachiasmatic nucleus**, and to the **ventrolateral preoptic nucleus** (a region involved in sleep regulation).

The optic nerves from both eyes meet and cross at the **optic chiasm**, at the base of the hypothalamus. At this point the information coming from both eyes is combined and then splits according to the visual field. The right side of the primary visual cortex deals with the left half of the field of view from both eyes, and vice versa for the left side of the visual cortex.

Information from the right visual field (now on the left side of the brain) travels in the left optic tract. Each optic tract terminates in the **lateral geniculate nucleus** in the thalamus.

The **lateral geniculate nucleus** is a sensory relay nucleus. It consists of six layers. Layers 1, 4 and 6 correspond to information from the contralateral fibres of the nasal visual field. Layers 2, 3 and 5 correspond to information from the ipsilateral fibres of the temporal visual field. Layer 1 contains M cells, which correspond to the magnocellular cells of the optic nerve of the opposite eye and are concerned with depth or motion. Layers 4 and 6 connect to P cells (parvocellular) of the opposite eye and are concerned with colour and edges. By contrast, layers 2, 3 and 5 connect to M cells and P cells of the optic nerve for the same side of the brain.

The **optic radiations** carry information from the thalamic lateral geniculate nucleus to layer 4 of the visual cortex. The visual cortex is the largest system in the brain and is responsible for processing the visual image. It lies at the rear of the brain above the cerebellum. The region that receives information directly from the lateral geniculate nucleus is called the **primary visual cortex** (also called V1 and striate cortex). Visual information then flows through a cortical hierarchy. These areas include V2, V3, V4 and area V5. These **secondary visual areas** (collectively termed the extrastriate visual cortex) process a wide variety of visual primitives.

**Visual Fields**

The left field maps to the nasal retina of the left eye and the temporal retina of the right eye. The right field maps to the temporal retina of the left eye and the nasal retina of the right eye. Note temporal fibres do not cross at the chiasm.

A lesion at A would result in loss of vision in the right eye. At B, it would cause **bitemporal hemianopia**. At C this would result in **homonomous hemianopia**. A lesion at D would cause **left superior quadrantanopia**, and a lesion at E would cause **left homonomous hemianopia with macular sparing**.

Visual processing continues beyond the striate visual cortex (V1) into the extrastriate regions (V2, V3, V4, V5/MT, V6, V7, V8). There is evidence of this through animal testing, clinical conditions (e.g. cerebral achromatopsia), and imaging (e.g. PET, fMRI).

**Circadian Visual System**

The circadian rhythm is an endogenously driven roughly 24-hour cycle. Although circadian rhythms are endogenous, they are adjusted (entrained) to the environment by external cues called **zeitgebers**, the primary one of which is daylight. The primary circadian clock is located in the **suprachiasmatic nucleus** in the hypothalamus. **Photosensitive retinal ganglion cells** project directly to the SCN, where they help in the entrainment of this master circadian clock. These cells contain the photopigment **melanopsin** and their signals follow a pathway called the **retinohypothalamic tract**, leading to the SCN.
The SCN takes the information on the lengths of the day and night from the retina, interprets it, and passes it on to the pineal gland located in the epithalamus. In response, the pineal gland secretes the hormone melatonin. Secretion of melatonin peaks at night, and its presence provides information about night-length.

The classic markers for measuring the timing of someone’s circadian rhythm are:
- Melatonin secreted by the pineal gland
- Core body temperature
- Plasma level of cortisol

Reflex Pathways

The pupillary light reflex controls the diameter of the pupil, in response to the intensity of light that falls on the retina of the eye, thereby assisting in adaptation to various levels of darkness and light. It therefore regulates light input (but note less than a 2 log unit change).

Greater intensity causes the pupil to become smaller (allowing less light in). This decrease spherical aberrations and glare, increases depth of focus and reduces bleaching of photopigments. In darker conditions, the visual field is enlarged and there is an overall lower threshold for light perception.

The photosensitive ganglion cells through the retinohypothalamic tract are responsible for the afferent limb of the pupillary reflex via the optic nerve. Rod and cone photoreceptors also do this. They exit at the posterior third of the optic tract, with three partial crossings. The optic nerve connects to the pretectal nucleus of the upper midbrain, bypassing the lateral geniculate nucleus and the primary visual cortex. From the pretectal nucleus, axons connect to neurons in the Edinger-Westphal nucleus (specific to the sphincter), whose axons run along both the left and right oculomotor nerves. The oculomotor nerve is responsible for the efferent limb of the pupillary reflex. The oculomotor nerve axons synapse on ciliary ganglion neurons.

A unilateral afferent defect will produce a reduced response in the affected eye when directly stimulated, and a normal response in the affected eye when stimulated consensually. A unilateral efferent defect will produce unequal pupil size (anisocoria).

The near reflex (complex / triad) is involved in pupillary miosis (sphincter pupillae), convergence (medial rectus) and accommodation (ciliary muscle). When someone accommodates to a near object, they also converge their eyes and constrict their pupils. The combination of these three movements is under the control of the Edinger-Westphal nucleus and is referred to as the near triad. Although, it is clear that convergence allows to focus the object’s image on the retina, the functional role of the pupillary contraction remains less clear. Arguably, it may increase the depth of field by reducing the aperture of the eye, and thus reduce the amount of accommodation needed to bring the image in focus on the retina. The common efferent pathway for each component if the near triad is the oculomotor nerve.

Argyll Robertson pupils are bilateral small pupils that constrict when the patient focuses on a near object, but do not constrict when exposed to bright light. They are a highly specific sign of neurosyphilis. In general, pupils that accommodate but do not react are said to show light-near dissociation. They were formerly known as "Prostitute’s Pupils" because of their association with tertiary syphilis.
The Control of Eye Movements
by Professor Michael Gresty

Eye movements only do two things. They allow us to look at things and to look from one thing to another.

