Text For BIO400 Neuroanatomy at Salem State University

Assembled by Nikolaus Sucher

Contents

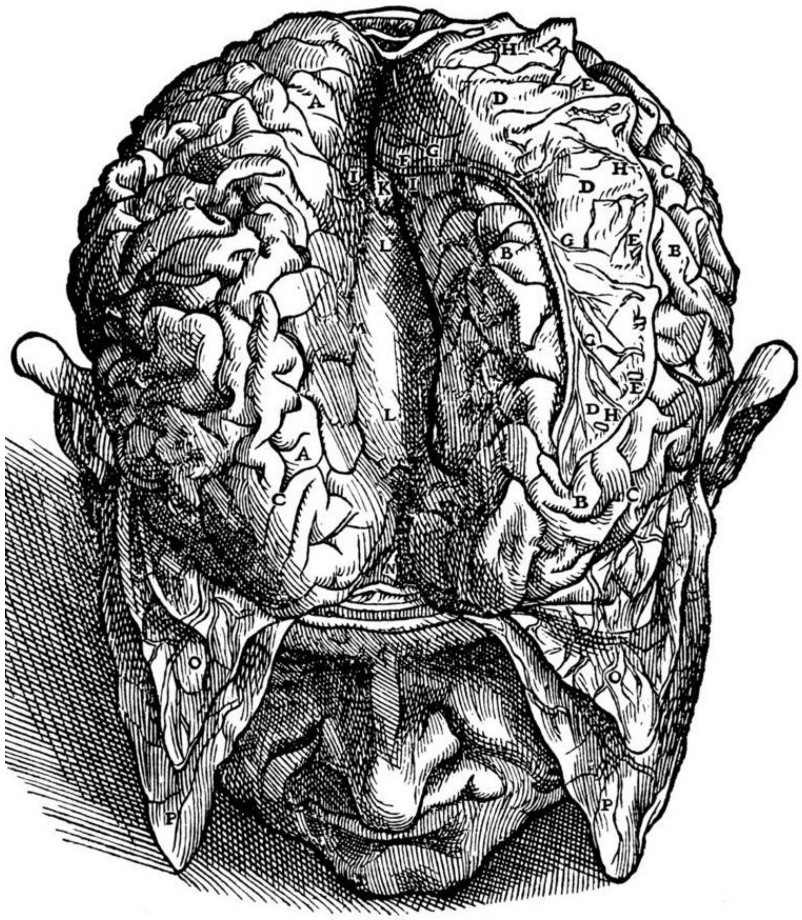
List of Tables

List of Figures

[1] https://commons.wikimedia.org/wiki/File:Cochlea-crosssection.svg

Welcome

This is a Text for the Neuroanatomy course (BIO400) at SSU



[2]https://creativecommons.org/licenses/by-sa/3.0/deed.en

Acknowledgements

The creation of this text was greatly facilitated and owes a major debt to Wikipedia[3] and its large number of voluntary contributors. I very liberally copied from many Wikipedia pages and then remixed, edited, adapted and added text. With your continued support and help this book can only get better over time. I urge you to email me with your criticisms and suggestions at nsucher@rcc.mass.edu[4]. This book is made available as an open educational resource under Creative Commons Attribution-Share Alike 3.0 Unported[5] United States License for others to do as I did and improve and adapt to specific requirements. I am grateful for the support provided by the Salem State University's OER initiative[6].

[3] https://www.wikipedia.org
[4] mailto:nsucher@rcc.mass.edu
[5] https://creativecommons.org/licenses/by-sa/3.0/deed.en
[6]

Chapter 1

The Nervous System

The nervous system is a highly complex part of an animal that coordinates its actions and sensory information by transmitting signals to and from different parts of its body. The nervous system detects environmental changes that impact the body, then works in tandem with the endocrine system to respond to such events. Nervous tissue first arose in wormlike organisms about 550 to 600 million years ago. In humans and other vertebrates it consists of two main parts, the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and spinal cord. The PNS consists mainly of nerves, which are enclosed bundles of the long fibers or axons, that connect the CNS to every other part of the body. Nerves that transmit signals from the brain are called motor or efferent nerves, while those nerves that transmit information from the body to the CNS are called sensory or afferent. Spinal nerves serve both functions and are called mixed nerves. The PNS is divided into three separate subsystems, the somatic, autonomic, and enteric nervous systems. Somatic nerves mediate voluntary movement. The autonomic nervous system is further subdivided into the sympathetic and the parasympathetic nervous systems. The sympathetic nervous system is activated in cases of emergencies to mobilize energy, while the parasympathetic nervous system is activated when organisms are in a relaxed state. The enteric nervous system functions to control the gastrointestinal system. Both autonomic and enteric nervous systems function involuntarily. Nerves that exit from the cranium are called cranial nerves while those exiting from the spinal cord are called spinal nerves.

At the cellular level, the nervous system is defined by the presence of a special type of cell, called the neuron, also known as a "nerve cell". Neurons have special structures that allow them to send signals rapidly and precisely to other cells. They send these signals in the form of electrochemical waves traveling along thin fibers called axons, which cause chemicals called neurotransmitters to be released at junctions called synapses. A cell that receives a synaptic signal from a neuron may be excited, inhibited, or otherwise modulated. The connections between neurons can form neural pathways, neural circuits, and larger networks that generate an organism's perception of the world and determine its behavior. Along with neurons, the nervous system contains other specialized cells called glial cells (or simply glia), which provide structural and metabolic support.

Nervous systems are found in most multicellular animals, but vary greatly in complexity. The only multicellular animals that have no nervous system at all are sponges, placozoans, and mesozoans, which have very simple body plans. The nervous systems of the radially symmetric organisms ctenophores (comb jellies) and cnidarians (which include anemones, hydras, corals and jellyfish) consist of a diffuse nerve net. All other animal species, with the exception of a few types of worm, have a nervous system containing a brain, a central cord (or two cords running in parallel), and nerves radiating from the brain and central cord. The size of the nervous system ranges from a few hundred cells in the simplest worms, to around 300 billion cells in African elephants.

The central nervous system functions to send signals from one cell to others, or from one part of the body to others and to receive feedback. Malfunction of the nervous system can occur as a result of genetic defects, physical damage due to trauma or toxicity, infection or simply of ageing. The medical specialty of neurology studies disorders of the nervous system and looks for interventions that can prevent or treat them. In the peripheral nervous system, the most common problem is the failure of nerve conduction, which can be due to different causes including diabetic neuropathy and demyelinating disorders such as multiple sclerosis and amyotrophic lateral sclerosis. Neuroscience is the field of science that focuses on the study of the nervous system.

The nervous system derives its name from nerves, which are cylindrical bundles of fibers (the axons of neurons), that emanate from the brain and spinal cord, and branch repeatedly to innervate every part of the body. Nerves are large enough to have been recognized by the ancient Egyptians, Greeks, and Romans, but their internal structure was not understood until it became possible to examine them using a microscope.

A microscopic examination shows that nerves consist primarily of axons, along with different membranes that wrap around them and segregate them into fascicles. The neurons that give rise to nerves do not lie entirely within the nerves themselves—their cell bodies reside within the brain, spinal cord, or peripheral ganglia.

All animals more advanced than sponges have nervous systems. However, even sponges, unicellular animals, and non-animals such as slime molds have cell-to-cell signalling mechanisms that are precursors to those of neurons. In radially symmetric animals such as the jellyfish and hydra, the nervous system consists of a nerve net, a diffuse network of isolated cells. In bilaterian animals, which make up the great majority of existing species, the nervous system has a common structure that originated early in the Ediacaran period, over 550 million years ago.

The nervous system contains two main categories or types of cells: neurons and glial cells.

The nervous system is defined by the presence of a special type of cell—the neuron (sometimes called “neurone” or “nerve cell”). Neurons can be distinguished from other cells in a number of ways, but their most fundamental property is that they communicate with other cells via synapses, which are membrane-to-membrane junctions containing molecular machinery that allows rapid transmission of signals, either electrical or chemical. Many types of neuron possess an axon, a protoplasmic protrusion that can extend to distant parts of the body and make thousands of synaptic contacts; axons typically extend throughout the body in bundles called nerves.

Even in the nervous system of a single species such as humans, hundreds of different types of neurons exist, with a wide variety of morphologies and functions. These include sensory neurons that transmute physical stimuli such as light and sound into neural signals, and motor neurons that transmute neural signals into activation of muscles or glands; however in many species the great majority of neurons participate in the formation of centralized structures (the brain and ganglia) and they receive all of their input from other neurons and send their output to other neurons.

Glial cells (named from the Greek for "glue") are non-neuronal cells that provide support and nutrition, maintain homeostasis, form myelin, and participate in signal transmission in the nervous system. In the human brain, it is estimated that the total number of glia roughly equals the number of neurons, although the proportions vary in different brain areas. Among the most important functions of glial cells are to support neurons and hold them in place; to supply nutrients to neurons; to insulate neurons electrically; to destroy pathogens and remove dead neurons; and to provide guidance cues directing the axons of neurons to their targets. A very important type of glial cell (oligodendrocytes in the central nervous system, and Schwann cells in the peripheral nervous system) generates layers of a fatty substance called myelin that wraps around axons and provides electrical insulation which allows them to transmit action potentials much more rapidly and efficiently. Recent findings indicate that glial cells, such as microglia and astrocytes, serve as important resident immune cells within the central nervous system.

The nervous system of vertebrates (including humans) is divided into the central nervous system (CNS) and the peripheral nervous system (PNS).

The (CNS) is the major division, and consists of the brain and the spinal cord. The spinal canal contains the spinal cord, while the cranial cavity contains the brain. The CNS is enclosed and protected by the meninges, a three-layered system of membranes, including a tough, leathery outer layer called the dura mater. The brain is also protected by the skull, and the spinal cord by the vertebrae.

The peripheral nervous system (PNS) is a collective term for the nervous system structures that do not lie within the CNS. The large majority of the axon bundles called nerves are considered to belong to the PNS, even when the cell bodies of the neurons to which they belong reside within the brain or spinal cord. The PNS is divided into somatic and visceral parts. The somatic part consists of the nerves that innervate the skin, joints, and muscles. The cell bodies of somatic sensory neurons lie in dorsal root ganglia of the spinal cord. The visceral part, also known as the autonomic nervous system, contains neurons that innervate the internal organs, blood vessels, and glands. The autonomic nervous system itself consists of two parts: the sympathetic nervous system and the parasympathetic nervous system. Some authors also include sensory neurons whose cell bodies lie in the periphery (for senses such as hearing) as part of the PNS; others, however, omit them.

The vertebrate nervous system can also be divided into areas called gray matter and white matter. Gray matter (which is only gray in preserved tissue, and is better described as pink or light brown in living tissue) contains a high proportion of cell bodies of neurons. White matter is composed mainly of myelinated axons, and takes its color from the myelin. White matter includes all of the nerves, and much of the interior of the brain and spinal cord. Gray matter is found in clusters of neurons in the brain and spinal cord, and in cortical layers that line their surfaces. There is an anatomical convention that a cluster of neurons in the brain or spinal cord is called a nucleus, whereas a cluster of neurons in the periphery is called a ganglion. There are, however, a few exceptions to this rule, notably including the part of the forebrain called the basal ganglia.

1.1 Comparative anatomy and evolution

1.1.1 Neural precursors in porifera

Sponges have no cells connected to each other by synaptic junctions, that is, no neurons, and therefore no nervous system. They do, however, have homologs of many genes that play key roles in synaptic function. Recent studies have shown that sponge cells express a group of proteins that cluster together to form a structure resembling a postsynaptic density (the signal-receiving part of a synapse). However, the function of this structure is currently unclear. Although sponge cells do not show synaptic transmission, they do communicate with each other via calcium waves and other impulses, which mediate some simple actions such as whole-body contraction.

1.1.2 Radiata

Jellyfish, comb jellies, and related animals have diffuse nerve nets rather than a central nervous system. In most jellyfish the nerve net is spread more or less evenly across the body; in comb jellies it is concentrated near the mouth. The nerve nets consist of sensory neurons, which pick up chemical, tactile, and visual signals; motor neurons, which can activate contractions of the body wall; and intermediate neurons, which detect patterns of activity in the sensory neurons and, in response, send signals to groups of motor neurons. In some cases groups of intermediate neurons are clustered into discrete ganglia.

The development of the nervous system in radiata is relatively unstructured. Unlike bilaterians, radiata only have two primordial cell layers, endoderm and ectoderm. Neurons are generated from a special set of ectodermal precursor cells, which also serve as precursors for every other ectodermal cell type.

The vast majority of existing animals are bilaterians, meaning animals with left and right sides that are approximate mirror images of each other. All bilateria are thought to have descended from a common wormlike ancestor that appeared in the Ediacaran period, 550–600 million years ago. The fundamental bilaterian body form is a tube with a hollow gut cavity running from mouth to anus, and a nerve cord with an enlargement (a “ganglion”) for each body segment, with an especially large ganglion at the front, called the “brain”.

Even mammals, including humans, show the segmented bilaterian body plan at the level of the nervous system. The spinal cord contains a series of segmental ganglia, each giving rise to motor and sensory nerves that innervate a portion of the body surface and underlying musculature. On the limbs, the layout of the innervation pattern is complex, but on the trunk it gives rise to a series of narrow bands. The top three segments belong to the brain, giving rise to the forebrain, midbrain, and hindbrain.

Bilaterians can be divided, based on events that occur very early in embryonic development, into two groups (superphyla) called protostomes and deuterostomes. Deuterostomes include vertebrates as well as echinoderms, hemichordates (mainly acorn worms), and Xenoturbellidans. Protostomes, the more diverse group, include arthropods, molluscs, and numerous types of worms. There is a basic difference between the two groups in the placement of the nervous system within the body: protostomes possess a nerve cord on the ventral (usually bottom) side of the body, whereas in deuterostomes the nerve cord is on the dorsal (usually top) side. In fact, numerous aspects of the body are inverted between the two groups, including the expression patterns of several genes that show dorsal-to-ventral gradients. Most anatomists now consider that the bodies of protostomes and deuterostomes are "flipped over" with respect to each other, a hypothesis that was first proposed by Geoffroy Saint-Hilaire for insects in comparison to vertebrates. Thus insects, for example, have nerve cords that run along the ventral midline of the body, while all vertebrates have spinal cords that run along the dorsal midline.

1.1.3 Bilateria

Worms are the simplest bilaterian animals, and reveal the basic structure of the bilaterian nervous system in the most straightforward way. As an example, earthworms have dual nerve cords running along the length of the body and merging at the tail and the mouth. These nerve cords are connected by transverse nerves like the rungs of a ladder. These transverse nerves help coordinate the two sides of the animal. Two ganglia at the head (the "nerve ring") end function similar to a simple brain. Photoreceptors on the animal's eyespots provide sensory information on light and dark.

The nervous system of one very small roundworm, the nematode Caenorhabditis elegans, has been completely mapped out in a connectome including its synapses. Every neuron and its cellular lineage has been recorded and most, if not all, of the neural connections are known. In this species, the nervous system is sexually dimorphic; the nervous systems of the two sexes, males and female hermaphrodites, have different numbers of neurons and groups of neurons that perform sex-specific functions. In C. elegans, males have exactly 383 neurons, while hermaphrodites have exactly 302 neurons.

Arthropods, such as insects and crustaceans, have a nervous system made up of a series of ganglia, connected by a ventral nerve cord made up of two parallel connectives running along the length of the belly. Typically, each body segment has one ganglion on each side, though some ganglia are fused to form the brain and other large ganglia. The head segment contains the brain, also known as the supraesophageal ganglion. In the insect nervous system, the brain is anatomically divided into the protocerebrum, deutocerebrum, and tritocerebrum. Immediately behind the brain is the subesophageal ganglion, which is composed of three pairs of fused ganglia. It controls the mouthparts, the salivary glands and certain muscles. Many arthropods have well-developed sensory organs, including compound eyes for vision and antennae for olfaction and pheromone sensation. The sensory information from these organs is processed by the brain.

In insects, many neurons have cell bodies that are positioned at the edge of the brain and are electrically passive—the cell bodies serve only to provide metabolic support and do not participate in signalling. A protoplasmic fiber runs from the cell body and branches profusely, with some parts transmitting signals and other parts receiving signals. Thus, most parts of the insect brain have passive cell bodies arranged around the periphery, while the neural signal processing takes place in a tangle of protoplasmic fibers called neuropil, in the interior.

At the most basic level, the function of the nervous system is to send signals from one cell to others, or from one part of the body to others. There are multiple ways that a cell can send signals to other cells. One is by releasing chemicals called hormones into the internal circulation, so that they can diffuse to distant sites. In contrast to this "broadcast" mode of signaling, the nervous system provides "point-to-point" signals—neurons project their axons to specific target areas and make synaptic connections with specific target cells. Thus, neural signaling is capable of a much higher level of specificity than hormonal signaling. It is also much faster: the fastest nerve signals travel at speeds that exceed 100 meters per second.