The movements which stabilise visual fixation during self or object motion are called slow phase eye movements and include pursuit and the vestibulo-ocular reflex.

The movements which shift fixation from one direction to another are very fast, termed saccades or fast phases.

Vergence movements combine slow and moderately fast disconjugate eye movements to look between near and far and to maintain accurate binocular alignment during all eye movement.

Different Eye Movements:
Gaze holding: maintain binocular visually fused fixation on objects in all directions of gaze.
Vergence: transfer gaze between near and far objects.
Saccades: look from one object to another, side to side, up and down.
Vestibulo-ocular reflex: stabilise vision on target during head movements.
Pursuit: follow moving objects.
Optokinetic reflex: stabilise on and follow large areas of moving visual field.

Saccades
These are the only eye movement that allow gaze transfer from one object to another. They are also termed “fast phase” or “beat” if they occur within a nystagmus. Saccades occur in all combinations of horizontal and vertical directions, and they may be voluntary or a reflex. They are very fast movements, transferring the eyes in a short as time as possible between objects. A saccade of 30° amplitude may be 600° per second in peak velocity. Saccades are approximately 90% accurate. Small corrective saccades may be generated to attain precise fixation.

The pontine paramedian reticular formation (PPRF) generates the intense burst of activity needed to drive the abducens and medial rectus nuclei motoneurons to make horizontal saccades. The right PPRF is for rightwards movements, and the left PPRF is for leftwards saccades. The rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) generates the burst activity for upwards/downwards and torsional saccades via the oculomotor and trochlear nuclei to vertical recti muscles and oblique muscles.

Cortical disease saccades can be highly erratic in timing, amplitude and direction. Basal ganglia disease (Parkinson’s disease) saccades may be small in amplitude becoming smaller and sometimes slow with repetitive tasks. Cerebellar disease saccades can over-shoot the target (hypermetria) or under-shoot (hypometria). Rapid sequences of functionless alternating direction saccades may be released involuntarily, and these are called saccadic oscillations. Brainstem disease saccades tend to be slow and restricted in amplitude - palsy or paresis. “Supra-nuclear palsy” is where a lesion of the brain may affect only saccades, leaving the vestibulo-ocular reflex movements intact.

Pursuit
Human beings use pursuit eye movements to follow targets moving with smooth (more or less) uniform motion. Most animals do not have pursuit. Pursuit movements can be made up to a velocity of about 60-80° per second in the horizontal plane and can follow targets which oscillate up to circa 1Hz. Pursuit eye movements in the vertical plane have a lower performance.

Pursuit is mediated by the visual cortex via the cerebellum to the brainstem oculomotor nuclei. The right cerebellum controls rightwards pursuit, and the left cerebellum controls leftwards pursuit.
Disorders of pursuit manifest themselves as an inability of the eyes to follow a target moving with reasonable velocity with the results that the eyes make small catch-up saccades to maintain the alignment of the eyes with the target. Disordered pursuit is a sensitive clinical sign of brainstem-cerebellar disease. A disorder of pursuit is non-specific and may be attributable to a wide range of neurological diseases (especially brainstem cerebellar disease) and drugs such as alcohol and anti-depressants.

Vestibulo-ocular reflex eye movements
The vestibular ocular reflex (VOR) compensates for movements of the head so that eyes maintain fixation on a target. The vestibular ocular reflex is a primitive, powerful eye movement mechanism and compensates for rotations of the head up to about 180° per second and at frequencies as high as around 8Hz. The semi-circular canals of the labyrinth are stimulated by angular acceleration of the head and drive eye movements that are compensatory for linear movements of the head and tilt. During a continuing rotation of the head the VOR drives the eyes to a progressively more eccentric orbital position. Frequent saccades reset eye position towards the centre: normal physiological vestibular nystagmus.

The acceleration phase of head rotation stimulates the semi-circular canal on the side to which the head is turning. The canal activation drives the eyes in the opposite direction via the vestibulocochlear nerve, relaying in the vestibular nuclei and then projecting to the III, IV, and V nuclei. The eye movement is in the opposite direction to the head movement with a compensatory matching velocity so that they cancel each other out maintaining a stable direction of gaze.

Bilateral disorders (loss of) the vestibular reflex reduce visual acuity during head movements and may cause oscillopsia because compensatory fixation is lost and the eyes are carried “fixed” in the head. Unilateral loss of vestibular function results in a vestibular nystagmus (usually predominantly binocular in the horizontal direction). The left and right vestibular organs have a tonic discharge. If function is lost on one side, the unopposed tonus of the intact vestibular apparatus pushes the eyes across the orbit in a “slow phase” movement towards the lesioned side. The saccade system detects this drift and repetitive “fast phases” reset the eyes to a more central position forming the vestibular nystagmus. Loss of vestibulo-ocular reflexes occurs most commonly in diseases of the labyrinth (e.g. oto-toxic antibiotics) or of the VIII nerve innervating the labyrinth (e.g. acoustic neuroma). More rarely, brainstem vascular, neoplastic and demyelinating disease may impair vestibular reflexes.

Optokinetic eye movements
Relative motion of large areas of the visual field with respect to the head induces involuntary tracking of the eyes in a direction of motion so that visual stability is more or less maintained on the moving area. This is referred to as the optokinetic reflex and should be distinguished from smooth pursuit of a small foveal object.

For continual motion of the visual field (e.g. looking out the window on the motorway) the eyes will frequently make saccades (fast phases) back to a more central position and thereafter drift once more with the area of visual motion. This cycle of slow phase drift and resetting saccades produces a pattern of nystagmus referred to as normal physiological optokinetic nystagmus. A curious feature of optokinetic nystagmus is that it is frequently accompanied by an illusion of self-motion (vection illusion). Vection is familiar as the railway train illusion of self-motion when you see the adjacent train move.

The optokinetic reflex is mediated primarily by the visual cortex via the cerebellum to the brainstem oculomotor nuclei. Severe disruption of optokinetic reflexes is a sign of cerebellar-brainstem disease.

Vergence
These are the eye movements used to transfer fixation between near and far targets and to track approaching or receding objects. These may be quite fast but are never of saccade velocity. Convergence on a near object is an active process of contracting the paired medial rectus muscles whereas divergence is primarily passive and attained by relaxation of the medial recti. Vergence is provoked by disparity of images (parallax) of an object on the retina and by the drive to adjust focus to image objects at different distances.

Vergence is mediated by the visual cortex, frontal cortex and mesencephalic structures, and involves coordination of all ocular muscles, primarily the adductors. Many ‘normal’ subjects may have poor vergence in
one eye due to an overdominant eye or anisometropia. People with congenital strabismus cannot converge or binocularly fuse. Acquired problems with vergence imply lesions of the mesencephalon.

**Gaze holding**
This is related to vergence and is mediated by the visual cortex, frontal cortex, cerebellum and brainstem structures, and involves co-ordination of all ocular muscles. If gaze holding is impaired, the eyes drift back towards the centre when attempting to hold an eccentric gaze position. The drift is corrected by repositioning saccades which produces an overall pattern of slow-fast-slow-fast-slow phases, called "gaze paretic nystagmus". Mild gaze paretic nystagmus is a sign of cerebellar disease, and pronounced nystagmus implies brainstem disease.

**Congenital nystagmus** is where a few weeks after birth the eyes can be seen to oscillate sinusoidally or in combinations of fast and slow phases, usually horizontal. This is sometimes associated with strabismus. A wide spectrum of congenital neurological and ophthalmological disorders also feature a congenital type of nystagmus. Acquired pendular nystagmus is where the eyes oscillate sinusoidally in conjugate, disconjugate, vertical, horizontal or combined trajectories. This may be a feature of brainstem demyelinating or vascular disease. Voluntary nystagmus is where some people can make their eyes wobble voluntarily!

**Internuclear pathway**
The neuronal activity required for abduction of the eye is relayed from interneurons in the contralateral VI nucleus to the portion of the III nucleus that controls the medial rectus. For example, saccade generating activity from the left PPRF relays to the left VI, abducting the left eye, and simultaneously relays across the midline, ascending in the MLF to the contralateral III nucleus, adducting the right eye.

A lesion of the MLF causes a failure or weakness of adduction with intact abduction, this is internuclear ophthalmoplegia, which may be unilateral or bilateral and causes disconjugacy of gaze movements.
Control of Posture and Gait
by Professor Michael Gresty

Sensory information for control of posture and movement includes information from the environment as well as from within the body, although if the balancing task is simple not all the information may be necessary (e.g. standing with eyes closed). The primary senses involved in the sensory motor control of posture and gait are vision, the vestibular system, and the somatosensory system. Of the somatosensory system, the important subdivisions are proprioception and touch/pressure sensation.

The contribution of each of these to the organisation of posture and gait are shown by the consequences of specific impairments of each of the senses.

Vision has panoramic and teloceptive properties which inform of the structure of both near and distant environments and of relative motion of the self and other objects in the environment. Vision gives feedback of posture by way of showing relative motion with respect to the environment. It is essential in general navigation in the environment and informing predictions of what kind of movements may be needed. Motor responses to visual changes mediated through the cortex are generally slow (greater than 125ms latency). However, visual-motor ‘reflexes’ can provide rapid adaptation of gait to sudden changes in where a foot must be placed for support (response time circa 100ms) possibly by a primitive subcortical pathway. A blind person is seriously handicapped in environmental navigation, but can walk and run and some may even ski or play drums.

The vestibular system signals motion of the head in all linear and angular directions of motion and tilt of the head with respect to gravitational upright. Vestibular signals are the only cues to absolute motion in space and thus help to interpret vision and somatosensory signals in determining how the body is oriented and moving in the environment. A patient with bilateral loss of vestibular function becomes mildly ataxic when walking, particularly over rough ground or in darkness when deprived of vision. He cannot perform challenging balancing tasks. When walking the world is seen to “bounce” because of the loss of visual stabilising vestibulo-ocular reflexes. A patient with unilateral loss of vestibular function will tend to veer or fall towards the lesioned side, particularly when balance is challenged. Frequent causes of vestibular loss are viral (herpetic ‘vestibular neuritis’) and oto-toxic drugs.

The somatosensory system involves muscle stretch, joint position sense (joint rotation) and touch pressure sensation, all providing critical feedback parameters for the motor control of posture and gait. Signals from the ankles and feet are particularly important; the foot providing information about loading on the support surface and the ankle signalling rotations of the mass of the body about the contact with the support surface. Although a rare disorder, a patient with substantial loss of somatosensory signals from the lower limbs is very seriously disabled or even unable to walk. The somatosensory loss may be hereditary or acquired and is frequently compounded with a motor impairment. Common causes of (partial) sensory loss are B12 deficiency and diabetes (foot drop).

Causes of sensory loss include illness like Menière’s disease, cataract and neuropathy; injuries like physical, poisoning or drug toxicity; and ageing, which worsens visual, proprioceptive and vestibular performance. We can function during a temporary loss of sensory information, and people can also manage if one sense is lost completely. Control is adaptive and there is some degree of redundancy, therefore people lacking information from one sense can perform remarkably well if the motor task is not too difficult.

Some of the more obvious compensatory strategies include having a wide base of stance front to back and side to side to increase stability, and hyperextending the knee to provide passive stability by locking the joint. Compensation for gait includes moving the trunk and arms very little to reduce the need for control of moving masses, and again hyperextending the knee to provide stability.