At a more integrative level, the primary function of the nervous system is to control the body. It does this by extracting information from the environment using sensory receptors, sending signals that encode this information into the central nervous system, processing the information to determine an appropriate response, and sending output signals to muscles or glands to activate the response. The evolution of a complex nervous system has made it possible for various animal species to have advanced perception abilities such as vision, complex social interactions, rapid coordination of organ systems, and integrated processing of concurrent signals. In humans, the sophistication of the nervous system makes it possible to have language, abstract representation of concepts, transmission of culture, and many other features of human society that would not exist without the human brain.

Most neurons send signals via their axons, although some types are capable of dendrite-to-dendrite communication. (In fact, the types of neurons called amacrine cells have no axons, and communicate only via their dendrites.) Neural signals propagate along an axon in the form of electrochemical waves called action potentials, which produce cell-to-cell signals at points where axon terminals make synaptic contact with other cells.

Synapses may be electrical or chemical. Electrical synapses make direct electrical connections between neurons, but chemical synapses are much more common, and much more diverse in function. At a chemical synapse, the cell that sends signals is called presynaptic, and the cell that receives signals is called postsynaptic. Both the presynaptic and postsynaptic areas are full of molecular machinery that carries out the signalling process. The presynaptic area contains large numbers of tiny spherical vessels called synaptic vesicles, packed with neurotransmitter chemicals. When the presynaptic terminal is electrically stimulated, an array of molecules embedded in the membrane are activated, and cause the contents of the vesicles to be released into the narrow space between the presynaptic and postsynaptic membranes, called the synaptic cleft. The neurotransmitter then binds to receptors embedded in the postsynaptic membrane, causing them to enter an activated state. Depending on the type of receptor, the resulting effect on the postsynaptic cell may be excitatory, inhibitory, or modulatory in more complex ways. For example, release of the neurotransmitter acetylcholine at a synaptic contact between a motor neuron and a muscle cell induces rapid contraction of the muscle cell. The entire synaptic transmission process takes only a fraction of a millisecond, although the effects on the postsynaptic cell may last much longer (even indefinitely, in cases where the synaptic signal leads to the formation of a memory trace).

Structure of a typical chemical synapse

There are literally hundreds of different types of synapses. In fact, there are over a hundred known neurotransmitters, and many of them have multiple types of receptors. Many synapses use more than one neurotransmitter—a common arrangement is for a synapse to use one fast-acting small-molecule neurotransmitter such as glutamate or GABA, along with one or more peptide neurotransmitters that play slower-acting modulatory roles. Molecular neuroscientists generally divide receptors into two broad groups: chemically gated ion channels and second messenger systems. When a chemically gated ion channel is activated, it forms a passage that allows specific types of ions to flow across the membrane. Depending on the type of ion, the effect on the target cell may be excitatory or inhibitory. When a second messenger system is activated, it starts a cascade of molecular interactions inside the target cell, which may ultimately produce a wide variety of complex effects, such as increasing or decreasing the sensitivity of the cell to stimuli, or even altering gene transcription.

According to a rule called Dale's principle, which has only a few known exceptions, a neuron releases the same neurotransmitters at all of its synapses. This does not mean, though, that a neuron exerts the same effect on all of its targets, because the effect of a synapse depends not on the neurotransmitter, but on the receptors that it activates. Because different targets can (and frequently do) use different types of receptors, it is possible for a neuron to have excitatory effects on one set of target cells, inhibitory effects on others, and complex modulatory effects on others still. Nevertheless, it happens that the two most widely used neurotransmitters, glutamate and GABA, each have largely consistent effects. Glutamate has several widely occurring types of receptors, but all of them are excitatory or modulatory. Similarly, GABA has several widely occurring receptor types, but all of them are inhibitory. Because of this consistency, glutamatergic cells are frequently referred to as "excitatory neurons", and GABAergic cells as "inhibitory neurons". Strictly speaking, this is an abuse of terminology—it is the receptors that are excitatory and inhibitory, not the neurons—but it is commonly seen even in scholarly publications.

One very important subset of synapses are capable of forming memory traces by means of long-lasting activity-dependent changes in synaptic strength. The best-known form of neural memory is a process called long-term potentiation (abbreviated LTP), which operates at synapses that use the neurotransmitter glutamate acting on a special type of receptor known as the NMDA receptor. The NMDA receptor has an "associative" property: if the two cells involved in the synapse are both activated at approximately the same time, a channel opens that permits calcium to flow into the target cell. The calcium entry initiates a second messenger cascade that ultimately leads to an increase in the number of glutamate receptors in the target cell, thereby increasing the effective strength of the synapse. This change in strength can last for weeks or longer. Since the discovery of LTP in 1973, many other types of synaptic memory traces have been found, involving increases or decreases in synaptic strength that are induced by varying conditions, and last for variable periods of time. The reward system, that reinforces desired behaviour for example, depends on a variant form of LTP that is conditioned on an extra input coming from a reward-signalling pathway that uses dopamine as neurotransmitter. All these forms of synaptic modifiability, taken collectively, give rise to neural plasticity, that is, to a capability for the nervous system to adapt itself to variations in the environment.

Neural circuits and systems

The basic neuronal function of sending signals to other cells includes a capability for neurons to exchange signals with each other. Networks formed by interconnected groups of neurons are capable of a wide variety of functions, including feature detection, pattern generation and timing, and there are seen to be countless types of information processing possible. Warren McCulloch and Walter Pitts showed in 1943 that even artificial neural networks formed from a greatly simplified mathematical abstraction of a neuron are capable of universal computation.

Historically, for many years the predominant view of the function of the nervous system was as a stimulus-response associator. In this conception, neural processing begins with stimuli that activate sensory neurons, producing signals that propagate through chains of connections in the spinal cord and brain, giving rise eventually to activation of motor neurons and thereby to muscle contraction, i.e., to overt responses. Descartes believed that all of the behaviors of animals, and most of the behaviors of humans, could be explained in terms of stimulus-response circuits, although he also believed that higher cognitive functions such as language were not capable of being explained mechanistically. Charles Sherrington, in his influential 1906 book The Integrative Action of the Nervous System, developed the concept of stimulus-response mechanisms in much more detail, and Behaviorism, the school of thought that dominated Psychology through the middle of the 20th century, attempted to explain every aspect of human behavior in stimulus-response terms.

However, experimental studies of electrophysiology, beginning in the early 20th century and reaching high productivity by the 1940s, showed that the nervous system contains many mechanisms for generating patterns of activity intrinsically, without requiring an external stimulus. Neurons were found to be capable of producing regular sequences of action potentials, or sequences of bursts, even in complete isolation. When intrinsically active neurons are connected to each other in complex circuits, the possibilities for generating intricate temporal patterns become far more extensive. A modern conception views the function of the nervous system partly in terms of stimulus-response chains, and partly in terms of intrinsically generated activity patterns—both types of activity interact with each other to generate the full repertoire of behavior.

Reflexes and other stimulus-response circuits

The simplest type of neural circuit is a reflex arc, which begins with a sensory input and ends with a motor output, passing through a sequence of neurons connected in series. This can be shown in the “withdrawal reflex” causing a hand to jerk back after a hot stove is touched. The circuit begins with sensory receptors in the skin that are activated by harmful levels of heat: a special type of molecular structure embedded in the membrane causes heat to change the electrical field across the membrane. If the change in electrical potential is large enough to pass the given threshold, it evokes an action potential, which is transmitted along the axon of the receptor cell, into the spinal cord. There the axon makes excitatory synaptic contacts with other cells, some of which project (send axonal output) to the same region of the spinal cord, others projecting into the brain. One target is a set of spinal interneurons that project to motor neurons controlling the arm muscles. The interneurons excite the motor neurons, and if the excitation is strong enough, some of the motor neurons generate action potentials, which travel down their axons to the point where they make excitatory synaptic contacts with muscle cells. The excitatory signals induce contraction of the muscle cells, which causes the joint angles in the arm to change, pulling the arm away.

In reality, this straightforward schema is subject to numerous complications. Although for the simplest reflexes there are short neural paths from sensory neuron to motor neuron, there are also other nearby neurons that participate in the circuit and modulate the response. Furthermore, there are projections from the brain to the spinal cord that are capable of enhancing or inhibiting the reflex.

Although the simplest reflexes may be mediated by circuits lying entirely within the spinal cord, more complex responses rely on signal processing in the brain. For example, when an object in the periphery of the visual field moves, and a person looks toward it many stages of signal processing are initiated. The initial sensory response, in the retina of the eye, and the final motor response, in the oculomotor nuclei of the brain stem, are not all that different from those in a simple reflex, but the intermediate stages are completely different. Instead of a one or two step chain of processing, the visual signals pass through perhaps a dozen stages of integration, involving the thalamus, cerebral cortex, basal ganglia, superior colliculus, cerebellum, and several brainstem nuclei. These areas perform signal-processing functions that include feature detection, perceptual analysis, memory recall, decision-making, and motor planning.

Feature detection is the ability to extract biologically relevant information from combinations of sensory signals. In the visual system, for example, sensory receptors in the retina of the eye are only individually capable of detecting "points of light" in the outside world. Second-level visual neurons receive input from groups of primary receptors, higher-level neurons receive input from groups of second-level neurons, and so on, forming a hierarchy of processing stages. At each stage, important information is extracted from the signal ensemble and unimportant information is discarded. By the end of the process, input signals representing "points of light" have been transformed into a neural representation of objects in the surrounding world and their properties. The most sophisticated sensory processing occurs inside the brain, but complex feature extraction also takes place in the spinal cord and in peripheral sensory organs such as the retina.

Intrinsic pattern generation Although stimulus-response mechanisms are the easiest to understand, the nervous system is also capable of controlling the body in ways that do not require an external stimulus, by means of internally generated rhythms of activity. Because of the variety of voltage-sensitive ion channels that can be embedded in the membrane of a neuron, many types of neurons are capable, even in isolation, of generating rhythmic sequences of action potentials, or rhythmic alternations between high-rate bursting and quiescence. When neurons that are intrinsically rhythmic are connected to each other by excitatory or inhibitory synapses, the resulting networks are capable of a wide variety of dynamical behaviors, including attractor dynamics, periodicity, and even chaos. A network of neurons that uses its internal structure to generate temporally structured output, without requiring a corresponding temporally structured stimulus, is called a central pattern generator.

Internal pattern generation operates on a wide range of time scales, from milliseconds to hours or longer. One of the most important types of temporal pattern is circadian rhythmicity—that is, rhythmicity with a period of approximately 24 hours. All animals that have been studied show circadian fluctuations in neural activity, which control circadian alternations in behavior such as the sleep-wake cycle. Experimental studies dating from the 1990s have shown that circadian rhythms are generated by a "genetic clock" consisting of a special set of genes whose expression level rises and falls over the course of the day. Animals as diverse as insects and vertebrates share a similar genetic clock system. The circadian clock is influenced by light but continues to operate even when light levels are held constant and no other external time-of-day cues are available. The clock genes are expressed in many parts of the nervous system as well as many peripheral organs, but in mammals, all of these "tissue clocks" are kept in synchrony by signals that emanate from a master timekeeper in a tiny part of the brain called the suprachiasmatic nucleus.

1.2 Development

In vertebrates, landmarks of embryonic neural development include the birth and differentiation of neurons from stem cell precursors, the migration of immature neurons from their birthplaces in the embryo to their final positions, outgrowth of axons from neurons and guidance of the motile growth cone through the embryo towards postsynaptic partners, the generation of synapses between these axons and their postsynaptic partners, and finally the lifelong changes in synapses which are thought to underlie learning and memory.

All bilaterian animals at an early stage of development form a gastrula, which is polarized, with one end called the animal pole and the other the vegetal pole. The gastrula has the shape of a disk with three layers of cells, an inner layer called the endoderm, which gives rise to the lining of most internal organs, a middle layer called the mesoderm, which gives rise to the bones and muscles, and an outer layer called the ectoderm, which gives rise to the skin and nervous system.

In vertebrates, the first sign of the nervous system is the appearance of a thin strip of cells along the center of the back, called the neural plate. The inner portion of the neural plate (along the midline) is destined to become the central nervous system (CNS), the outer portion the peripheral nervous system (PNS). As development proceeds, a fold called the neural groove appears along the midline. This fold deepens, and then closes up at the top. At this point the future CNS appears as a cylindrical structure called the neural tube, whereas the future PNS appears as two strips of tissue called the neural crest, running lengthwise above the neural tube. The sequence of stages from neural plate to neural tube and neural crest is known as neurulation.

In the early 20th century, a set of famous experiments by Hans Spemann and Hilde Mangold showed that the formation of nervous tissue is "induced" by signals from a group of mesodermal cells called the organizer region. For decades, though, the nature of neural induction defeated every attempt to figure it out, until finally it was resolved by genetic approaches in the 1990s. Induction of neural tissue requires inhibition of the gene for a so-called bone morphogenetic protein, or BMP. Specifically the protein BMP4 appears to be involved. Two proteins called Noggin and Chordin, both secreted by the mesoderm, are capable of inhibiting BMP4 and thereby inducing ectoderm to turn into neural tissue. It appears that a similar molecular mechanism is involved for widely disparate types of animals, including arthropods as well as vertebrates. In some animals, however, another type of molecule called Fibroblast Growth Factor or FGF may also play an important role in induction.

Induction of neural tissues causes formation of neural precursor cells, called neuroblasts. In drosophila, neuroblasts divide asymmetrically, so that one product is a "ganglion mother cell" (GMC), and the other is a neuroblast. A GMC divides once, to give rise to either a pair of neurons or a pair of glial cells. In all, a neuroblast is capable of generating an indefinite number of neurons or glia.

One factor common to all bilateral organisms (including humans) is a family of secreted signaling molecules called neurotrophins which regulate the growth and survival of neurons. Zhu et al. identified DNT1, the first neurotrophin found in flies. DNT1 shares structural similarity with all known neurotrophins and is a key factor in the fate of neurons in Drosophila. Because neurotrophins have now been identified in both vertebrate and invertebrates, this evidence suggests that neurotrophins were present in an ancestor common to bilateral organisms and may represent a common mechanism for nervous system formation.

Chapter 2

Development of Human Nervous System

The development of the nervous system, or neural development, or neurodevelopment, refers to the processes that generate, shape, and reshape the nervous system of animals, from the earliest stages of embryonic development to adulthood. The field of neural development draws on both neuroscience and developmental biology to describe and provide insight into the cellular and molecular mechanisms by which complex nervous systems develop, from nematodes and fruit flies to mammals. Defects in neural development can lead to malformations and a wide variety of sensory, motor, and cognitive impairments, including holoprosencephaly and other neurological disorders in the human such as Rett syndrome, Down syndrome and intellectual disability.

The central nervous system (CNS) is derived from the ectoderm—the outermost tissue layer of the embryo. In the third week of human embryonic development the neuroectoderm appears and forms the neural plate along the dorsal side of the embryo. The neural plate is the source of the majority of neurons and glial cells of the CNS. A groove forms along the long axis of the neural plate and, by week four of development, the neural plate wraps in on itself to give rise to the neural tube, which is filled with cerebrospinal fluid (CSF). As the embryo develops, the anterior part of the neural tube forms three primary brain vesicles, which become the primary anatomical regions of the brain: the forebrain (prosencephalon), midbrain (mesencephalon), and hindbrain (rhombencephalon). These simple, early vesicles enlarge and further divide into the five secondary brain vesicles – the telencephalon (future cerebral cortex and basal ganglia), diencephalon (future thalamus and hypothalamus), mesencephalon (future colliculi), metencephalon (future pons and cerebellum), and myelencephalon (future medulla). The CSF-filled central chamber is continuous from the telencephalon to the spinal cord, and constitutes the developing ventricular system of the CNS. Because the neural tube gives rise to the brain and spinal cord any mutations at this stage in development can lead to fatal deformities like anencephaly or lifelong disabilities like spina bifida. During this time, the walls of the neural tube contain neural stem cells, which drive brain growth as they divide many times. Gradually some of the cells stop dividing and differentiate into neurons and glial cells, which are the main cellular components of the CNS. The newly generated neurons migrate to different parts of the developing brain to self-organize into different brain structures.

Once the neurons have reached their regional positions, they extend axons and dendrites, which allow them to communicate with other neurons via synapses. Synaptic communication between neurons leads to the establishment of functional neural circuits that mediate sensory and motor processing, and underlie behavior.

During early embryonic development the ectoderm becomes specified to give rise to the epidermis (skin) and the neural plate. The conversion of undifferentiated ectoderm to neuro-ectoderm requires signals from the mesoderm. At the onset of gastrulation presumptive mesodermal cells move through the dorsal blastopore lip and form a layer in between the endoderm and the ectoderm. These mesodermal cells that migrate along the dorsal midline give rise to a structure called the notochord. Ectodermal cells overlying the notochord develop into the neural plate in response to a diffusible signal produced by the notochord. The remainder of the ectoderm gives rise to the epidermis (skin). The ability of the mesoderm to convert the overlying ectoderm into neural tissue is called neural induction.

The neural plate folds outwards during the third week of gestation to form the neural groove. Beginning in the future neck region, the neural folds of this groove close to create the neural tube. The formation of the neural tube from the ectoderm is called neurulation. The ventral part of the neural tube is called the basal plate; the dorsal part is called the alar plate. The hollow interior is called the neural canal. By the end of the fourth week of gestation, the open ends of the neural tube, called the neuropores, close off.