Information from all the senses is used to deduce position and motion. Normally all the information is congruent, i.e. has the same interpretation. If different senses disagree the nervous system may give more weight to one than another, e.g. illusion of vection (self motion) in a stationary train. Prolonged or severe sensory conflict produces motion sickness.
**Organisation of the Cerebral Cortex**
by Dr Maggie Lowrie

The cerebral cortex is the outermost sheet of neural tissue in the cerebrum of the brain. It plays key roles in memory, attention, perceptual awareness, thought, language, and consciousness. It is the grey matter, and the surface of the cerebral cortex is folded in such a way that more than two thirds of it is buried in grooves called sulci.

The neocortex is the largest and most complex part of the cerebral cortex. The cells of the neocortex are arranged both vertically into layers and horizontally into columns. The layers are differentiated by their connections.

Layers 1 to 3 make intracortical connections only. Layer 4 receives inputs from the thalamus. Layers 5 to 6 project out of the cortex to the corpus striatum, brainstem, spinal cord and thalamus.

In addition all the layers of the cortex receive modulatory inputs from the reticular activating system and the brainstem monoaminergic nuclei. In terms of columnar organisation, the inputs and outputs are matched for all cells in each column, which is the basis of topographical maps.

The archicortex is the hippocampus, and is the more ancient part (phylogenetically older) of the cerebral cortex, as is the paleocortex, which is the layer between the neocortex and the archicortex (includes anterior olfactory nucleus, anterior perforated substance, prepyriform area and periamygdalar area).

In contrast to grey matter that is formed from neurons and their unmyelinated fibres, the white matter below them is formed predominantly by myelinated axons interconnecting neurons in different regions of the cerebral cortex with each other and neurons in other parts of the central nervous system.

There is a large volume of subcortical white matter in the cerebral hemispheres. Association fibres connect one area of the cortex with another within the same hemisphere. Commissural fibres interconnect corresponding areas of two hemispheres. The corpus callosum interconnects the frontal, parietal, occipital and some temporal cortex. The anterior commissure provides additional temporal links.

Projection fibres interconnect cortex with subcortical regions. The incoming fibres are mainly from the thalamus, but also from the hypothalamus and brainstem. The outgoing fibres are to the corpus striatum, thalamus, brainstem and spinal cord. Most go through the corona radiata and internal capsule.

Corticospinal and corticobulbar fibres pass through the posterior limb, therefore posterior limb lesions result in motor deficits. Thalamocortical, corticothalamic and corticopontine fibres pass through both limbs. Sensory deficits can arise from any capsular lesion, but the modality depends on the exact position.
Methods of Studying Cortical Function

Lesions were historically the main method was observing the effects of cerebral lesions on behaviour. Interpretation is limited by poor reproducibility, inter-subject variation, lack of pre-morbid measures, and plasticity/redundancy. Another method is stimulation, which involves e.g. using electrodes during surgery.

However to study complex behaviour, it is better to monitor brain activity while the subject is performing a task. Evoked potential (EP), or Event-Related Potential (ERP) is non-invasive, and is essentially a refined form of EEG recording. It is a direct measure of neuronal activity, revealing that brain activity is related to specific behavioural events. It has very good temporal resolution (measured in msecs), but poor spatial resolution (measured in cms). Computer analysis reveals waveforms which are time-linked to particular events. For example, response of the visual cortex to light, activity related to movement, object recognition, cognition, etc.

Functional imaging is minimally invasive and usually measures neuronal activity indirectly. It has poor temporal resolution (measured in msecs), but has better spatial resolution than EEG (measured in mms). Computer analysis can reveal activity linked to behaviour and levels of neurotransmitter. Examples include positron emission tomography and functional magnetic resonance imaging.

Localisation of Function

Parts of the cortex that receive sensory inputs from the thalamus are called primary sensory areas. In general, the two hemispheres receive information from the contralateral side of the body. The organisation of sensory maps in the cortex reflects that of the corresponding sensing organ, in what is known as the topographic map. The functions are predictable, and there is left-right symmetry.

The motor areas are located in both hemispheres of the cortex. They are shaped like a pair of headphones stretching from ear to ear. Two areas of the motor cortex are the primary motor cortex (executes voluntary movements) and the premotor cortex (selects voluntary movements).

Association areas function to produce a meaningful perceptual experience of the world, enable us to interact effectively, and support abstract thinking and language. The functions are less predictable and the areas are not organised topographically. Left-right symmetry is weak or absent.

The occipital association cortex is the visual association cortex, which analyses different attributes of visual image in different places. Form and colour are analysed along the ventral pathway, while spatial relationships and movement are along the dorsal pathway. Lesions affect specific aspects of visual perception.

The posterior parietal association cortex creates a spatial map of the body in its surroundings, from multimodality information. Injury may cause disorientation, inability to read, map or understand spatial relationships, apraxia, and hemispatial neglect.

The temporal association cortex is involved in language, object recognition, memory and emotion. Injury here leads to agnosia, and receptive aphasia.
The **frontal** association cortex is involved in motor planning, judgement, foresight, personality, and appreciation of self in relation to the world. Injury here leads to deficits in planning, and inappropriate behaviour.

There are some **interhemispheric differences**. The left hemisphere is more concerned with language and sequential analysis. The right hemisphere is more concerned with things like shape, spatial relationships and music.
**Introduction to Consciousness**

by Dr Maggie Lowrie

Consciousness is defined as a certain level of arousal, and a state of self awareness. There are certain structures in the brain involved in regulating the level of arousal. The reticular formation is a polysynaptic network in the core of the midbrain, pons and upper medulla. The reticular formation has many functions besides control of consciousness, for example it regulates body systems such as the cardiovascular and respiratory systems, and it also regulates bladder and motor patterns.

The reticular formation receives information from all sensory pathways. It receives **touch** and **pain** information from the ascending tracts, **vestibular** info from the medial vestibular nerve, **auditory** info from the inferior colliculus, **visual** info from the superior colliculus, and **olfactory** into via the medial forebrain bundle.

The reticular formation **modulates cerebral activity**. The **locus coeruleus** is a nucleus in the brain stem involved in physiological responses to stress and panic. It is located in the dorsal wall of the rostral pons in the lateral floor of the fourth ventricle. This nucleus is the principal site for brain synthesis of noradrenaline. The norepinephrinic neurones project directly to the cerebral cortex. **Dopaminergic neurons** of the ventral tegmental nucleus project directly into the cortex. The ventral tegmental area is a group of neurons located close to the midline on the floor of the midbrain. It is the origin of the dopaminergic cell bodies of the mesocorticolimbic dopamine system and is widely implicated in the drug and natural **reward** circuitry of the brain. It is important in cognition, motivation, drug addiction, and several psychiatric disorders. **Cholinergic neurons** from the reticular formation project into the thalamus. **Raphe nuclei** in the midline are the main source of serotonergic projections to the brain and spinal cord. The main function of the raphe nuclei is to release serotonin to the rest of the brain. Selective serotonin reuptake inhibitor (SSRI) antidepressants act in these nuclei.

The reticular formation has a whole host of nuclei, each one using different transmitters - dopaminergic, serotonergic, noradrenergic, etc. They all contribute to controlling consciousness, but the main pathway emerging in research is the cholinergic nuclei. The **cholinergic neurons** seem to be the most important for regulating the level of arousal, as they increase the level of activity in the cerebral cortex via the thalamus. They influence the activity of the thalamus by several different mechanisms. The thalamus is a collection of nuclei which relay information back and forth to the cortex. By influencing the thalamus, you modulate the activity of the cerebral cortex itself.

There are three main mechanisms at work in the thalamus:
- Cholinergic projections excite **individual** thalamic relay nuclei leading to activation of the cortex.
- Cholinergic projections project to the **intralaminar** nuclei (white matter between each section of the thalamus), which in turn project to all areas of the cortex.
- Cholinergic projections to **reticular** nucleus (wraps around most of the thalamus), which regulates flow of information through other thalamic nuclei to the cortex. By activating the reticular nucleus, you modulate the amount of information reaching each nucleus and onto the cortex.

There is also the **tuberomammillary nucleus** (histaminergic) in the hypothalamus. It projects widely to the cortex and is involved in maintaining the awake state.

The **reticular activating system** is triggered by **sensory input**, projecting via cholinergic projections to the thalamus, which then stimulates the cerebral cortex. Normally there is **always some level of activity** in the system, and the more active it is, the more alert you are. The level of activity is controlled by the amount of sensory information coming into the system. Sensory inputs include olfactory, somatosensory, visual, auditory and vestibular. Sleep is a natural alternative to being awake, but it involves specific sleep promoting pathways as well as reduced activity in the reticular activating system.
Detection of the level of arousal

Different levels of arousal can be seen as a change of waveform in an EEG, which records activity from the cerebral cortex. Four basic rhythms are recognised, defined by their frequency.

**Alpha** rhythms have a characteristic frequency of 8-13Hz. You would see this rhythm in a subject who is sitting quietly in a relaxed way with their eyes closed. If you asked the subject to open their eyes, think about something, do a calculation etc, the rhythm would become a **Beta** rhythm. This has a lower amplitude, but a higher frequency of 13-30Hz. The lowest trace on the diagram shows a subject sitting quietly with their eyes closed (alpha), at the arrow they open their eyes (beta), and then shut them again.

**Theta** rhythm has larger amplitude but is much slower (4-8Hz). This is typically seen in a subject who is feeling drowsy, or is just about to go to sleep. **Delta** rhythm is the slowest (0.5-4Hz), and this is a normal rhythm seen during sleep.

Altered states of consciousness

**Concussion** or **contrusion** may cause temporary loss of consciousness, which usually only lasts for a few minutes (transient). In concussion, there is usually a blow to the head, the brain wobbles about in the cranial cavity, you lose consciousness transiently, but then you regain consciousness. **Contrusion** is where the brain actually bangs against the inside of the cranial cavity and there is bruising on the surface of the brain.

**Confusion** (delirium) is a sustained disturbance of consciousness where mental processes are slowed. The person may be inattentive, disorientated, or have difficulty in carrying out simple commands or speaking. A **stupor** is much more profound, and the patient actually appears to be unconscious. They can only be roused by strong sensory stimuli. A **coma** is where the patient can’t be roused even by strong sensory stimuli. It is different from sleep as metabolic activity of the brain is depressed and there is total amnesia for the period in a coma.

A standardised method of assessing conscious/unconscious patients is the Glasgow Coma Scale. It depends on three different responses you could get out of the patient. For each section there is a score (1 being lowest). All the scores are added up to give a total score.

The lowest possible total score is 3 (totally unconscious patient), and the top score for a normal conscious person is 15.

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<thead>
<tr>
<th>Eyes open</th>
<th>Verbal responses</th>
<th>Motor responses</th>
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<tr>
<td>none</td>
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<tr>
<td>in response to pain</td>
<td>incomprehensible sounds</td>
<td>extensor response to pain</td>
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<td>in response to speech</td>
<td>inappropriate words</td>
<td>flexor response to pain</td>
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<td>spontaneous</td>
<td>disoriented speech</td>
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<td>oriented speech</td>
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**Coma**

A coma can be caused by a variety of things. Causes can be classified into **metabolic** or due to a **CNS lesion**. Examples of metabolic causes include hypoxia, hypoglycaemia and intoxication. There are also a whole host of drugs which can cause intoxication and cause you to become unconscious. When it comes to CNS lesions, these can be related to the pathway of the reticular activating system. A lesion in any part of this system will disrupt the methods of controlling consciousness. Widespread cerebral cortical damage is likely to make you unconsciousness, but also smaller discrete lesions in the brainstem, reticular formation or thalamus could disrupt the reticular activating system and cause unconsciousness.