A transplanted blastopore lip can convert ectoderm into neural tissue and is said to have an inductive effect. Neural inducers are molecules that can induce the expression of neural genes in ectoderm explants without inducing mesodermal genes as well. Neural induction is often studied in xenopus embryos since they have a simple body pattern and there are good markers to distinguish between neural and non-neural tissue. Examples of neural inducers are the molecules noggin and chordin.

When embryonic ectodermal cells are cultured at low density in the absence of mesodermal cells they undergo neural differentiation (express neural genes), suggesting that neural differentiation is the default fate of ectodermal cells. In explant cultures (which allow direct cell-cell interactions) the same cells differentiate into epidermis. This is due to the action of BMP4 (a TGF- family protein) that induces ectodermal cultures to differentiate into epidermis. During neural induction, noggin and chordin are produced by the dorsal mesoderm (notochord) and diffuse into the overlying ectoderm to inhibit the activity of BMP4. This inhibition of BMP4 causes the cells to differentiate into neural cells. Inhibition of TGF- and BMP (bone morphogenetic protein) signaling can efficiently induce neural tissue from human pluripotent stem cells, a model of early human development.

The early brain

Late in the fourth week, the superior part of the neural tube flexes at the level of the future midbrain—the mesencephalon. Above the mesencephalon is the prosencephalon (future forebrain) and beneath it is the rhombencephalon (future hindbrain). The optical vesicle (which will eventually become the optic nerve, retina and iris) forms at the basal plate of the prosencephalon.

The spinal cord forms from the lower part of the neural tube. The wall of the neural tube consists of neuroepithelial cells, which differentiate into neuroblasts, forming the mantle layer (the gray matter). Nerve fibers emerge from these neuroblasts to form the marginal layer (the white matter). The ventral part of the mantle layer (the basal plates) forms the motor areas of the spinal cord, whilst the dorsal part (the alar plates) forms the sensory areas. Between the basal and alar plates is an intermediate layer that contains neurons of the autonomic nervous system.

In the fifth week, the alar plate of the prosencephalon expands to form the cerebral hemispheres (the telencephalon). The basal plate becomes the diencephalon.

The diencephalon, mesencephalon and rhombencephalon constitute the brain stem of the embryo. It continues to flex at the mesencephalon. The rhombencephalon folds posteriorly, which causes its alar plate to flare and form the fourth ventricle of the brain. The pons and the cerebellum form in the upper part of the rhombencephalon, whilst the medulla oblongata forms in the lower part.

Some landmarks of neural development include the birth and differentiation of neurons from stem cell precursors, the migration of immature neurons from their birthplaces in the embryo to their final positions, outgrowth of axons and dendrites from neurons, guidance of the motile growth cone through the embryo towards postsynaptic partners, the generation of synapses between these axons and their postsynaptic partners, and finally the lifelong changes in synapses, which are thought to underlie learning and memory.

Typically, these neurodevelopmental processes can be broadly divided into two classes: activity-independent mechanisms and activity-dependent mechanisms. Activity-independent mechanisms are generally believed to occur as hardwired processes determined by genetic programs played out within individual neurons. These include differentiation, migration and axon guidance to their initial target areas. These processes are thought of as being independent of neural activity and sensory experience. Once axons reach their target areas, activity-dependent mechanisms come into play. Although synapse formation is an activity-independent event, modification of synapses and synapse elimination requires neural activity.

Developmental neuroscience uses a variety of animal models including the mouse Mus musculus, the fruit fly Drosophila melanogaster, the zebrafish Danio rerio, the frog Xenopus laevis, and the roundworm Caenorhabditis elegans.

Myelination, formation of the lipid myelin bilayer around neuronal axons, is a process that is essential for normal brain function. The myelin sheath provides insulation for the nerve impulse when communicating between neural systems. Without it, the impulse would be disrupted and the signal would not reach its target, thus impairing normal functioning. Because so much of brain development occurs in the prenatal stage and infancy, it is crucial that myelination, along with cortical development occur properly. Magnetic resonance imaging (MRI) is a non-invasive technique used to investigate myelination and cortical maturation (the cortex is the outer layer of the brain composed of gray matter). Rather than showing the actual myelin, the MRI picks up on the myelin water fraction (MWF), a measure of myelin content. Multicomponent relaxometry (MCR) allow visualization and quantification of myelin content. MCR is also useful for tracking white matter maturation, which plays an important role in cognitive development. It has been discovered that in infancy, myelination occurs in a posterior-to-anterior pattern. Because there is little evidence of a relationship between myelination and cortical thickness, it was revealed that cortical thickness is independent of white matter MWF. This allows various aspects of the brain to grow simultaneously, leading to a more fully developed brain.

2.1 Neural induction

During early embryonic development the ectoderm becomes specified to give rise to the epidermis (skin) and the neural plate. The conversion of undifferentiated ectoderm to neuro-ectoderm requires signals from the mesoderm. At the onset of gastrulation presumptive mesodermal cells move through the dorsal blastopore lip and form a layer in between the endoderm and the ectoderm. These mesodermal cells that migrate along the dorsal midline give rise to a structure called the notochord. Ectodermal cells overlying the notochord develop into the neural plate in response to a diffusible signal produced by the notochord. The remainder of the ectoderm gives rise to the epidermis (skin). The ability of the mesoderm to convert the overlying ectoderm into neural tissue is called neural induction.

In the early embryo, the neural plate folds outwards to form the neural groove. Beginning in the future neck region, the neural folds of this groove close to create the neural tube. The formation of the neural tube from the ectoderm is called neurulation. The ventral part of the neural tube is called the basal plate; the dorsal part is called the alar plate. The hollow interior is called the neural canal, and the open ends of the neural tube, called the neuropores, close off.

A transplanted blastopore lip can convert ectoderm into neural tissue and is said to have an inductive effect. Neural inducers are molecules that can induce the expression of neural genes in ectoderm explants without inducing mesodermal genes as well. Neural induction is often studied in xenopus embryos since they have a simple body pattern and there are good markers to distinguish between neural and non-neural tissue. Examples of neural inducers are the molecules noggin and chordin.

When embryonic ectodermal cells are cultured at low density in the absence of mesodermal cells they undergo neural differentiation (express neural genes), suggesting that neural differentiation is the default fate of ectodermal cells. In explant cultures (which allow direct cell-cell interactions) the same cells differentiate into epidermis. This is due to the action of BMP4 (a TGF- family protein) that induces ectodermal cultures to differentiate into epidermis. During neural induction, noggin and chordin are produced by the dorsal mesoderm (notochord) and diffuse into the overlying ectoderm to inhibit the activity of BMP4. This inhibition of BMP4 causes the cells to differentiate into neural cells. Inhibition of TGF- and BMP (bone morphogenetic protein) signaling can efficiently induce neural tissue from pluripotent stem cells.

2.2 Regionalization

In a later stage of development the superior part of the neural tube flexes at the level of the future midbrain—the mesencephalon, at the mesencephalic flexure or cephalic flexure. Above the mesencephalon is the prosencephalon (future forebrain) and beneath it is the rhombencephalon (future hindbrain).

The alar plate of the prosencephalon expands to form the telencephalon which gives rise to the cerebral hemispheres, whilst its basal plate becomes the diencephalon. The optical vesicle (which eventually become the optic nerve, retina and iris) forms at the basal plate of the prosencephalon.

2.3 Patterning of the nervous system

In chordates, dorsal ectoderm forms all neural tissue and the nervous system. Patterning occurs due to specific environmental conditions - different concentrations of signaling molecules

The ventral half of the neural plate is controlled by the notochord, which acts as the 'organiser'. The dorsal half is controlled by the ectoderm plate, which flanks either side of the neural plate.

Ectoderm follows a default pathway to become neural tissue. Evidence for this comes from single, cultured cells of ectoderm, which go on to form neural tissue. This is postulated to be because of a lack of BMPs, which are blocked by the organiser. The organiser may produce molecules such as follistatin, noggin and chordin that inhibit BMPs.

The ventral neural tube is patterned by sonic hedgehog (Shh) from the notochord, which acts as the inducing tissue. Notochord-derived Shh signals to the floor plate, and induces Shh expression in the floor plate. Floor plate-derived Shh subsequently signals to other cells in the neural tube, and is essential for proper specification of ventral neuron progenitor domains. Loss of Shh from the notochord and/or floor plate prevents proper specification of these progenitor domains. Shh binds Patched1, relieving Patched-mediated inhibition of Smoothened, leading to activation of the Gli family of transcription factors (GLI1, GLI2, and GLI3).

In this context Shh acts as a morphogen - it induces cell differentiation dependent on its concentration. At low concentrations it forms ventral interneurons, at higher concentrations it induces motor neuron development, and at highest concentrations it induces floor plate differentiation. Failure of Shh-modulated differentiation causes holoprosencephaly.

The dorsal neural tube is patterned by BMPs from the epidermal ectoderm flanking the neural plate. These induce sensory interneurons by activating Sr/Thr kinases and altering SMAD transcription factor levels.

Signals that control anteroposterior neural development include FGF and retinoic acid, which act in the hindbrain and spinal cord. The hindbrain, for example, is patterned by Hox genes, which are expressed in overlapping domains along the anteroposterior axis under the control of retinoic acid. The 3 (3 prime end) genes in the Hox cluster are induced by retinoic acid in the hindbrain, whereas the 5 (5 prime end) Hox genes are not induced by retinoic acid and are expressed more posteriorly in the spinal cord. Hoxb-1 is expressed in rhombomere 4 and gives rise to the facial nerve. Without this Hoxb-1 expression, a nerve similar to the trigeminal nerve arises.

2.4 Neurogenesis

Neurogenesis is the process by which neurons are generated from neural stem cells and progenitor cells. Neurons are 'post-mitotic', meaning that they will never divide again for the lifetime of the organism.

Epigenetic modifications play a key role in regulating gene expression in differentiating neural stem cells and are critical for cell fate determination in the developing and adult mammalian brain. Epigenetic modifications include DNA cytosine methylation to form 5-methylcytosine and 5-methylcytosine demethylation. DNA cytosine methylation is catalyzed by DNA methyltransferases (DNMTs). Methylcytosine demethylation is catalyzed in several sequential steps by TET enzymes that carry out oxidative reactions (e.g. 5-methylcytosine to 5-hydroxymethylcytosine) and enzymes of the DNA base excision repair (BER) pathway.

2.5 Neuronal migration

Neuronal migration is the method by which neurons travel from their origin or birthplace to their final position in the brain. There are several ways they can do this, e.g. by radial migration or tangential migration. This time lapse displays sequences of radial migration (also known as glial guidance) and somal translocation.

Neuronal precursor cells proliferate in the ventricular zone of the developing neocortex, where the principal neural stem cell is the radial glial cell. The first postmitotic cells must leave the stem cell niche and migrate outward to form the preplate, which is destined to become Cajal-Retzius cells and subplate neurons. These cells do so by somal translocation. Neurons migrating with this mode of locomotion are bipolar and attach the leading edge of the process to the pia. The soma is then transported to the pial surface by nucleokinesis, a process by which a microtubule "cage" around the nucleus elongates and contracts in association with the centrosome to guide the nucleus to its final destination. Radial glial cells, whose fibers serve as a scaffolding for migrating cells and a means of radial communication mediated by calcium dynamic activity, act as the main excitatory neuronal stem cell of the cerebral cortex or translocate to the cortical plate and differentiate either into astrocytes or neurons. Somal translocation can occur at any time during development.

Subsequent waves of neurons split the preplate by migrating along radial glial fibres to form the cortical plate. Each wave of migrating cells travel past their predecessors forming layers in an inside-out manner, meaning that the youngest neurons are the closest to the surface. It is estimated that glial guided migration represents 90% of migrating neurons in human and about 75% in rodents.

Most interneurons migrate tangentially through multiple modes of migration to reach their appropriate location in the cortex. An example of tangential migration is the movement of interneurons from the ganglionic eminence to the cerebral cortex. One example of ongoing tangential migration in a mature organism, observed in some animals, is the rostral migratory stream connecting subventricular zone and olfactory bulb.

Many neurons migrating along the anterior-posterior axis of the body use existing axon tracts to migrate along; this is called axophilic migration. An example of this mode of migration is in GnRH-expressing neurons, which make a long journey from their birthplace in the nose, through the forebrain, and into the hypothalamus. Many of the mechanisms of this migration have been worked out, starting with the extracellular guidance cues that trigger intracellular signaling. These intracellular signals, such as calcium signaling, lead to actin and microtubule cytoskeletal dynamics, which produce cellular forces that interact with the extracellular environment through cell adhesion proteins to cause the movement of these cells.

There is also a method of neuronal migration called multipolar migration. This is seen in multipolar cells, which in the human, are abundantly present in the cortical intermediate zone. They do not resemble the cells migrating by locomotion or somal translocation. Instead these multipolar cells express neuronal markers and extend multiple thin processes in various directions independently of the radial glial fibers.

2.6 Neurotrophic factors

The survival of neurons is regulated by survival factors, called trophic factors. The neurotrophic hypothesis was formulated by Victor Hamburger and Rita Levi Montalcini based on studies of the developing nervous system. Victor Hamburger discovered that implanting an extra limb in the developing chick led to an increase in the number of spinal motor neurons. Initially he thought that the extra limb was inducing proliferation of motor neurons, but he and his colleagues later showed that there was a great deal of motor neuron death during normal development, and the extra limb prevented this cell death. According to the neurotrophic hypothesis, growing axons compete for limiting amounts of target-derived trophic factors and axons that fail to receive sufficient trophic support die by apoptosis. It is now clear that factors produced by a number of sources contribute to neuronal survival.

- ddNerve Growth Factor (NGF): Rita Levi Montalcini and Stanley Cohen purified the first trophic factor, Nerve Growth Factor (NGF), for which they received the Nobel Prize. There are three NGF-related trophic factors: BDNF, NT3, and NT4, which regulate survival of various neuronal populations. The Trk proteins act as receptors for NGF and related factors. Trk is a receptor tyrosine kinase. Trk dimerization and phosphorylation leads to activation of various intracellular signaling pathways including the MAP kinase, Akt, and PKC pathways.
- CNTF: Ciliary neurotrophic factor is another protein that acts as a survival factor for motor neurons. CNTF acts via a receptor complex that includes CNTFR , GP130, and LIFR . Activation of the receptor leads to phosphorylation and recruitment of the JAK kinase, which in turn phosphorylates LIFR . LIFR acts as a docking site for the STAT transcription factors. JAK kinase phosphorylates STAT proteins, which dissociate from the receptor and translocate to the nucleus to regulate gene expression.
- GDNF: Glial derived neurotrophic factor is a member of the TGFb family of proteins, and is a potent trophic factor for striatal neurons. The functional receptor is a heterodimer, composed of type 1 and type 2 receptors. Activation of the type 1 receptor leads to phosphorylation of Smad proteins, which translocate to the nucleus to activate gene expression.

2.7 Activity dependent mechanisms in the assembly of neural circuits[edit]

The processes of neuronal migration, differentiation and axon guidance are generally believed to be activity-independent mechanisms and rely on hard-wired genetic programs in the neurons themselves. Research findings however have implicated a role for activity-dependent mechanisms in mediating some aspects of these processes such as the rate of neuronal migration, aspects of neuronal differentiation and axon pathfinding. Activity-dependent mechanisms influence neural circuit development and are crucial for laying out early connectivity maps and the continued refinement of synapses which occurs during development. There are two distinct types of neural activity we observe in developing circuits -early spontaneous activity and sensory-evoked activity. Spontaneous activity occurs early during neural circuit development even when sensory input is absent and is observed in many systems such as the developing visual system,auditory system,motor system,hippocampus,cerebellum and neocortex.

Experimental techniques such as direct electrophysiological recording, fluorescence imaging using calcium indicators and optogenetic techniques have shed light on the nature and function of these early bursts of activity. They have distinct spatial and temporal patterns during development and their ablation during development has been known to result in deficits in network refinement in the visual system. In the immature retina, waves of spontaneous action potentials arise from the retinal ganglion cells and sweep across the retinal surface in the first few postnatal weeks. These waves are mediated by neurotransmitter acetylcholine in the initial phase and later on by glutamate. They are thought to instruct the formation of two sensory maps- the retinotopic map and eye-specific segregation. Retinotopic map refinement occurs in downstream visual targets in the brain-the superior colliculus (SC) and dorsal lateral geniculate nucleus (LGN). Pharmacological disruption and mouse models lacking the 2 subunit of the nicotinic acetylcholine receptor has shown that the lack of spontaneous activity leads to marked defects in retinotopy and eye-specific segregation.

In the developing auditory system, developing cochlea generate bursts of activity which spreads across the inner hair cells and spiral ganglion neurons which relay auditory information to the brain. ATP release from supporting cells triggers action potentials in inner hair cells. In the auditory system, spontaneous activity is thought to be involved in tonotopic map formation by segregating cochlear neuron axons tuned to high and low frequencies. In the motor system, periodic bursts of spontaneous activity are driven by excitatory GABA and glutamate during the early stages and by acetylcholine and glutamate at later stages. In the developing zebrafish spinal cord, early spontaneous activity is required for the formation of increasingly synchronous alternating bursts between ipsilateral and contralateral regions of the spinal cord and for the integration of new cells into the circuit. In the cortex, early waves of activity have been observed in the cerebellum and cortical slices. Once sensory stimulus becomes available, final fine-tuning of sensory-coding maps and circuit refinement begins to rely more and more on sensory-evoked activity as demonstrated by classic experiments about the effects of sensory deprivation during critical periods.

Chapter 3

Neurons And Glial Cells

3.1 Neurons

The neuron doctrine is the now fundamental idea that neurons are the basic structural and functional units of the nervous system. The theory was put forward by Santiago Ramón y Cajal in the late 19th century. It held that neurons are discrete cells (not connected in a meshwork), acting as metabolically distinct units.

Later discoveries yielded refinements to the doctrine. For example, glial cells, which are not considered neurons, play an essential role in information processing. Also, electrical synapses are more common than previously thought, comprising direct, cytoplasmic connections between neurons. In fact, neurons can form even tighter couplings: the squid giant axon arises from the fusion of multiple axons.

Ramón y Cajal also postulated the Law of Dynamic Polarization, which states that a neuron receives signals at its dendrites and cell body and transmits them, as action potentials, along the axon in one direction: away from the cell body. The Law of Dynamic Polarization has important exceptions; dendrites can serve as synaptic output sites of neurons and axons can receive synaptic inputs.

The number of neurons in the brain varies dramatically from species to species. In a human, there are an estimated 10–20 billion neurons in the cerebral cortex and 55–70 billion neurons in the cerebellum. By contrast, the nematode worm Caenorhabditis elegans has just 302 neurons, making it an ideal model organism as scientists have been able to map all of its neurons. The fruit fly Drosophila melanogaster, a common subject in biological experiments, has around 100,000 neurons and exhibits many complex behaviors. Many properties of neurons, from the type of neurotransmitters used to ion channel composition, are maintained across species, allowing scientists to study processes occurring in more complex organisms in much simpler experimental systems.

A neuron, neurone (old British spelling) or nerve cell, is an electrically excitable cell that communicates with other cells via specialized connections called synapses. It is the main component of nervous tissue. All animals except sponges and placozoans have neurons, but other multicellular organisms such as plants do not.

Neurons are typically classified into three types based on their function. Sensory neurons respond to stimuli such as touch, sound, or light that affect the cells of the sensory organs, and they send signals to the spinal cord or brain. Motor neurons receive signals from the brain and spinal cord to control everything from muscle contractions to glandular output. Interneurons connect neurons to other neurons within the same region of the brain or spinal cord. A group of connected neurons is called a neural circuit.

A typical neuron consists of a cell body (soma), dendrites, and a single axon. The soma is usually compact. The axon and dendrites are filaments that extrude from it. Dendrites typically branch profusely and extend a few hundred micrometers from the soma. The axon leaves the soma at a swelling called the axon hillock, and travels for as far as 1 meter in humans or more in other species. It branches but usually maintains a constant diameter. At the farthest tip of the axon's branches are axon terminals, where the neuron can transmit a signal across the synapse to another cell. Neurons may lack dendrites or have no axon. The term neurite is used to describe either a dendrite or an axon, particularly when the cell is undifferentiated.

Most neurons receive signals via the dendrites and soma and send out signals down the axon. At the majority of synapses, signals cross from the axon of one neuron to a dendrite of another. However, synapses can connect an axon to another axon or a dendrite to another dendrite.

The signaling process is partly electrical and partly chemical. Neurons are electrically excitable, due to maintenance of voltage gradients across their membranes. If the voltage changes by a large enough amount over a short interval, the neuron generates an all-or-nothing electrochemical pulse called an action potential. This potential travels rapidly along the axon, and activates synaptic connections as it reaches them. Synaptic signals may be excitatory or inhibitory, increasing or reducing the net voltage that reaches the soma.

In most cases, neurons are generated by neural stem cells during brain development and childhood. Neurogenesis largely ceases during adulthood in most areas of the brain. However, strong evidence supports generation of substantial numbers of new neurons in the hippocampus and olfactory bulb.

Neurons are highly specialized for the processing and transmission of cellular signals. Given their diversity of functions performed in different parts of the nervous system, there is a wide variety in their shape, size, and electrochemical properties. For instance, the soma of a neuron can vary from 4 to 100 micrometers in diameter.

The soma is the body of the neuron. As it contains the nucleus, most protein synthesis occurs here. The nucleus can range from 3 to 18 micrometers in diameter. The dendrites of a neuron are cellular extensions with many branches. This overall shape and structure is referred to metaphorically as a dendritic tree. This is where the majority of input to the neuron occurs via the dendritic spine. The axon is a finer, cable-like projection that can extend tens, hundreds, or even tens of thousands of times the diameter of the soma in length. The axon primarily carries nerve signals away from the soma, and carries some types of information back to it. Many neurons have only one axon, but this axon may—and usually will—undergo extensive branching, enabling communication with many target cells. The part of the axon where it emerges from the soma is called the axon hillock. Besides being an anatomical structure, the axon hillock also has the greatest density of voltage-dependent sodium channels. This makes it the most easily excited part of the neuron and the spike initiation zone for the axon. In electrophysiological terms, it has the most negative threshold potential. While the axon and axon hillock are generally involved in information outflow, this region can also receive input from other neurons. The axon terminal is found at the end of the axon farthest from the soma and contains synapses. Synaptic boutons are specialized structures where neurotransmitter chemicals are released to communicate with target neurons. In addition to synaptic boutons at the axon terminal, a neuron may have en passant boutons, which are located along the length of the axon.

Neuron cell body The accepted view of the neuron attributes dedicated functions to its various anatomical components; however, dendrites and axons often act in ways contrary to their so-called main function.

Diagram of a typical myelinated vertebrate motor neuron Axons and dendrites in the central nervous system are typically only about one micrometer thick, while some in the peripheral nervous system are much thicker. The soma is usually about 10–25 micrometers in diameter and often is not much larger than the cell nucleus it contains. The longest axon of a human motor neuron can be over a meter long, reaching from the base of the spine to the toes.

Sensory neurons can have axons that run from the toes to the posterior column of the spinal cord, over 1.5 meters in adults. Giraffes have single axons several meters in length running along the entire length of their necks. Much of what is known about axonal function comes from studying the squid giant axon, an ideal experimental preparation because of its relatively immense size (0.5–1 millimeters thick, several centimeters long).

Fully differentiated neurons are permanently postmitotic however, stem cells present in the adult brain may regenerate functional neurons throughout the life of an organism (see neurogenesis). Astrocytes are star-shaped glial cells. They have been observed to turn into neurons by virtue of their stem cell-like characteristic of pluripotency.

Membrane Like all animal cells, the cell body of every neuron is enclosed by a plasma membrane, a bilayer of lipid molecules with many types of protein structures embedded in it. A lipid bilayer is a powerful electrical insulator, but in neurons, many of the protein structures embedded in the membrane are electrically active. These include ion channels that permit electrically charged ions to flow across the membrane and ion pumps that chemically transport ions from one side of the membrane to the other. Most ion channels are permeable only to specific types of ions. Some ion channels are voltage gated, meaning that they can be switched between open and closed states by altering the voltage difference across the membrane. Others are chemically gated, meaning that they can be switched between open and closed states by interactions with chemicals that diffuse through the extracellular fluid. The ion materials include sodium, potassium, chloride, and calcium. The interactions between ion channels and ion pumps produce a voltage difference across the membrane, typically a bit less than 1/10 of a volt at baseline. This voltage has two functions: first, it provides a power source for an assortment of voltage-dependent protein machinery that is embedded in the membrane; second, it provides a basis for electrical signal transmission between different parts of the membrane.

Histology and internal structure

Golgi-stained neurons in human hippocampal tissue

Actin filaments in a mouse Cortical Neuron in culture Numerous microscopic clumps called Nissl bodies (or Nissl substance) are seen when nerve cell bodies are stained with a basophilic ("base-loving") dye. These structures consist of rough endoplasmic reticulum and associated ribosomal RNA. Named after German psychiatrist and neuropathologist Franz Nissl (1860–1919), they are involved in protein synthesis and their prominence can be explained by the fact that nerve cells are very metabolically active. Basophilic dyes such as aniline or (weakly) haematoxylin highlight negatively charged components, and so bind to the phosphate backbone of the ribosomal RNA.

The cell body of a neuron is supported by a complex mesh of structural proteins called neurofilaments, which together with neurotubules (neuronal microtubules) are assembled into larger neurofibrils. Some neurons also contain pigment granules, such as neuromelanin (a brownish-black pigment that is byproduct of synthesis of catecholamines), and lipofuscin (a yellowish-brown pigment), both of which accumulate with age. Other structural proteins that are important for neuronal function are actin and the tubulin of microtubules. Class III -tubulin is found almost exclusively in neurons. Actin is predominately found at the tips of axons and dendrites during neuronal development. There the actin dynamics can be modulated via an interplay with microtubule.

There are different internal structural characteristics between axons and dendrites. Typical axons almost never contain ribosomes, except some in the initial segment. Dendrites contain granular endoplasmic reticulum or ribosomes, in diminishing amounts as the distance from the cell body increases.

Classification

Image of pyramidal neurons in mouse cerebral cortex expressing green fluorescent protein. The red staining indicates GABAergic interneurons.

SMI32-stained pyramidal neurons in cerebral cortex See also: List of distinct cell types in the adult human body § Nervous system Neurons vary in shape and size and can be classified by their morphology and function. The anatomist Camillo Golgi grouped neurons into two types; type I with long axons used to move signals over long distances and type II with short axons, which can often be confused with dendrites. Type I cells can be further classified by the location of the soma. The basic morphology of type I neurons, represented by spinal motor neurons, consists of a cell body called the soma and a long thin axon covered by a myelin sheath. The dendritic tree wraps around the cell body and receives signals from other neurons. The end of the axon has branching terminals (axon terminal) that release neurotransmitters into a gap called the synaptic cleft between the terminals and the dendrites of the next neuron.

Structural classification Polarity

Different kinds of neurons: 1 Unipolar neuron 2 Bipolar neuron 3 Multipolar neuron 4 Pseudounipolar neuron Most neurons can be anatomically characterized as:

Unipolar: single process Bipolar: 1 axon and 1 dendrite Multipolar: 1 axon and 2 or more dendrites Golgi I: neurons with projecting axonal processes; examples are pyramidal cells, Purkinje cells, and anterior horn cells Golgi II: neurons whose axonal process projects locally; the best example is the granule cell Anaxonic: where the axon cannot be distinguished from the dendrite(s) Pseudounipolar: 1 process which then serves as both an axon and a dendrite Other Some unique neuronal types can be identified according to their location in the nervous system and distinct shape. Some examples are:

Basket cells, interneurons that form a dense plexus of terminals around the soma of target cells, found in the cortex and cerebellum Betz cells, large motor neurons Lugaro cells, interneurons of the cerebellum Medium spiny neurons, most neurons in the corpus striatum Purkinje cells, huge neurons in the cerebellum, a type of Golgi I multipolar neuron Pyramidal cells, neurons with triangular soma, a type of Golgi I Renshaw cells, neurons with both ends linked to alpha motor neurons Unipolar brush cells, interneurons with unique dendrite ending in a brush-like tuft Granule cells, a type of Golgi II neuron Anterior horn cells, motoneurons located in the spinal cord Spindle cells, interneurons that connect widely separated areas of the brain Functional classification Direction Afferent neurons convey information from tissues and organs into the central nervous system and are also called sensory neurons. Efferent neurons (motor neurons) transmit signals from the central nervous system to the effector cells. Interneurons connect neurons within specific regions of the central nervous system. Afferent and efferent also refer generally to neurons that, respectively, bring information to or send information from the brain.

Action on other neurons A neuron affects other neurons by releasing a neurotransmitter that binds to chemical receptors. The effect upon the postsynaptic neuron is determined by the type of receptor that is activated, not by the presynaptic neuron or by the neurotransmitter. A neurotransmitter can be thought of as a key, and a receptor as a lock: the same neurotransmitter can activate multiple types of receptors. Receptors can be classified broadly as excitatory (causing an increase in firing rate), inhibitory (causing a decrease in firing rate), or modulatory (causing long-lasting effects not directly related to firing rate).

The two most common (90%+) neurotransmitters in the brain, glutamate and GABA, have largely consistent actions. Glutamate acts on several types of receptors, and has effects that are excitatory at ionotropic receptors and a modulatory effect at metabotropic receptors. Similarly, GABA acts on several types of receptors, but all of them have inhibitory effects (in adult animals, at least). Because of this consistency, it is common for neuroscientists to refer to cells that release glutamate as "excitatory neurons", and cells that release GABA as "inhibitory neurons". Some other types of neurons have consistent effects, for example, "excitatory" motor neurons in the spinal cord that release acetylcholine, and "inhibitory" spinal neurons that release glycine.

The distinction between excitatory and inhibitory neurotransmitters is not absolute. Rather, it depends on the class of chemical receptors present on the postsynaptic neuron. In principle, a single neuron, releasing a single neurotransmitter, can have excitatory effects on some targets, inhibitory effects on others, and modulatory effects on others still. For example, photoreceptor cells in the retina constantly release the neurotransmitter glutamate in the absence of light. So-called OFF bipolar cells are, like most neurons, excited by the released glutamate. However, neighboring target neurons called ON bipolar cells are instead inhibited by glutamate, because they lack typical ionotropic glutamate receptors and instead express a class of inhibitory metabotropic glutamate receptors. When light is present, the photoreceptors cease releasing glutamate, which relieves the ON bipolar cells from inhibition, activating them; this simultaneously removes the excitation from the OFF bipolar cells, silencing them.

It is possible to identify the type of inhibitory effect a presynaptic neuron will have on a postsynaptic neuron, based on the proteins the presynaptic neuron expresses. Parvalbumin-expressing neurons typically dampen the output signal of the postsynaptic neuron in the visual cortex, whereas somatostatin-expressing neurons typically block dendritic inputs to the postsynaptic neuron.

Discharge patterns Neurons have intrinsic electroresponsive properties like intrinsic transmembrane voltage oscillatory patterns. So neurons can be classified according to their electrophysiological characteristics:

Tonic or regular spiking. Some neurons are typically constantly (tonically) active, typically firing at a constant frequency. Example: interneurons in neurostriatum. Phasic or bursting. Neurons that fire in bursts are called phasic. Fast spiking. Some neurons are notable for their high firing rates, for example some types of cortical inhibitory interneurons, cells in globus pallidus, retinal ganglion cells. Neurotransmitter Cholinergic neurons—acetylcholine. Acetylcholine is released from presynaptic neurons into the synaptic cleft. It acts as a ligand for both ligand-gated ion channels and metabotropic (GPCRs) muscarinic receptors. Nicotinic receptors are pentameric ligand-gated ion channels composed of alpha and beta subunits that bind nicotine. Ligand binding opens the channel causing influx of $Na+$ depolarization and increases the probability of presynaptic neurotransmitter release. Acetylcholine is synthesized from choline and acetyl coenzyme A. GABAergic neurons—gamma aminobutyric acid. GABA is one of two neuroinhibitors in the central nervous system (CNS), along with glycine. GABA has a homologous function to ACh, gating anion channels that allow $Cl-$ ions to enter the post synaptic neuron. $Cl-$ causes hyperpolarization within the neuron, decreasing the probability of an action potential firing as the voltage becomes more negative (for an action potential to fire, a positive voltage threshold must be reached). GABA is synthesized from glutamate neurotransmitters by the enzyme glutamate decarboxylase. Glutamatergic neurons—glutamate. Glutamate is one of two primary excitatory amino acid neurotransmitters, along with aspartate. Glutamate receptors are one of four categories, three of which are ligand-gated ion channels and one of which is a G-protein coupled receptor (often referred to as GPCR). AMPA and Kainate receptors function as cation channels permeable to $Na+$ cation channels mediating fast excitatory synaptic transmission. NMDA receptors are another cation channel that is more permeable to $Ca2+$. The function of NMDA receptors depend on glycine receptor binding as a co-agonist within the channel pore. NMDA receptors do not function without both ligands present. Metabotropic receptors, GPCRs modulate synaptic transmission and postsynaptic excitability. Glutamate can cause excitotoxicity when blood flow to the brain is interrupted, resulting in brain damage. When blood flow is suppressed, glutamate is released from presynaptic neurons, causing greater NMDA and AMPA receptor activation than normal outside of stress conditions, leading to elevated $Ca2+$ and $Na+$ entering the post synaptic neuron and cell damage. Glutamate is synthesized from the amino acid glutamine by the enzyme glutamate synthase. Dopaminergic neurons—dopamine. Dopamine is a neurotransmitter that acts on D1 type (D1 and D5) Gs-coupled receptors, which increase cAMP and PKA, and D2 type (D2, D3, and D4) receptors, which activate Gi-coupled receptors that decrease cAMP and PKA. Dopamine is connected to mood and behavior and modulates both pre- and post-synaptic neurotransmission. Loss of dopamine neurons in the substantia nigra has been linked to Parkinson's disease. Dopamine is synthesized from the amino acid tyrosine. Tyrosine is catalyzed into levadopa (or L-DOPA) by tyrosine hydroxlase, and levadopa is then converted into dopamine by the aromatic amino acid decarboxylase. Serotonergic neurons—serotonin. Serotonin (5-Hydroxytryptamine, 5-HT) can act as excitatory or inhibitory. Of its four 5-HT receptor classes, 3 are GPCR and 1 is a ligand-gated cation channel. Serotonin is synthesized from tryptophan by tryptophan hydroxylase, and then further by decarboxylase. A lack of 5-HT at postsynaptic neurons has been linked to depression. Drugs that block the presynaptic serotonin transporter are used for treatment, such as Prozac and Zoloft.