Reversible coma has a much better outcome as the patient eventually wakes up. A situation of irreversible coma is where unfortunately this doesn’t happen. Here we need to think in terms of where the lesion is precisely, as this determines a lot of how the patient is tested, and how the decision is made whether the patient should be allowed to die.
Every person in irreversible coma is considered as an individual case, but generally there are two general categories of irreversible coma.

**Brain death** is irreversible coma due to brainstem death. A lesion in the brainstem which is sufficient to disrupt the reticular formation means the patient will be in an irreversible coma. The body can be kept alive artificially with life support machines. They may have a normal EEG, and look like they are asleep, so an EEG is not diagnostic. The decision to cease treatment depends on the demonstration of absent brainstem reflexes, and no response to hypercapnoea.

**Persistent vegetative state** is where the damage is in one of two places. It is either very extensive cortical damage, or a smaller lesion somewhere in the reticular activating system above the level of the brainstem (so in the thalamus or in the connection between the top of the reticular formation and the thalamus). The brainstem is still functioning, so reflexes, postural movements and sleep-wake cycles may be present.
Sleep
by Dr Maggie Lowrie

About a third of our lives are spent asleep. Sleep can be defined by a list of behavioural criteria. There are stereotypic or species specific postures, minimal movement, reduced responsiveness to external stimuli, but it is reversible with stimulation (unlike coma, anaesthesia or death).

Until very recently, behavioural criteria were all we had when we thought about sleep. It was generally assumed that the brain closed down when we went to sleep, the level of activity reduced until we woke up. During the 1950s, various brain activity recording techniques revolutionised these understandings of sleep.

The basic methods included an EEG (recording brain activity), an EOG (electrodes around the eyes record eye movements), and an EMG (records the level of tone in muscles).

These studies found that there are stages of sleep. In the awake individual, there is a reasonable EEG level, eye movements, and muscle tone is high. As the subject goes into sleep, the EEG frequency reduces (Theta rhythm), much fewer or completely absent eye movements, and the muscle tone is reduced. Deeper sleep through stages 3 and 4 shows continuation of those trends, but you see Theta rhythm going into Delta rhythm. In Stage 5 there is Beta rhythm, lots of eye movement, and almost a complete suppression of muscle tone. This is also referred to as REM (rapid eye movement) sleep. The first 4 stages are referred to as non-REM sleep.

The whole process of a single sleep cycle takes up to an hour and a half. So during an average night’s sleep, you go through several of these cycles. Muscle tone is moderately reduced during stages 1-4, and very low during REM sleep. Dreams may occur during any stage but are most prominent in REM sleep, and most easily recalled. During dreams the limbic system is more active and the frontal cortex is less active. Descending through stages 1-4 takes about 1 hour, followed by several minutes of REM sleep.
There has been quite a lot of research recently into how sleep is controlled. There is still a lot that we don’t actually know.

The brainstem has various nuclei which either project directly to the cerebral cortex, or in the case of cholinergic nuclei, to the thalamus. They alter the activity of the cerebral cortex. Generally speaking, the higher the level of activity going through the reticular activating system, the higher the level of arousal. There is also the tuberomammillary nucleus in the hypothalamus, which projects directly to the cerebral cortex and is important in maintaining wakefulness.

Sleep is not just the absence or severe reduction in activity of the reticular activating system. There is a system which governs the sleep-wake cycle, and impinges on the basic system of maintaining consciousness. This involves two nuclei in the hypothalamus.

The lateral hypothalamus (LH) is active when we are awake, and it keeps the reticular activating system going by stimulating various nuclei in the brainstem. It also has connections to the cortex. The ventrolateral preoptic nucleus (VLPO) promotes sleep through GABAergic projections that inhibit the nuclei in the brainstem. The VLPO and the LH nuclei have an antagonistic relationship with each other (they have synapses between them), and when one is active, the other is acquiescent. Alternations between these two nuclei controls the sleep-wake cycle. They also probably control the alterations between REM and non-REM sleep.

Another nucleus has been found, which is active in REM sleep - the caudal pontine reticular formation (CPRF). This nucleus activates the eye movements seen during REM sleep, via the superior colliculus. At the same time, it suppresses muscle tone through the reticular formation. It also probably activates the cholinergic nuclei to turn on Beta rhythm in the cerebral cortex.

The sleep-wake cycle is synchronised with daylight. There is the suprachiasmatic nucleus (SCN) in the hypothalamus that receives input from the retina via the optic nerve, from special photoreceptor cells which detect falling light levels. The SCN has widespread projections. It inhibits the lateral hypothalamic nucleus (which normally promotes wakefulness) and stimulates the ventrolateral preoptic nucleus (which promotes sleep) and also inhibits the nuclei in the reticular formation. As this is all happening as light levels fall, this explains why we become sleepier at night. It also has connections that project to the pineal gland, which secretes melatonin. The melatonin goes into the circulation and alters various physiological processes. It is responsible for reducing respiration rate, heart rate, temperature, etc. This is called circadian synchronisation of the sleep-wake cycle. The sleep-wake pattern is always co-ordinated with day length.