Neurons communicate with each another via synapses, where either the axon terminal of one cell contacts another neuron's dendrite, soma or, less commonly, axon. Neurons such as Purkinje cells in the cerebellum can have over 1000 dendritic branches, making connections with tens of thousands of other cells; other neurons, such as the magnocellular neurons of the supraoptic nucleus, have only one or two dendrites, each of which receives thousands of synapses.

Synapses can be excitatory or inhibitory, either increasing or decreasing activity in the target neuron, respectively. Some neurons also communicate via electrical synapses, which are direct, electrically conductive junctions between cells.

When an action potential reaches the axon terminal, it opens voltage-gated calcium channels, allowing calcium ions to enter the terminal. Calcium causes synaptic vesicles filled with neurotransmitter molecules to fuse with the membrane, releasing their contents into the synaptic cleft. The neurotransmitters diffuse across the synaptic cleft and activate receptors on the postsynaptic neuron. High cytosolic calcium in the axon terminal triggers mitochondrial calcium uptake, which, in turn, activates mitochondrial energy metabolism to produce ATP to support continuous neurotransmission.

An autapse is a synapse in which a neuron's axon connects to its own dendrites.

The human brain has some 8.6 x 1010 (eighty six billion) neurons. Each neuron has on average 7,000 synaptic connections to other neurons. It has been estimated that the brain of a three-year-old child has about 1015 synapses (1 quadrillion). This number declines with age, stabilizing by adulthood. Estimates vary for an adult, ranging from 1014 to 5 x 1014 synapses (100 to 500 trillion).

3.2 Glia

Glia, also called glial cells or neuroglia, are non-neuronal cells in the central nervous system (brain and spinal cord) and the peripheral nervous system that do not produce electrical impulses. They maintain homeostasis, form myelin, and provide support and protection for neurons. In the central nervous system, glial cells include oligodendrocytes, astrocytes, ependymal cells, and microglia, and in the peripheral nervous system glial cells include Schwann cells and satellite cells. They have four main functions: (1) to surround neurons and hold them in place; (2) to supply nutrients and oxygen to neurons; (3) to insulate one neuron from another; (4) to destroy pathogens and remove dead neurons. They also play a role in neurotransmission and synaptic connections, and in physiological processes like breathing. While glia were thought to outnumber neurons by a ratio of 10:1, a recent study provides evidence for a ratio of less than 1:1.

Table 3.1: Comparison of the main features of prokaryotic and eukaryotic cells.

Location	Name	Description
		The most abundant type of macroglial cell in the CNS, astrocytes (also called astroglia) have numerous projections that link neurons to their blood supply while forming the blood-brain barrier. They regulate the external chemicalenvironment of neurons by removing excess potassium ions, and recycling neurotransmitters released during synaptic transmission. Astrocytes may regulate vasoconstriction and vasodilation by producing substances such as arachidonic acid, whose metabolites are vasoactive.

		Astrocytes signal each other using ATP. The gap junctions (also known as electrical synapses) between astrocytes allow the messenger molecule IP3 to diffuse from one astrocyte to another. IP3 activates calcium channels on cellular organelles, releasing calcium into the cytoplasm. This calcium may stimulate the production of IP3 and cause release of ATP through channels in the membrane made of pannexins. net effect is a calcium wave that propagates from cell to cell. Extracellular release of and consequent activation of purinergic receptors on other astrocytes, may also medi calcium waves in some cases.
	Astrocytes	In general, there are two types of astrocytes, protoplasmic and fibrous, similar in func but distinct in morphology and distribution. Protoplasmic astrocytes have short, thic highly branched processes and are typically found in gray matter. Fibrous astrocytes long, thin, less branched processes and are more commonly found in white matter.
		It has recently been shown that astrocyte activity is linked to blood flow in the brain that this is what is actually being measured in fMRI. They also have been involved i neuronal circuits playing an inhibitory role after sensing changes in extracellular calci
	Oligodendroc	Oligodendrocytes are cells that coat axons in the central nervous system (CNS) with cell membrane, forming a specialized membrane differentiation called myelin, produci the myelin sheath. The myelin sheath provides insulation to the axon that allows electrical signals to propagate more efficiently.
CNS	Ependymal cells	Ependymal cells, also named ependymocytes, line the spinal cord and the ventricula system of the brain. These cells are involved in the creation and secretion of cerebro fluid (CSF) and beat their cilia to help circulate the CSF and make up the blood-C barrier. They are also thought to act as neural stem cells.
	Radial glia	Radial glia cells arise from neuroepithelial cells after the onset of neurogenesis. Their differentiation abilities are more restricted than those of neuroepithelial cells. In the developing nervous system, radial glia function both as neuronal progenitors and as a scaffold upon which newborn neurons migrate. In the mature brain, the cerebellum a retina retain characteristic radial glial cells. In the cerebellum, these are Bergmann g which regulate synaptic plasticity. In the retina, the radial Müller cell is the glial cel spans the thickness of the retina and, in addition to astroglial cells,[14] participates i bidirectional communication with neurons.
	Schwann cells	Similar in function to oligodendrocytes, Schwann cells provide myelination to axons the peripheral nervous system(PNS). They also have phagocytotic activity and clear cellular debris that allows for regrowth of PNS neurons.
PNS	Satellite cells	Satellite glial cells are small cells that surround neurons in sensory, sympathetic, and parasympathetic ganglia.[17]These cells help regulate the external chemical environm Like astrocytes, they are interconnected by gap junctions and respond to ATP by ele intracellular concentration of calcium ions. They are highly sensitive to injury and inflammation, and appear to contribute to pathological states, such as chronic pain.
	Enteric glial cells	Are found in the intrinsic ganglia of the digestive system. They are thought to have r roles in the enteric system, some related to homeostasis and muscular digestive proce

Glial cells exhibit great cellular and functional diversity. Glial cells can respond to and manipulate neurotransmission in many ways.

Glia were discovered in 1856, by the pathologist Rudolf Virchow in his search for a “connective tissue" in the brain. The term derives from Greek and "glue" (/ li ə/ or / la ə/), and suggests the original impression that they were the glue of the nervous system.

In general, neuroglial cells are smaller than neurons. There are approximately 85 billion glia cells in the human brain, about the same number as neurons. Glial cells make up about half the total volume of the brain and spinal cord. The glia to neuron-ratio varies from one part of the brain to another. The glia to neuron-ratio in the cerebral cortex is 3.72 (60.84 billion glia (72%); 16.34 billion neurons), while that of the cerebellum is only 0.23 (16.04 billion glia; 69.03 billion neurons). The ratio in the cerebral cortex gray matter is 1.48, with 3.76 for the gray and white matter combined. The ratio of the basal ganglia, diencephalon and brainstem combined is 11.35.

The total number of glia cells in the human brain is distributed into the different types with oligodendrocytes being the most frequent (45–75%), followed by astrocytes (19–40%) and microglia (about 10% or less).

Most glia are derived from ectodermal tissue of the developing embryo, in particular the neural tube and crest. The exception is microglia, which are derived from hemopoietic stem cells. In the adult, microglia are largely a self-renewing population and are distinct from macrophages and monocytes, which infiltrate an injured and diseased CNS.

In the central nervous system, glia develop from the ventricular zone of the neural tube. These glia include the oligodendrocytes, ependymal cells, and astrocytes. In the peripheral nervous system, glia derive from the neural crest. These PNS glia include Schwann cells in nerves and satellite glial cells in ganglia.

Glia retain the ability to undergo cell division in adulthood, whereas most neurons cannot. The view is based on the general inability of the mature nervous system to replace neurons after an injury, such as a stroke or trauma, where very often there is a substantial proliferation of glia, or gliosis, near or at the site of damage. However, detailed studies have found no evidence that 'mature' glia, such as astrocytes or oligodendrocytes, retain mitotic capacity. Only the resident oligodendrocyte precursor cells seem to keep this ability once the nervous system matures.

Glial cells are known to be capable of mitosis. By contrast, scientific understanding of whether neurons are permanently post-mitotic, or capable of mitosis, is still developing. In the past, glia had been considered[by whom?] to lack certain features of neurons. For example, glial cells were not believed to have chemical synapses or to release transmitters. They were considered to be the passive bystanders of neural transmission. However, recent studies have shown this to not be entirely true.

Some glial cells function primarily as the physical support for neurons. Others provide nutrients to neurons and regulate the extracellular fluid of the brain, especially surrounding neurons and their synapses. During early embryogenesis, glial cells direct the migration of neurons and produce molecules that modify the growth of axons and dendrites.

Glia are crucial in the development of the nervous system and in processes such as synaptic plasticity and synaptogenesis. Glia have a role in the regulation of repair of neurons after injury. In the central nervous system (CNS), glia suppress repair. Glial cells known as astrocytes enlarge and proliferate to form a scar and produce inhibitory molecules that inhibit regrowth of a damaged or severed axon. In the peripheral nervous system (PNS), glial cells known as Schwann cells promote repair. After axonal injury, Schwann cells regress to an earlier developmental state to encourage regrowth of the axon. This difference between the CNS and the PNS, raises hopes for the regeneration of nervous tissue in the CNS. For example, a spinal cord may be able to be repaired following injury or severance. Schwann cells are also known as neuri-lemmocytes. These cells envelop nerve fibers of the PNS by winding repeatedly around a nerve fiber with the nucleus inside of it. This process creates a myelin sheath, which not only aids in conductivity but also assists in the regeneration of damaged fibers.

Oligodendrocytes are found in the CNS and resemble an octopus: they have bulbous cell bodies with up to fifteen arm-like processes. Each “arm” reaches out to a nerve fiber and spirals around it, creating a myelin sheath. The myelin sheath insulates the nerve fiber from the extracellular fluid and speeds up signal conduction along the nerve fiber.

Astrocytes are crucial participants in the tripartite synapse. They have several crucial functions, including clearance of neurotransmitters from within the synaptic cleft, which aids in distinguishing between separate action potentials and prevents toxic build-up of certain neurotransmitters such as glutamate, which would otherwise lead to excitotoxicity. Furthermore, astrocytes release gliotransmitters such as glutamate, ATP, and D-serine in response to stimulation.

Microglia are specialized macrophages capable of phagocytosis that protect neurons of the central nervous system. They are derived from the earliest wave of mononuclear cells that originate in yolk sac blood islands early in development, and colonize the brain shortly after the neural precursors begin to differentiate.

These cells are found in all regions of the brain and spinal cord. Microglial cells are small relative to macroglial cells, with changing shapes and oblong nuclei. They are mobile within the brain and multiply when the brain is damaged. In the healthy central nervous system, microglia processes constantly sample all aspects of their environment (neurons, macroglia and blood vessels). In a healthy brain, microglia direct the immune response to brain damage and play an important role in the inflammation that accompanies the damage. Many diseases and disorders are associated with deficient microglia, such as Alzheimer’s disease, Parkinson’s disease, and ALS.

Chapter 4

Electrical Basis of Neuronal Function

4.1 The Membrane potential

Membrane potential (also transmembrane potential or membrane voltage) is the difference in electric potential between the interior and the exterior of a biological cell. With respect to the exterior of the cell, typical values of membrane potential, normally given in units of millivolts and denoted as mV, ranges from –40 mV to –80 mV.

All animal cells are surrounded by a membrane composed of a lipid bilayer with proteins embedded in it. The membrane serves as both an insulator and a diffusion barrier to the movement of ions. Transmembrane proteins, also known as ion transporter or ion pump proteins, actively push ions across the membrane and establish concentration gradients across the membrane, and ion channels allow ions to move across the membrane down those concentration gradients. Ion pumps and ion channels are electrically equivalent to a set of batteries and resistors inserted in the membrane, and therefore create a voltage between the two sides of the membrane.

Almost all plasma membranes have an electrical potential across them, with the inside usually negative with respect to the outside. The membrane potential has two basic functions. First, it allows a cell to function as a battery, providing power to operate a variety of "molecular devices" embedded in the membrane. Second, in electrically excitable cells such as neurons and muscle cells, it is used for transmitting signals between different parts of a cell. Signals are generated by opening or closing of ion channels at one point in the membrane, producing a local change in the membrane potential. This change in the electric field can be quickly affected by either adjacent or more distant ion channels in the membrane. Those ion channels can then open or close as a result of the potential change, reproducing the signal.

In non-excitable cells, and in excitable cells in their baseline states, the membrane potential is held at a relatively stable value, called the resting potential. For neurons, typical values of the resting potential range from –70 to –80 millivolts; that is, the interior of a cell has a negative baseline voltage of a bit less than one-tenth of a volt. The opening and closing of ion channels can induce a departure from the resting potential. This is called a depolarization if the interior voltage becomes less negative (say from −70 mV to −60 mV), or a hyperpolarization if the interior voltage becomes more negative (say from −70 mV to −80 mV). In excitable cells, a sufficiently large depolarization can evoke an action potential, in which the membrane potential changes rapidly and significantly for a short time (on the order of 1 to 100 milliseconds), often reversing its polarity. Action potentials are generated by the activation of certain voltage-gated ion channels.

In neurons, the factors that influence the membrane potential are diverse. They include numerous types of ion channels, some of which are chemically gated and some of which are voltage-gated. Because voltage-gated ion channels are controlled by the membrane potential, while the membrane potential itself is influenced by these same ion channels, feedback loops that allow for complex temporal dynamics arise, including oscillations and regenerative events such as action potentials.

The membrane potential in a cell derives ultimately from two factors: electrical force and diffusion. Electrical force arises from the mutual attraction between particles with opposite electrical charges (positive and negative) and the mutual repulsion between particles with the same type of charge (both positive or both negative). Diffusion arises from the statistical tendency of particles to redistribute from regions where they are highly concentrated to regions where the concentration is low.

Voltage

Voltage, which is synonymous with difference in electrical potential, is the ability to drive an electric current across a resistance. Indeed, the simplest definition of a voltage is given by Ohm's law: V=IR, where V is voltage, I is current and R is resistance. If a voltage source such as a battery is placed in an electrical circuit, the higher the voltage of the source the greater the amount of current that it will drive across the available resistance. The functional significance of voltage lies only in potential differences between two points in a circuit. The idea of a voltage at a single point is meaningless. It is conventional in electronics to assign a voltage of zero to some arbitrarily chosen element of the circuit, and then assign voltages for other elements measured relative to that zero point. There is no significance in which element is chosen as the zero point—the function of a circuit depends only on the differences not on voltages per se. However, in most cases and by convention, the zero level is most often assigned to the portion of a circuit that is in contact with ground.

The same principle applies to voltage in cell biology. In electrically active tissue, the potential difference between any two points can be measured by inserting an electrode at each point, for example one inside and one outside the cell, and connecting both electrodes to the leads of what is in essence a specialized voltmeter. By convention, the zero potential value is assigned to the outside of the cell and the sign of the potential difference between the outside and the inside is determined by the potential of the inside relative to the outside zero.

In mathematical terms, the definition of voltage begins with the concept of an electric field E, a vector field assigning a magnitude and direction to each point in space. In many situations, the electric field is a conservative field, which means that it can be expressed as the gradient of a scalar function V, that is, E = – V. This scalar field V is referred to as the voltage distribution. Note that the definition allows for an arbitrary constant of integration—this is why absolute values of voltage are not meaningful. In general, electric fields can be treated as conservative only if magnetic fields do not significantly influence them, but this condition usually applies well to biological tissue.

Because the electric field is the gradient of the voltage distribution, rapid changes in voltage within a small region imply a strong electric field; on the converse, if the voltage remains approximately the same over a large region, the electric fields in that region must be weak. A strong electric field, equivalent to a strong voltage gradient, implies that a strong force is exerted on any charged particles that lie within the region.

Ions and the forces driving their motion

Electrical signals within biological organisms are, in general, driven by ions. The most important cations for the action potential are sodium (Na+) and potassium (K+). Both of these are monovalent cations that carry a single positive charge. Action potentials can also involve calcium (Ca^{2+}), which is a divalent cation that carries a double positive charge. The chloride anion (Cl^{-}) plays a major role in the action potentials of some algae, but plays a negligible role in the action potentials of most animals.

Ions cross the cell membrane under two influences: diffusion and electric fields. A simple example wherein two solutions—A and B—are separated by a porous barrier illustrates that diffusion will ensure that they will eventually mix into equal solutions. This mixing occurs because of the difference in their concentrations. The region with high concentration will diffuse out toward the region with low concentration. To extend the example, let solution A have 30 sodium ions and 30 chloride ions. Also, let solution B have only 20 sodium ions and 20 chloride ions. Assuming the barrier allows both types of ions to travel through it, then a steady state will be reached whereby both solutions have 25 sodium ions and 25 chloride ions. If, however, the porous barrier is selective to which ions are let through, then diffusion alone will not determine the resulting solution. Returning to the previous example, let's now construct a barrier that is permeable only to sodium ions. Now, only sodium is allowed to diffuse cross the barrier from its higher concentration in solution A to the lower concentration in solution B. This will result in a greater accumulation of sodium ions than chloride ions in solution B and a lesser number of sodium ions than chloride ions in solution A.

This means that there is a net positive charge in solution B from the higher concentration of positively charged sodium ions than negatively charged chloride ions. Likewise, there is a net negative charge in solution A from the greater concentration of negative chloride ions than positive sodium ions. Since opposite charges attract and like charges repel, the ions are now also influenced by electrical fields as well as forces of diffusion. Therefore, positive sodium ions will be less likely to travel to the now-more-positive B solution and remain in the now-more-negative A solution. The point at which the forces of the electric fields completely counteract the force due to diffusion is called the equilibrium potential. At this point, the net flow of the specific ion (in this case sodium) is zero.

Plasma membranes

The cell membrane, also called the plasma membrane or plasmalemma, is a semipermeable lipid bilayer common to all living cells. It contains a variety of biological molecules, primarily proteins and lipids, which are involved in a vast array of cellular processes. Every animal cell is enclosed in a plasma membrane, which has the structure of a lipid bilayer with many types of large molecules embedded in it. Because it is made of lipid molecules, the plasma membrane intrinsically has a high electrical resistivity, in other words a low intrinsic permeability to ions. However, some of the molecules embedded in the membrane are capable either of actively transporting ions from one side of the membrane to the other or of providing channels through which they can move.

In electrical terminology, the plasma membrane functions as a combined resistor and capacitor. Resistance arises from the fact that the membrane impedes the movement of charges across it. Capacitance arises from the fact that the lipid bilayer is so thin that an accumulation of charged particles on one side gives rise to an electrical force that pulls oppositely charged particles toward the other side. The capacitance of the membrane is relatively unaffected by the molecules that are embedded in it, so it has a more or less invariant value estimated at about 2 F/cm2 (the total capacitance of a patch of membrane is proportional to its area). The conductance of a pure lipid bilayer is so low, on the other hand, that in biological situations it is always dominated by the conductance of alternative pathways provided by embedded molecules. Thus, the capacitance of the membrane is more or less fixed, but the resistance is highly variable.

The thickness of a plasma membrane is estimated to be about 7-8 nanometers. Because the membrane is so thin, it does not take a very large transmembrane voltage to create a strong electric field within it. Typical membrane potentials in animal cells are on the order of 100 millivolts (that is, one tenth of a volt), but calculations show that this generates an electric field close to the maximum that the membrane can sustain—it has been calculated that a voltage difference much larger than 200 millivolts could cause dielectric breakdown, that is, arcing across the membrane.

Facilitated diffusion and transport

Facilitated diffusion in cell membranes, showing ion channels and carrier proteins The resistance of a pure lipid bilayer to the passage of ions across it is very high, but structures embedded in the membrane can greatly enhance ion movement, either actively or passively, via mechanisms called facilitated transport and facilitated diffusion. The two types of structure that play the largest roles are ion channels and ion pumps, both usually formed from assemblages of protein molecules. Ion channels provide passageways through which ions can move. In most cases, an ion channel is permeable only to specific types of ions (for example, sodium and potassium but not chloride or calcium), and sometimes the permeability varies depending on the direction of ion movement. Ion pumps, also known as ion transporters or carrier proteins, actively transport specific types of ions from one side of the membrane to the other, sometimes using energy derived from metabolic processes to do so.

Ion pumps

The sodium-potassium pump uses energy derived from ATP to exchange sodium for potassium ions across the membrane. Main articles: Ion transporter and Active transport Ion pumps are integral membrane proteins that carry out active transport, i.e., use cellular energy (ATP) to “pump” the ions against their concentration gradient. Such ion pumps take in ions from one side of the membrane (decreasing its concentration there) and release them on the other side (increasing its concentration there).

The ion pump most relevant to the action potential is the sodium–potassium pump, which transports three sodium ions out of the cell and two potassium ions in. As a consequence, the concentration of potassium ions K^+ inside the neuron is roughly 20-fold larger than the outside concentration, whereas the sodium concentration outside is roughly ninefold larger than inside. In a similar manner, other ions have different concentrations inside and outside the neuron, such as calcium, chloride and magnesium.

If the numbers of each type of ion were equal, the sodium–potassium pump would be electrically neutral, but, because of the three-for-two exchange, it gives a net movement of one positive charge from intracellular to extracellular for each cycle, thereby contributing to a positive voltage difference. The pump has three effects: (1) it makes the sodium concentration high in the extracellular space and low in the intracellular space; (2) it makes the potassium concentration high in the intracellular space and low in the extracellular space; (3) it gives the intracellular space a negative voltage with respect to the extracellular space.

The sodium-potassium pump is relatively slow in operation. If a cell were initialized with equal concentrations of sodium and potassium everywhere, it would take hours for the pump to establish equilibrium. The pump operates constantly, but becomes progressively less efficient as the concentrations of sodium and potassium available for pumping are reduced.

Ion pumps influence the action potential only by establishing the relative ratio of intracellular and extracellular ion concentrations. The action potential involves mainly the opening and closing of ion channels not ion pumps. If the ion pumps are turned off by removing their energy source, or by adding an inhibitor such as ouabain, the axon can still fire hundreds of thousands of action potentials before their amplitudes begin to decay significantly. In particular, ion pumps play no significant role in the repolarization of the membrane after an action potential.

Another functionally important ion pump is the sodium-calcium exchanger. This pump operates in a conceptually similar way to the sodium-potassium pump, except that in each cycle it exchanges three Na+ from the extracellular space for one Ca++ from the intracellular space. Because the net flow of charge is inward, this pump runs "downhill", in effect, and therefore does not require any energy source except the membrane voltage. Its most important effect is to pump calcium outward—it also allows an inward flow of sodium, thereby counteracting the sodium-potassium pump, but, because overall sodium and potassium concentrations are much higher than calcium concentrations, this effect is relatively unimportant. The net result of the sodium-calcium exchanger is that in the resting state, intracellular calcium concentrations become very low.

Ion channels Main articles: Ion channel and Passive transport Seven spheres whose radii are proportional to the radii of mono-valent lithium, sodium, potassium, rubidium, cesium cations (0.76, 1.02, 1.38, 1.52, and 1.67 Å, respectively), divalent calcium cation (1.00 Å) and mono-valent chloride (1.81 Å).

Ion channels are integral membrane proteins with a pore through which ions can travel between extracellular space and cell interior. Most channels are specific (selective) for one ion; for example, most potassium channels are characterized by 1000:1 selectivity ratio for potassium over sodium, though potassium and sodium ions have the same charge and differ only slightly in their radius. The channel pore is typically so small that ions must pass through it in single-file order. Channel pores can be either open or closed for ion passage, although a number of channels demonstrate various sub-conductance levels. When a channel is open, ions permeate through the channel pore down the transmembrane concentration gradient for that particular ion. Rate of ionic flow through the channel, i.e. single-channel current amplitude, is determined by the maximum channel conductance and electrochemical driving force for that ion, which is the difference between the instantaneous value of the membrane potential and the value of the reversal potential.

Schematic stick diagram of a tetrameric potassium channel where each of the monomeric sub-units is symmetrically arranged around a central ion conduction pore. The pore axis is displayed perpendicular to the screen. Carbon, oxygen, and nitrogen atom are represented by grey, red, and blue spheres, respectively. A single potassium cation is depicted as a purple sphere in the center of the channel.

A channel may have several different states (corresponding to different conformations of the protein), but each such state is either open or closed. In general, closed states correspond either to a contraction of the pore—making it impassable to the ion—or to a separate part of the protein, stoppering the pore. For example, the voltage-dependent sodium channel undergoes inactivation, in which a portion of the protein swings into the pore, sealing it. This inactivation shuts off the sodium current and plays a critical role in the action potential.

Ion channels can be classified by how they respond to their environment. For example, the ion channels involved in the action potential are voltage-sensitive channels; they open and close in response to the voltage across the membrane. Ligand-gated channels form another important class; these ion channels open and close in response to the binding of a ligand molecule, such as a neurotransmitter. Other ion channels open and close with mechanical forces. Still other ion channels—such as those of sensory neurons—open and close in response to other stimuli, such as light, temperature or pressure.

Leakage channels are the simplest type of ion channel, in that their permeability is more or less constant. The types of leakage channels that have the greatest significance in neurons are potassium and chloride channels. Even these are not perfectly constant in their properties: First, most of them are voltage-dependent in the sense that they conduct better in one direction than the other (in other words, they are rectifiers); second, some of them are capable of being shut off by chemical ligands even though they do not require ligands in order to operate.

Ligand-gated ion channels are channels whose permeability is greatly increased when some type of chemical ligand binds to the protein structure. Animal cells contain hundreds, if not thousands, of types of these. A large subset function as neurotransmitter receptors—they occur at postsynaptic sites, and the chemical ligand that gates them is released by the presynaptic axon terminal. One example of this type is the AMPA receptor, a receptor for the neurotransmitter glutamate that when activated allows passage of sodium and potassium ions. Another example is the GABAA receptor, a receptor for the neurotransmitter GABA that when activated allows passage of chloride ions.

Neurotransmitter receptors are activated by ligands that appear in the extracellular area, but there are other types of ligand-gated channels that are controlled by interactions on the intracellular side.

Voltage-gated ion channels, also known as voltage dependent ion channels, are channels whose permeability is influenced by the membrane potential. They form another very large group, with each member having a particular ion selectivity and a particular voltage dependence. Many are also time-dependent—in other words, they do not respond immediately to a voltage change but only after a delay.

One of the most important members of this group is a type of voltage-gated sodium channel that underlies action potentials—these are sometimes called Hodgkin-Huxley sodium channels because they were initially characterized by Alan Lloyd Hodgkin and Andrew Huxley in their Nobel Prize-winning studies of the physiology of the action potential. The channel is closed at the resting voltage level, but opens abruptly when the voltage exceeds a certain threshold, allowing a large influx of sodium ions that produces a very rapid change in the membrane potential. Recovery from an action potential is partly dependent on a type of voltage-gated potassium channel that is closed at the resting voltage level but opens as a consequence of the large voltage change produced during the action potential.

4.2 The Reversal Potential

The reversal potential (or equilibrium potential) of an ion is the value of transmembrane voltage at which diffusive and electrical forces counterbalance, so that there is no net ion flow across the membrane. This means that the transmembrane voltage exactly opposes the force of diffusion of the ion, such that the net current of the ion across the membrane is zero and unchanging. The reversal potential is important because it gives the voltage that acts on channels permeable to that ion—in other words, it gives the voltage that the ion concentration gradient generates when it acts as a battery.

The equilibrium potential of a particular ion is usually designated by the notation Eion.The equilibrium potential for any ion can be calculated using the Nernst equation. For example, reversal potential for potassium ions will be as follows:

$$E_{eq,K^+} = \frac{RT}{zF} \ln \frac{[K^+]_o}{[K^+]_i}$$

where

E_eq,K^+_ is the equilibrium potential for potassium, measured in volts R is the universal gas constant, equal to 8.314 Joule $\cdot$ K^{-1} $\cdot$ mol^{-1} T is the absolute temperature, measured in Kelvin z is the number of elementary charges of the ion in question involved in the reaction F is the Faraday constant, equal to 96,485 Coulomb $\cdot$ mol–1 or J $\cdot$ V^{-1} $\cdot$ mol^{-1} [K^+]*o* is the extracellular concentration of potassium, measured in mol $\cdot$ m^{-3} or mmol $\cdot$ l^{-1} [K^+]i is the intracellular concentration of potassium

Even if two different ions have the same charge (i.e., K^+ and Na^+), they can still have very different equilibrium potentials, provided their outside and/or inside concentrations differ. Take, for example, the equilibrium potentials of potassium and sodium in neurons. The potassium equilibrium potential EK is −84 mV with 5 mM potassium outside and 140 mM inside. On the other hand, the sodium equilibrium potential, ENa, is approximately +66 mV with approximately 12 mM sodium inside and 140 mM outside.[note 1]

A neuron's resting membrane potential actually changes during the development of an organism. In order for a neuron to eventually adopt its full adult function, its potential must be tightly regulated during development. As an organism progresses through development the resting membrane potential becomes more negative. Glial cells are also differentiating and proliferating as development progresses in the brain. The addition of these glial cells increases the organism's ability to regulate extracellular potassium. The drop in extracellular potassium can lead to a decrease in membrane potential of 35 mV.

Cell excitability is the change in membrane potential that is necessary for cellular responses in various tissues. Cell excitability is a property that is induced during early embriogenesis. Excitability of a cell has also been defined as the ease with which a response may be triggered. The resting potential forms the basis of cell excitability and these processes are fundamental for the generation of graded and action potentials.

The most important regulators of cell excitability are the extracellular calcium concentration and the calcium-sensing receptor. Calcium ion is also the most important second messenger in excitable cell signaling. Other important proteins that regulate cell excitability are voltage-gated ion channels, ion transporters, membrane receptors and hyperpolarization-activated cyclic-nucleotide-gated channels. For example, potassium channels are important regulators of excitability in neurons, cardiac myocytes and many other excitable cells like astrocytes. Activation of synaptic receptors initiates long-lasting changes in neuronal excitability.

Many cell types are considered to have an excitable membrane. Excitable cells are neurons, cardiac myocytes, skeletal myocytes, smooth muscle cells, many types of endothelial cells (e.g. beta cells), glial cells (e.g. astrocytes), mechanoreceptor cells (e.g. hair cells and Merkel cells), chemoreceptor cells (e.g. glomus cells, taste receptors), some plant cells and possibly immune cells. Astrocytes display a form of non-electrical excitability based on intracellular calcium variations related to the expression of several receptors through which they can detect the synaptic signal. In neurons, there are different membrane properties in some portions of the cell, for example, dendritic excitability endows neurons with the capacity for coincidence detection of spatially separated inputs.

4.3 The Resting potential

When the membrane potential of a cell goes for a long period of time without changing significantly, it is referred to as a resting potential or resting voltage. This term is used for the membrane potential of non-excitable cells, but also for the membrane potential of excitable cells in the absence of excitation. In excitable cells, the other possible states are graded membrane potentials (of variable amplitude), and action potentials, which are large, all-or-nothing rises in membrane potential that usually follow a fixed time course. Excitable cells include neurons, muscle cells, and some secretory cells in glands. Even in other types of cells, however, the membrane voltage can undergo changes in response to environmental or intracellular stimuli. For example, depolarization of the plasma membrane appears to be an important step in programmed cell death.

The interactions that generate the resting potential are modeled by the Goldman equation. This is similar in form to the Nernst equation shown above, in that it is based on the charges of the ions in question, as well as the difference between their inside and outside concentrations. However, it also takes into consideration the relative permeability of the plasma membrane to each ion in question.

$$E_m = \frac{RT}{F} \ln \left(\frac{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathrm{out}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathrm{out}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathrm{in}}}{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathrm{in}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathrm{in}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathrm{out}}} \right)$$

The three ions that appear in this equation are potassium (K+), sodium (Na+), and chloride (Cl^-). Calcium is omitted, but can be added to deal with situations in which it plays a significant role. Being an anion, the chloride terms are treated differently from the cation terms; the intracellular concentration is in the numerator, and the extracellular concentration in the denominator, which is reversed from the cation terms. Pi stands for the relative permeability of the ion type i.

In essence, the Goldman formula expresses the membrane potential as a weighted average of the reversal potentials for the individual ion types, weighted by permeability. (Although the membrane potential changes about 100 mV during an action potential, the concentrations of ions inside and outside the cell do not change significantly. They remain close to their respective concentrations when then membrane is at resting potential.) In most animal cells, the permeability to potassium is much higher in the resting state than the permeability to sodium. As a consequence, the resting potential is usually close to the potassium reversal potential. The permeability to chloride can be high enough to be significant, but, unlike the other ions, chloride is not actively pumped, and therefore equilibrates at a reversal potential very close to the resting potential determined by the other ions.

Values of resting membrane potential in most animal cells usually vary between the potassium reversal potential (usually around -80 mV) and around -40 mV. The resting potential in excitable cells (capable of producing action potentials) is usually near -60 mV—more depolarized voltages would lead to spontaneous generation of action potentials. Immature or undifferentiated cells show highly variable values of resting voltage, usually significantly more positive than in differentiated cells. In such cells, the resting potential value correlates with the degree of differentiation: undifferentiated cells in some cases may not show any transmembrane voltage difference at all.