Sleep is definitely necessary. If you try to deprive someone of sleep, you can’t kill them. Individuals who have tried to keep themselves awake have managed to do so for about 2 or 3 weeks, and then you end up involuntarily falling asleep. Most or in fact all animals that have been studied go through a period of sleep or acquiescence which is equivalent to human sleep. Sleep deprivation is detrimental. Sleep is regulated very accurately.
If you’ve lost a night’s sleep, there is likely to be a change in mood, you’ll feel sleepy, you’ll be irritable and impatient. You are also less able to carry out normal tasks; you may be slower at tasks and will make more mistakes. You won’t be able to concentrate very well, and this is particularly important for children as they could develop learning difficulties. You can also get glucose intolerance, and suffer an increased appetite as a result of a reduction in leptin secretion from the adipose tissue. Both of these are to do with energy conservation. After prolonged sleep deprivation you may suffer hallucinations. Rats can actually be killed by depriving them of sleep (14 to 40 days). Humans have a protective mechanism which forces you to go to sleep if you are deprived. Fatal familial insomnia can occur due to a particular lesion in the brainstem, which affects sleep patterns. In the later stages, the patient can’t sleep, and this is fatal.

After sleep loss, there is a reduced latency to sleep onset, so there is actually a drive to want to sleep when you haven’t had enough. There is an increase of slow wave sleep (non-REM). If you deprive a subject of REM sleep, then afterwards there is a selective increase in REM sleep to make up for the deprivation. All of this data tells us that sleep is important and sleep is necessary.

**Functions of sleep**

There have been lots of suggestions over the years, perhaps the most obvious is that we need regular periods of rest (restoration and recovery), which is certainly a function of sleep. This is, however, difficult to prove as you’ll find that active individuals do not necessarily sleep more than non-active individuals. Energy conservation is also another function of sleep. There is a 10% drop in basal metabolic rate, but lying still is just as effective. Another evolutionary function might be predator avoidance, but if this was a simple function why would sleep be so complex? During sleep the brain has specific functions to carry out.

**Dreams** have fascinated mankind for a long time. They tend to occur at any time during a night of sleep, but are more frequent in REM sleep and are recalled more easily if they occur in REM sleep. Dreams are often about very ordinary situations, but they are in a heightened emotional environment than in real life. This correlates well with studies of brain activity. Brain activity in the limbic system is higher during sleep than activity in the frontal lobe.

Is there a function of dreams? They could be a safety valve for antisocial emotions. This originates from ideas that Freud had, that in our everyday situations we sometimes become quite upset by the way other people respond to us but we do not react to it fully because of the social situation. In our dreams, we may go over that situation again and get the emotion out of our system. There hasn’t been much research on this. Another hypothesis is that during the day, we absorb an enormous amount of knowledge and information. We use our sleep to sort through all these memories and throw out the ones we don’t need to keep. This was an idea suggested by Francis Krick, the disposal of unwanted memories. A third possibility is that sleep is used for memory consolidation. There has been research on this. For example, you can give people a list of things to remember, let them sleep or deprive them of sleep, and then ask them to recall it. You’ll find the people who have slept will remember the list better. Non-REM sleep is important for declarative memory (for facts and events), whereas REM sleep is more important for procedural memory (learning new skills).

**Sleep disorders**

There are two basic types of sleep disorders - you either don’t get enough or you get too much. Insomnia is quite highly prevalent. It is estimated that between 20-50% of the population aren’t getting enough sleep at any one time. Potentially, it is an enormous clinical problem. Most cases of insomnia are transient, as they tend to be due to a stressful situation, emotional upset in life or temporary illness. There are also cases of chronic insomnia which is more difficult to deal with. One of these is sleep apnoea, where people will feel very tired and not realise why. Other causes of chronic cases include chronic pain, or brain dysfunctions like depression and fatal familial insomnia. Most hypnotic drugs enhance the GABAergic circuits of the brain. Problems with pharmacological treatments of insomnia are that they can become addictive.

Narcolepsy is a very debilitating illness. You fall asleep repeatedly through the day. It is often associated with cataplexy, which is a sudden reduction in muscle tone sufficient to make you fall over from standing up. This seems to be a dysfunction of the control of REM sleep. The patient goes straight into REM sleep instead of going through the first four stages. It is probably due to a genetic mutation, where there is a deficiency in orexin, which is the transmitter used by the neurones of the LH nucleus. Treatments include giving stimulants, but more recently there are trials of giving them orexin.
**Olfaction and the Limbic System**

by Dr Steve Gentleman

We can discriminate somewhere between 2000 and 4000 different odours, but unfortunately the molecular mechanism of this is largely unknown.

We have our olfactory epithelium at the top of the nose, where the bipolar olfactory neurons are connected through the cribriform plate to the olfactory bulbs on the underside of the frontal lobe.

Sustentacular cells are support cells. There are also basal cells, as there is a turnover and production of new olfactory neurons through life, but we lose this capacity as time goes on. This is why there is progressive loss of smell with age.

The olfactory bulbs (aka mitral cells) integrate the information. The axons of the mitral cells form the olfactory tract. The olfactory tract carries information back towards the brain. Dispersed within the olfactory tract are a series of cell bodies called the anterior olfactory nucleus. These apparently have a role in reducing the activation on one side. So there is actually a directionality to smell, though it’s not very good.

The olfactory tract splits into the lateral and medial olfactory stria. Medial olfactory stria also go to the limbic system. The highest cortical areas for olfactory processing are the piriform cortex (part of the temporal lobe), and the orbitofrontal cortex (area just above the olfactory tract). There are clear connections to the brainstem, because olfaction will promote autonomic responses such as salivation. The clinical deficit of the olfactory system is anosmia. The most common cause of anosmia is trauma to the face, as if there is fracture in the ethmoid bone/cribriform plate all the olfactory neurons shear off. Anosmia is also associated with degenerative diseases such as Alzheimer’s disease and Parkinson’s disease.