Maintenance of the resting potential can be metabolically costly for a cell because of its requirement for active pumping of ions to counteract losses due to leakage channels. The cost is highest when the cell function requires an especially depolarized value of membrane voltage. For example, the resting potential in daylight-adapted blowfly (Calliphora vicina) photoreceptors can be as high as -30 mV. This elevated membrane potential allows the cells to respond very rapidly to visual inputs; the cost is that maintenance of the resting potential may consume more than 20% of overall cellular ATP.

On the other hand, the high resting potential in undifferentiated cells can be a metabolic advantage. This apparent paradox is resolved by examination of the origin of that resting potential. Little-differentiated cells are characterized by extremely high input resistance, which implies that few leakage channels are present at this stage of cell life. As an apparent result, potassium permeability becomes similar to that for sodium ions, which places resting potential in-between the reversal potentials for sodium and potassium as discussed above. The reduced leakage currents also mean there is little need for active pumping in order to compensate, therefore low metabolic cost.

4.4 Graded potentials

As explained above, the potential at any point in a cell's membrane is determined by the ion concentration differences between the intracellular and extracellular areas, and by the permeability of the membrane to each type of ion. The ion concentrations do not normally change very quickly (with the exception of Ca^{2+}, where the baseline intracellular concentration is so low that even a small influx may increase it by orders of magnitude), but the permeabilities of the ions can change in a fraction of a millisecond, as a result of activation of ligand-gated ion channels. The change in membrane potential can be either large or small, depending on how many ion channels are activated and what type they are, and can be either long or short, depending on the lengths of time that the channels remain open. Changes of this type are referred to as graded potentials, in contrast to action potentials, which have a fixed amplitude and time course.

As can be derived from the Goldman equation shown above, the effect of increasing the permeability of a membrane to a particular type of ion shifts the membrane potential toward the reversal potential for that ion. Thus, opening Na+ channels shifts the membrane potential toward the Na+ reversal potential, which is usually around +100 mV. Likewise, opening K^+ channels shifts the membrane potential toward about –90 mV, and opening Cl^- channels shifts it toward about –70 mV (resting potential of most membranes). Thus, Na+ channels shift the membrane potential in a positive direction, K^+ channels shift it in a negative direction (except when the membrane is hyperpolarized to a value more negative than the K^+ reversal potential), and Cl^- channels tend to shift it towards the resting potential.

Chapter 5

Neurotransmission

The presynaptic neuron (top) releases a neurotransmitter, which activates receptors on the postsynaptic cell (bottom). Neurotransmission (Latin: transmissio "passage, crossing" from transmittere "send, let through") is the process by which signaling molecules called neurotransmitters are released by the axon terminal of a neuron (the presynaptic neuron), and bind to and react with the receptors on the dendrites of another neuron (the postsynaptic neuron) a short distance away. A similar process occurs in retrograde neurotransmission, where the dendrites of the postsynaptic neuron release retrograde neurotransmitters (e.g., endocannabinoids; synthesized in response to a rise in intracellular calcium levels) that signal through receptors that are located on the axon terminal of the presynaptic neuron, mainly at GABAergic and glutamatergic synapses.

Neurotransmission is regulated by several different factors: the availability and rate-of-synthesis of the neurotransmitter, the release of that neurotransmitter, the baseline activity of the postsynaptic cell, the number of available postsynaptic receptors for the neurotransmitter to bind to, and the subsequent removal or deactivation of the neurotransmitter by enzymes or presynaptic reuptake.

In response to a threshold action potential or graded electrical potential, a neurotransmitter is released at the presynaptic terminal. The released neurotransmitter may then move across the synapse to be detected by and bind with receptors in the postsynaptic neuron. Binding of neurotransmitters may influence the postsynaptic neuron in either an inhibitory or excitatory way. The binding of neurotransmitters to receptors in the postsynaptic neuron can trigger either short term changes, such as changes in the membrane potential called postsynaptic potentials, or longer term changes by the activation of signaling cascades.

During the 1950s, Bernard Katz and Paul Fatt observed spontaneous miniature synaptic currents at the frog neuromuscular junction. Based on these observations, they developed the 'quantal hypothesis' that is the basis for our current understanding of neurotransmitter release as exocytosis and for which Katz received the Nobel Prize in Physiology or Medicine in 1970. In the late 1960s, Ricardo Miledi and Katz advanced the hypothesis that depolarization-induced influx of calcium ions triggers exocytosis.

Neurons form complex biological neural networks through which nerve impulses (action potentials) travel. Neurons do not touch each other (except in the case of an electrical synapse through a gap junction); instead, neurons interact at close contact points called synapses. A neuron transports its information by way of an action potential. When the nerve impulse arrives at the synapse, it may cause the release of neurotransmitters, which influence another (postsynaptic) neuron. The postsynaptic neuron may receive inputs from many additional neurons, both excitatory and inhibitory. The excitatory and inhibitory influences are summed, and if the net effect is inhibitory, the neuron will be less likely to "fire" (i.e., generate an action potential), and if the net effect is excitatory, the neuron will be more likely to fire. How likely a neuron is to fire depends on how far its membrane potential is from the threshold potential, the voltage at which an action potential is triggered because enough voltage-dependent sodium channels are activated so that the net inward sodium current exceeds all outward currents. Excitatory inputs bring a neuron closer to threshold, while inhibitory inputs bring the neuron farther from threshold. An action potential is an "all-or-none" event; neurons whose membranes have not reached threshold will not fire, while those that do must fire. Once the action potential is initiated (traditionally at the axon hillock), it will propagate along the axon, leading to release of neurotransmitters at the synaptic bouton to pass along information to yet another adjacent neuron.

Stages in neurotransmission at the synapse

- Synthesis of the neurotransmitter. This can take place in the cell body, in the axon, or in the axon terminal.
- Storage of the neurotransmitter in storage granules or vesicles in the axon terminal.
- Calcium enters the axon terminal during an action potential, causing release of the neurotransmitter into the synaptic cleft.
- After its release, the transmitter binds to and activates a receptor in the postsynaptic membrane.
- Deactivation of the neurotransmitter. The neurotransmitter is either destroyed enzymatically, or taken back into the terminal from which it came, where it can be reused, or degraded and removed.

5.1 The Synapse

In the nervous system, a synapse is a structure that permits a neuron (or nerve cell) to pass an electrical or chemical signal to another neuron or to the target effector cell.

Santiago Ramón y Cajal proposed that neurons are not continuous throughout the body, yet still communicate with each other, an idea known as the neuron doctrine. The word "synapse" – from the Greek synapsis ( ), meaning "conjunction", in turn from (("together") and ("to fasten")) – was introduced in 1897 by the English neurophysiologist Charles Sherrington in Michael Foster's Textbook of Physiology. Sherrington struggled to find a good term that emphasized a union between two separate elements, and the actual term "synapse" was suggested by the English classical scholar Arthur Woollgar Verrall, a friend of Foster. Some authors generalize the concept of the synapse to include the communication from a neuron to any other cell type, such as to a motor cell, although such non-neuronal contacts may be referred to as junctions (a historically older term).A landmark study by Sanford Palay demonstrated the existence of synapses.

Synapses are essential to neuronal function: neurons are cells that are specialized to pass signals to individual target cells, and synapses are the means by which they do so. At a synapse, the plasma membrane of the signal-passing neuron (the presynaptic neuron) comes into close apposition with the membrane of the target (postsynaptic) cell. Both the presynaptic and postsynaptic sites contain extensive arrays of molecular machinery that link the two membranes together and carry out the signaling process. In many synapses, the presynaptic part is located on an axon and the postsynaptic part is located on a dendrite or soma. Astrocytes also exchange information with the synaptic neurons, responding to synaptic activity and, in turn, regulating neurotransmission. Synapses (at least chemical synapses) are stabilized in position by synaptic adhesion molecules (SAMs) projecting from both the pre- and post-synaptic neuron and sticking together where they overlap; SAMs may also assist in the generation and functioning of synapses.

There are two fundamentally different types of synapses:

In a chemical synapse, electrical activity in the presynaptic neuron is converted (via the activation of voltage-gated calcium channels) into the release of a chemical called a neurotransmitter that binds to receptors located in the plasma membrane of the postsynaptic cell. The neurotransmitter may initiate an electrical response or a secondary messenger pathway that may either excite or inhibit the postsynaptic neuron. Chemical synapses can be classified according to the neurotransmitter released: glutamatergic (often excitatory), GABAergic (often inhibitory), cholinergic (e.g. vertebrate neuromuscular junction), and adrenergic (releasing norepinephrine). Because of the complexity of receptor signal transduction, chemical synapses can have complex effects on the postsynaptic cell.

In an electrical synapse, the presynaptic and postsynaptic cell membranes are connected by special channels called gap junctions or synaptic cleft that are capable of passing an electric current, causing voltage changes in the presynaptic cell to induce voltage changes in the postsynaptic cell. The main advantage of an electrical synapse is the rapid transfer of signals from one cell to the next. Synaptic communication is distinct from an ephaptic coupling, in which communication between neurons occurs via indirect electric fields.

An autapse is a chemical or electrical synapse that forms when the axon of one neuron synapses onto dendrites of the same neuron.

The adult human brain is estimated to contain from 10^{14} to 5×10^{14} (100–500 trillion) synapses. Every cubic millimeter of cerebral cortex contains roughly a billion (short scale, i.e. 109) of them. The number of synapses in the human cerebral cortex has separately been estimated at 0.15 quadrillion (150 trillion) Synapses can be classified by the type of cellular structures serving as the pre- and post-synaptic components. The vast majority of synapses in the mammalian nervous system are classical axo-dendritic synapses (axon synapsing upon a dendrite), however, a variety of other arrangements exist. These include but are not limited to axo-axonic, dendro-dendritic, axo-secretory, somato-dendritic, dendro-somatic, and somato-somatic synapses.

The axon can synapse onto a dendrite, onto a cell body, or onto another axon or axon terminal, as well as into the bloodstream or diffusely into the adjacent nervous tissue.

It is widely accepted that the synapse plays a role in the formation of memory. As neurotransmitters activate receptors across the synaptic cleft, the connection between the two neurons is strengthened when both neurons are active at the same time, as a result of the receptor's signaling mechanisms. The strength of two connected neural pathways is thought to result in the storage of information, resulting in memory. This process of synaptic strengthening is known as long-term potentiation.

Synaptic transmission can be changed by previous activity. These changes are called synaptic plasticity and may result in either a decrease in the efficacy of the synapse, called depression, or an increase in efficacy, called potentiation. These changes can either be long-term or short-term. Forms of short-term plasticity include synaptic fatigue or depression and synaptic augmentation. Forms of long-term plasticity include long-term depression and long-term potentiation. Synaptic plasticity can be either homosynaptic (occurring at a single synapse) or heterosynaptic (occurring at multiple synapses).

By altering the release of neurotransmitters, the plasticity of synapses can be controlled in the presynaptic cell. The postsynaptic cell can be regulated by altering the function and number of its receptors. Changes in postsynaptic signaling are most commonly associated with a N-methyl-d-aspartic acid receptor (NMDAR)-dependent long-term potentiation (LTP) and long-term depression (LTD) due to the influx of calcium into the post-synaptic cell, which are the most analyzed forms of plasticity at excitatory synapses.

Each neuron has as many as 15,000 connections with neighboring neurons.

Neurons do not touch each other (except in the case of an electrical synapse through a gap junction); instead, neurons interact at contact points called synapses: a junction within two nerve cells, consisting of a miniature gap within which impulses are carried by a neurotransmitter. A neuron transports its information by way of a nerve impulse called an action potential. When an action potential arrives at the synapse's presynaptic terminal button, it may stimulate the release of neurotransmitters. These neurotransmitters are released into the synaptic cleft to bind onto the receptors of the postsynaptic membrane and influence another cell, either in an inhibitory or excitatory way. The next neuron may be connected to many more neurons, and if the total of excitatory influences minus inhibitory influences is great enough, it will also "fire". That is to say, it will create a new action potential at its axon hillock, releasing neurotransmitters and passing on the information to yet another neighboring neuron.

Excitatory and inhibitory A neurotransmitter can influence the function of a neuron through a remarkable number of mechanisms. In its direct actions in influencing a neuron's electrical excitability, however, a neurotransmitter acts in only one of two ways: excitatory or inhibitory. A neurotransmitter influences trans-membrane ion flow either to increase (excitatory) or to decrease (inhibitory) the probability that the cell with which it comes in contact will produce an action potential. Thus, despite the wide variety of synapses, they all convey messages of only these two types, and they are labeled as such. Type I synapses are excitatory in their actions, whereas type II synapses are inhibitory. Each type has a different appearance and is located on different parts of the neurons under its influence.

Type I (excitatory) synapses are typically located on the shafts or the spines of dendrites, whereas type II (inhibitory) synapses are typically located on a cell body. In addition, Type I synapses have round synaptic vesicles, whereas the vesicles of type II synapses are flattened. The material on the presynaptic and post-synaptic membranes is denser in a Type I synapse than it is in a type II, and the type I synaptic cleft is wider. Finally, the active zone on a Type I synapse is larger than that on a Type II synapse.

The different locations of type I and type II synapses divide a neuron into two zones: an excitatory dendritic tree and an inhibitory cell body. From an inhibitory perspective, excitation comes in over the dendrites and spreads to the axon hillock to trigger an action potential. If the message is to be stopped, it is best stopped by applying inhibition on the cell body, close to the axon hillock where the action potential originates. Another way to conceptualize excitatory–inhibitory interaction is to picture excitation overcoming inhibition. If the cell body is normally in an inhibited state, the only way to generate an action potential at the axon hillock is to reduce the cell body's inhibition. In this "open the gates" strategy, the excitatory message is like a racehorse ready to run down the track, but first the inhibitory starting gate must be removed.

Here is a summary of the sequence of events that take place in synaptic transmission from a presynaptic neuron to a postsynaptic cell. Each step is explained in more detail below. Note that with the exception of the final step, the entire process may run only a few hundred microseconds, in the fastest synapses.

- The process begins with a wave of electrochemical excitation called an action potential traveling along the membrane of the presynaptic cell, until it reaches the synapse.
- The electrical depolarization of the membrane at the synapse causes channels to open that are permeable to calcium ions.
- Calcium ions flow through the presynaptic membrane, rapidly increasing the calcium concentration in the interior.
- The high calcium concentration activates a set of calcium-sensitive proteins attached to vesicles that contain a neurotransmitter chemical.
- These proteins change shape, causing the membranes of some "docked" vesicles to fuse with the membrane of the presynaptic cell, thereby opening the vesicles and dumping their neurotransmitter contents into the synaptic cleft, the narrow space between the membranes of the pre- and postsynaptic cells.
- The neurotransmitter diffuses within the cleft. Some of it escapes, but some of it binds to chemical receptor molecules located on the membrane of the postsynaptic cell.
- The binding of neurotransmitter causes the receptor molecule to be activated in some way. Several types of activation are possible, as described in more detail below. In any case, this is the key step by which the synaptic process affects the behavior of the postsynaptic cell.
- Due to thermal vibration, the motion of atoms, vibrating about their equilibrium positions in a crystalline solid, neurotransmitter molecules eventually break loose from the receptors and drift away.
- The neurotransmitter is either reabsorbed by the presynaptic cell, and then repackaged for future release, or else it is broken down metabolically.

In general, if an excitatory synapse is strong enough, an action potential in the presynaptic neuron will trigger an action potential in the postsynaptic cell. In many cases the excitatory postsynaptic potential (EPSP) will not reach the threshold for eliciting an action potential. When action potentials from multiple presynaptic neurons fire simultaneously, or if a single presynaptic neuron fires at a high enough frequency, the EPSPs can overlap and summate. If enough EPSPs overlap, the summated EPSP can reach the threshold for initiating an action potential. This process is known as summation, and can serve as a high pass filter for neurons.

On the other hand, a presynaptic neuron releasing an inhibitory neurotransmitter, such as GABA, can cause an inhibitory postsynaptic potential (IPSP) in the postsynaptic neuron, bringing the membrane potential farther away from the threshold, decreasing its excitability and making it more difficult for the neuron to initiate an action potential. If an IPSP overlaps with an EPSP, the IPSP can in many cases prevent the neuron from firing an action potential. In this way, the output of a neuron may depend on the input of many different neurons, each of which may have a different degree of influence, depending on the strength and type of synapse with that neuron. John Carew Eccles performed some of the important early experiments on synaptic integration, for which he received the Nobel Prize for Physiology or Medicine in 1963.