Smell can actually evoke very strong emotions and memories. The limbic system is sometimes referred to as the “Rhinencephalon” or the “nose-brain”.

The limbic system is a very diffuse system, and anatomically it is almost impossible to pin down. In 1878, Broca described the rim or limbus of the cortex adjacent to the corpus callosum and diencephalon as a functional system. The best way to define the limbic system is as a series of structurally and functionally interrelated areas considered as a single functional complex. Emotions are all about complex, interconnected systems. This is increasingly researched in functional MRI studies.

The limbic system is responsible for processes aimed at our survival. For example, maintenance of homeostasis via activation of visceral effector mechanisms (the hypothalamus is an important part of the limbic system). It modulates hormone release and initiation of feeding and drinking. It is important in our decisions of defence and attack, sexual and reproductive behaviour, and also in memory (past experience modifies the way we react to the outside world).

Going back to Broca’s original description, what he described was the rim of cortex above the corpus callosum. Lying just above it is the cingulate gyrus. The cingulate gyrus can herniate underneath the falx cerebri, because if there is a mass occupying lesion on one side of the brain, it can push the cortical tissue down, and it can
herniate underneath the pre-edge of the falx cerebri. In the diencephalon at the base of the brain you see the **mammillary body**. This is a very important part of the limbic system. The **Hippocampus** is also very important in memory function. The **fornix** is the main output from the hippocampus, and it sits just under the corpus callosum.

In the 1930’s, an anatomist described the **Papez Circuit**. This is a way of trying to visualise the anatomical basis of our emotional processing. What he described was this rim of cortex (**cingulate cortex**) which has connections to the hippocampus via a fibre pathway called the **cingulum bundle**. The large fibre pathway going forward to mammillary bodies in the hypothalamus is the fornix.

From the mammillary body, there are protrusions to the **anterior nucleus of the thalamus**. This is the **mammalo-thalamic tract**. To complete the loop, there is the anterior nucleus of the thalamus projecting back up to the cingulate cortex. All these structures are involved in processing the incoming sensory information and determining what our emotional response is going to be. **Memory** is also very important, as we modulate our responses on the basis of previous experience.

The **hippocampus** is a vital structure of the brain. Its main connections are from the cortex that lies next to it (the **entorhinal cortex** or **parahippocampal gyrus**), where the input comes from. This is a very special part of the cortex, as it receives fibres from all other neocortical areas. The information passes into the hippocampus, processing carries on, and then the output is via the fornix. The ‘fornix’ when still attached to the hippocampus is called the ‘fimbria’. The most important function of the hippocampus is in memory and learning. Laying down short-term memories is in the hippocampus. Long-term memories are more of a parietal lobe function. This is where the pathology of Alzheimer’s disease is. In epilepsy, people sometimes have an “olfactory prodromal aura”, as in they know when they are going to have a seizure because they smell a familiar smell as a warning of the onset of a seizure. This is because of the abnormal electrical activity in the temporal lobe near the hippocampus. ‘Hippocampus’ classically means “sea-horse”, because in coronal section looks a bit like a seahorse.

Another structure just anterior to the hippocampus, not directly connected, but sitting in the white matter of the anterior part of the temporal lobe is called the **amygdala**.

The very early symptoms of **Alzheimer’s disease** are short-term memory problems, associated with the hippocampus and entorhinal cortex. As the disease pathology progresses to the **parietal lobe**, people lose the ability to carry out normal functions like **dressing apraxia** - buttoning up a shirt. At later stages, the disease progresses to the **frontal lobe**, which the seat of our personality, our interactions with the outside world, decision making, recognition of close relatives, etc. In the later stages of the disease, people become completely detached from the outside world. It is a very distressing disease.

The **amygdala** is a very important limbic structure. It is a highly interconnected structure, receiving input directly from the **olfactory cortex** (piriform cortex in the anterior frontal lobe), the septal nuclei at the base of the septum, the temporal neocortex, hippocampus, and the brainstem. The main output pathway which terminates in the anterior hypothalamus is called the **stria terminalis**. The main functions of the amygdala,
based on lesion studies and animal studies, are in **fear** and **anxiety**, and also in **rage**. There is a clinical syndrome called **Kluver-Bucy syndrome**, which was described in monkeys with a bilateral temporal lobectomy. These animals completely lost their fear, had visual agnosia, hyperorality and hypersexuality.

The amygdala is also very important in **aggression**, along with a number of other brain structures like the anterior hypothalamus and the brainstem (periaqueductal grey matter). This was shown in rodents who had their cerebral cortex removed. The neurotransmitter involved in this is **serotonin** (5-HT) produced in the raphe nuclei.

The **septal nuclei** are found at the base of the interventricular **septum** between the two lateral ventricles. The septum is connected via the diagonal band to the **amygdala**, has connections directly from the medial stria of the **olfactory tract**, and has connections with **hippocampus** and **brainstem**. The main output is the **stria medularis thalami**, and there is also output to the hippocampus and hypothalamus. The main functions are in **reinforcement** and **reward**.

The **mesolimbic pathway** is a dopaminergic pathway that is involved in drug dependence. They are A10 dopaminergic cells, which project via the median forebrain bundle to a number of different areas, like the amygdala, the nucleus accumbens, and to the cortex.

The dopaminergic cells in the **ventral tegmental area** project into the nucleus accumbens. It is the stimulation of these dopaminergic neurons that seems to underlie drug dependence.

All of the drugs of dependence somehow modulate the system. Opioids, nicotine, amphetamines, ethanol and cocaine all **increase dopamine release in the nucleus accumbens**, leading to a pleasurable reward stimulus. There are many mechanisms for this.

For example, **cocaine** blocks the reuptake of dopamine from the synapse by blocking the dopamine reuptake transporter. Dopamine persists in the synapse, and can act for longer. Other drugs promote dopamine release.