Understanding the effects of drugs on neurotransmitters comprises a significant portion of research initiatives in the field of neuroscience. Most neuroscientists involved in this field of research believe that such efforts may further advance our understanding of the circuits responsible for various neurological diseases and disorders, as well as ways to effectively treat and someday possibly prevent or cure such illnesses.[medical citation needed]

5.1.1 The Synaptic Potential

Synaptic potential refers to the potential difference across the postsynaptic membrane that results from the action of neurotransmitters at a neuronal synapse. In other words, it is the "incoming" signal that a neuron receives. There are two forms of synaptic potential: excitatory and inhibitory. The type of potential produced depends on both the postsynaptic receptor, more specifically the changes in conductance of ion channels in the post synaptic membrane, and the nature of the released neurotransmitter. Excitatory post-synaptic potentials (EPSPs) depolarize the membrane and move the potential closer to the threshold for an action potential to be generated. Inhibitory postsynaptic potentials (IPSPs) hyperpolarize the membrane and move the potential farther away from the threshold, decreasing the likelihood of an action potential occurring. The Excitatory Post Synaptic potential is most likely going to be carried out by the neurotransmitters glutamate and acetylcholine, while the Inhibitory post synaptic potential will most likely be carried out by the neurotransmitters gamma-aminobutyric acid (GABA) and glycine. In order to depolarize a neuron enough to cause an action potential, there must be enough EPSPs to both depolarize the postsynaptic membrane from its resting membrane potential to its threshold and counterbalance the concurrent IPSPs that hyperpolarize the membrane. As an example, consider a neuron with a resting membrane potential of -70 mV (millivolts) and a threshold of -50 mV. It will need to be raised 20 mV in order to pass the threshold and fire an action potential. The neuron will account for all the many incoming excitatory and inhibitory signals via summative neural integration, and if the result is an increase of 20 mV or more, an action potential will occur.

Both EPSP and IPSPs generation is contingent upon the release of neurotransmitters from a terminal button of the presynaptic neuron. The first phase of synaptic potential generation is the same for both excitatory and inhibitory potentials. As an action potential travels through the presynaptic neuron, the membrane depolarization causes voltage-gated calcium channels to open. Consequently, calcium ions flow into the cell, promoting neurotransmitter-filled vesicles to travel down to the terminal button. These vesicles fuse with the membrane, releasing the neurotransmitter into the synaptic cleft. The released neurotransmitter then binds to its receptor on the postsynaptic neuron causing an excitatory or inhibitory response. EPSPs on the postsynaptic neuron result from the main excitatory neurotransmitter, glutamate, binding to its corresponding receptors on the postsynaptic membrane. By contrast, IPSPs are induced by the binding of GABA(gamma-aminobutyric acid), or glycine.

Synaptic potentials are small and many are needed to add up to reach the threshold. This means a single EPSP/IPSP is typically not enough to trigger an action potential. The two ways that synaptic potentials can add up to potentially form an action potential are spatial summation and temporal summation. Spatial summation refers to several excitatory stimuli from different synapses converging on the same postsynaptic neuron at the same time to reach the threshold needed to reach an action potential. Temporal summation refers to successive excitatory stimuli on the same location of the postsynaptic neuron. Both types of summation are the result of adding together many excitatory potentials; the difference being whether the multiple stimuli are coming from different locations at the same time (spatial) or at different times from the same location (temporal). Summation has been referred to as a “neurotransmitter induced tug-of-war” between excitatory and inhibitory stimuli. Whether the effects are combined in space or in time, they are both additive properties that require many stimuli acting together to reach the threshold. Synaptic potentials, unlike action potentials, degrade quickly as they move away from the synapse. This is the case for both excitatory and inhibitory postsynaptic potentials.

Synaptic potentials are not static. The concept of synaptic plasticity refers to the changes in synaptic potential. A synaptic potential may get stronger or weaker over time, depending on a few factors. The quantity of neurotransmitters released can play a large role in the future strength of that synapse’s potential. Additionally, the receptors on the post-synaptic side also play a role, both in their numbers, composition, and physical orientation. Some of these mechanisms rely on changes in both the presynaptic and postsynaptic neurons, resulting in a prolonged modification of the synaptic potential. The strength of changes in synaptic potentials across multiple synapses must be properly regulated. Otherwise, the activity across the entire neural circuit would become uncontrollable.

In recent years, there has been an abundance of research on how to prolong the effects of a synaptic potential, and more importantly, how to enhance or reduce its amplitude. The enhancement of synaptic potential would mean that fewer would be needed to have the same or larger effect, which could have far-reaching medical uses. The research indicates that this long term potentiation or in the case of inhibitory synapses, long term depression of the synapse occurs after prolonged stimulation of two neurons at the same time. Long term potentiation is known to have a role in memory and learning, which could be useful in treating diseases like Alzheimers.

Synaptic Potential Mechanism[edit] The way that synaptic potential is created involves the theories behind potential difference and current through a conductor. When an action potential fires at the dendritic spine where the action potential is initiated from the presynaptic terminal to the post synaptic terminal. This action potential is then carried down the length of the dendrite and then is propagated down the length of the axon inn order to get the presynaptic terminal to then perpetuate the process. The way that this process actually occurs is more complex than it may seem at first glance. The action potential actually occurs because of the synaptic potential across the membrane of the neuron. The potential difference between the inside of the neuron and the outside of the neuron is what will cause this process to occur once it has been initiated.

First, we must need an understanding of how the actual neuron creates this difference across its membrane. It does this first by having a strong dependence on ions both in the cell and outside of the cell. The ion potassium (K+) is the most important ion for this process of setting the membrane potential which the difference in potential across the inner and outer portion of the neuron. The second most important ion is sodium (Na+) and this ion is most prominent outside of the cell. When there is a greater concentration of sodium ions outside of the cell and a greater concentration of potassium ions inside of the cell this will cause a slight negative charge to be present within the cell. This difference across the membrane is what the neuron uses to actually do the work of sending messages from the axon hillock of the neuron all the way down to the presynaptic terminal and then on to the postsynaptic terminal because of the release of neurotransmitter into the synaptic cleft.

5.1.2 Synaptic Pruning

Synaptic pruning, which includes both axon and dendrite completely decaying and dying off, is the process of synapse elimination that occurs between early childhood and the onset of puberty in many mammals, including humans. Pruning starts near the time of birth and continues into the mid-20s. It was traditionally considered to be complete by the time of sexual maturation but this has been discounted by MRI studies. The infant brain will increase in size by a factor of up to 5 by adulthood, reaching a final size of approximately 86 (± 8) billion neurons. Two factors contribute to this growth: the growth of synaptic connections between neurons, and the myelination of nerve fibers; the total number of neurons, however, remains the same. Pruning is influenced by environmental factors and is widely thought to represent learning. After adolescence, the volume of the synaptic connections decreases again due to synaptic pruning.

At birth, the neurons in the visual and motor cortices have connections to the superior colliculus, spinal cord, and pons. The neurons in each cortex are selectively pruned, leaving connections that are made with the functionally appropriate processing centers. Therefore, the neurons in the visual cortex prune the synapses with neurons in the spinal cord, and the motor cortex severs connections with the superior colliculus. This variation of pruning is known as large-scaled stereotyped axon pruning. Neurons send long axon branches to appropriate and inappropriate target areas, and the inappropriate connections are eventually pruned away.

Regressive events refine the abundance of connections, seen in neurogenesis, to create a specific and mature circuitry. Apoptosis and pruning are the two main methods of severing the undesired connections. In apoptosis, the neuron is killed and all connections associated with the neuron are also eliminated. In contrast, the neuron does not die in pruning, but requires the retraction of axons from synaptic connections that are not functionally appropriate.

It is believed that the purpose of synaptic pruning is to remove unnecessary neuronal structures from the brain; as the human brain develops, the need to understand more complex structures becomes much more pertinent, and simpler associations formed at childhood are thought to be replaced by complex structures.

Despite the fact it has several connotations with regulation of cognitive childhood development, pruning is thought to be a process of removing neurons which may have become damaged or degraded in order to further improve the "networking" capacity of a particular area of the brain. Furthermore, it has been stipulated that the mechanism not only works in regard to development and reparation, but also as a means of continually maintaining more efficient brain function by removing neurons by their synaptic efficiency.

The pruning that is associated with learning is known as small-scale axon terminal arbor pruning. Axons extend short axon terminal arbors toward neurons within a target area. Certain terminal arbors are pruned by competition. The selection of the pruned terminal arbors follow the "use it or lose it" principle seen in synaptic plasticity. This means synapses that are frequently used have strong connections while the rarely used synapses are eliminated. Examples seen in vertebrate include pruning of axon terminals in the neuromuscular junction in the peripheral nervous system and the pruning of climbing fiber inputs to the cerebellum in the central nervous system.

In terms of humans, synaptic pruning has been observed through the inference of differences in the estimated numbers of glial cells and neurons between children and adults, which differs greatly in the mediodorsal thalamic nucleus.

In a study conducted in 2007 by Oxford University, researchers compared 8 newborn human brains with those of 8 adults using estimates based upon size and evidence gathered from stereological fractionation. They showed that, on average, estimates of adult neuron populations were 41% lower than those of the newborns in the region they measured, the mediodorsal thalamic nucleus.

However, in terms of glial cells, adults had far larger estimates than those in newborns; 36.3 million on average in adult brains, compared to 10.6 million in the newborn samples. The structure of the brain is thought to change when degeneration and deafferentation occur in postnatal situations, although these phenomena have not been observed in some studies. In the case of development, neurons which are in the process of loss via programmed cell death are unlikely to be re-used, but rather replaced by new neuronal structures or synaptic structures, and have been found to occur alongside the structural change in the sub-cortical gray matter.

Synaptic pruning is classified separately from the regressive events seen during older ages. While developmental pruning is experience dependent, the deteriorating connections that are synonymous with old age are not. The stereotyped pruning can be compared to the process of chiseling and molding of stone into a statue. Once the statue is complete, the weather will begin to erode the statue and this represents the experience-independent deletion of connections.

5.2 Neurotransmitters

Neurotransmitters are endogenous chemicals that enable neurotransmission. It is a type of chemical messenger which transmits signals across a chemical synapse, such as a neuromuscular junction, from one neuron (nerve cell) to another "target" neuron, muscle cell, or gland cell. Neurotransmitters are released from synaptic vesicles in synapses into the synaptic cleft, where they are received by neurotransmitter receptors on the target cells. Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which are readily available from the diet and only require a small number of biosynthetic steps for conversion. Neurotransmitters play a major role in shaping everyday life and functions. Their exact numbers are unknown, but more than 200 unique chemical messengers have been identified.

Neurotransmitters are stored in synaptic vesicles, clustered close to the cell membrane at the axon terminal of the presynaptic neuron. Neurotransmitters are released into and diffuse across the synaptic cleft, where they bind to specific receptors on the membrane of the postsynaptic neuron.

Most neurotransmitters are about the size of a single amino acid; however, some neurotransmitters may be the size of larger proteins or peptides. A released neurotransmitter is typically available in the synaptic cleft for a short time before it is metabolized by enzymes, pulled back into the presynaptic neuron through reuptake, or bound to a postsynaptic receptor. Nevertheless, short-term exposure of the receptor to a neurotransmitter is typically sufficient for causing a postsynaptic response by way of synaptic transmission.

In response to a threshold action potential or graded electrical potential, a neurotransmitter is released at the presynaptic terminal. Low level "baseline" release also occurs without electrical stimulation. The released neurotransmitter may then move across the synapse to be detected by and bind with receptors in the postsynaptic neuron. Binding of neurotransmitters may influence the postsynaptic neuron in either an inhibitory or excitatory way. This neuron may be connected to many more neurons, and if the total of excitatory influences are greater than those of inhibitory influences, the neuron will also "fire". Ultimately it will create a new action potential at its axon hillock to release neurotransmitters and pass on the information to yet another neighbouring neuron.

A neurotransmitter must be broken down once it reaches the post-synaptic cell to prevent further excitatory or inhibitory signal transduction. This allows new signals to be produced from the adjacent nerve cells. When the neurotransmitter has been secreted into the synaptic cleft, it binds to specific receptors on the postsynaptic cell, thereby generating a postsynaptic electrical signal. The transmitter must then be removed rapidly to enable the postsynaptic cell to engage in another cycle of neurotransmitter release, binding, and signal generation. Neurotransmitters are terminated in three different ways:

- Diffusion – the neurotransmitter detaches from receptor, drifting out of the synaptic cleft, here it becomes absorbed by glial cells.
- Enzyme degradation – special chemicals called enzymes break it down. Usually, astrocytes absorb the excess neurotransmitters and pass them on to enzymes or pump them directly into the presynaptic neuron.
- Reuptake – re-absorption of a neurotransmitter into the neuron. Transporters, or membrane transport proteins, pump neurotransmitters from the synaptic cleft back into axon terminals (the presynaptic neuron) where they are stored.

For example, choline is taken up and recycled by the pre-synaptic neuron to synthesize more ACh. Other neurotransmitters such as dopamine are able to diffuse away from their targeted synaptic junctions and are eliminated from the body via the kidneys, or destroyed in the liver. Each neurotransmitter has very specific degradation pathways at regulatory points, which may be targeted by the body's regulatory system or by recreational drugs.

Until the early 20th century, scientists assumed that the majority of synaptic communication in the brain was electrical. However, through the careful histological examinations by Ramón y Cajal (1852–1934), a 20 to 40 nm gap between neurons, known today as the synaptic cleft, was discovered. The presence of such a gap suggested communication via chemical messengers traversing the synaptic cleft, and in 1921 German pharmacologist Otto Loewi (1873–1961) confirmed that neurons can communicate by releasing chemicals. Through a series of experiments involving the vagus nerves of frogs, Loewi was able to manually slow the heart rate of frogs by controlling the amount of saline solution present around the vagus nerve. Upon completion of this experiment, Loewi asserted that sympathetic regulation of cardiac function can be mediated through changes in chemical concentrations. Furthermore, Otto Loewi is credited with discovering acetylcholine (ACh)—the first known neurotransmitter. Some neurons do, however, communicate via electrical synapses through the use of gap junctions, which allow specific ions to pass directly from one cell to another.

There are four main criteria for identifying neurotransmitters:

1. The chemical must be synthesized in the neuron or otherwise be present in it.

2. When the neuron is active, the chemical must be released and produce a response in some target.
3. The same response must be obtained when the chemical is experimentally placed on the target.
4. A mechanism must exist for removing the chemical from its site of activation after its work is done.

However, given advances in pharmacology, genetics, and chemical neuroanatomy, the term "neurotransmitter" can be applied to chemicals that:

- Carry messages between neurons via influence on the postsynaptic membrane.
- Have little or no effect on membrane voltage, but have a common carrying function such as changing the structure of the synapse.
- Communicate by sending reverse-direction messages that affect the release or reuptake of transmitters.

The anatomical localization of neurotransmitters is typically determined using immunocytochemical techniques, which identify the location of either the transmitter substances themselves, or of the enzymes that are involved in their synthesis. Immunocytochemical techniques have also revealed that many transmitters, particularly the neuropeptides, are co-localized, that is, one neuron may release more than one transmitter from its synaptic terminal. Various techniques and experiments such as staining, stimulating, and collecting can be used to identify neurotransmitters throughout the central nervous system.

There are many different ways to classify neurotransmitters. Dividing them into amino acids, peptides, and monoamines is sufficient for some classification purposes.

Major neurotransmitters:

- Amino acids: glutamate, aspartate, D-serine, -aminobutyric acid (GABA),[nb 1] glycine
- Gasotransmitters: nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H2S)
- Monoamines: dopamine (DA), norepinephrine (noradrenaline; NE, NA), epinephrine (adrenaline), histamine, serotonin (SER, 5-HT)
- Trace amines: phenethylamine, N-methylphenethylamine, tyramine, 3-iodothyronamine, octopamine, tryptamine, etc.
- Peptides: oxytocin, somatostatin, substance P, cocaine and amphetamine regulated transcript, opioid peptides
- Purines: adenosine triphosphate (ATP), adenosine
- Catecholamines: dopamine, norepinephrine (noradrenaline), epinephrine (adrenaline)
- Others: acetylcholine (ACh), anandamide, etc.

In addition, over 50 neuroactive peptides have been found, and new ones are discovered regularly. Many of these are "co-released" along with a small-molecule transmitter. Nevertheless, in some cases a peptide is the primary transmitter at a synapse. -endorphin is a relatively well-known example of a peptide neurotransmitter because it engages in highly specific interactions with opioid receptors in the central nervous system.

Single ions (such as synaptically released zinc) are also considered neurotransmitters by some, as well as some gaseous molecules such as nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H2S). The gases are produced in the neural cytoplasm and are immediately diffused through the cell membrane into the extracellular fluid and into nearby cells to stimulate production of second messengers. Soluble gas neurotransmitters are difficult to study, as they act rapidly and are immediately broken down, existing for only a few seconds.

The most prevalent transmitter is glutamate, which is excitatory at well over 90% of the synapses in the human brain. The next most prevalent is Gamma-Aminobutyric Acid, or GABA, which is inhibitory at more than 90% of the synapses that do not use glutamate. Although other transmitters are used in fewer synapses, they may be very important functionally: the great majority of psychoactive drugs exert their effects by altering the actions of some neurotransmitter systems, often acting through transmitters other than glutamate or GABA. Addictive drugs such as cocaine and amphetamines exert their effects primarily on the dopamine system. The addictive opiate drugs exert their effects primarily as functional analogs of opioid peptides, which, in turn, regulate dopamine levels.

5.3 Neurotransmitter receptor

In postsynaptic cells, neurotransmitter receptors receive signals that trigger an electrical signal, by regulating the activity of ion channels. The influx of ions through ion channels opened due to the binding of neurotransmitters to specific receptors can change the membrane potential of a neuron. This can result in a signal that runs along the axon (see action potential) and is passed along at a synapse to another neuron and possibly on to a neural network. On presynaptic cells, there can be receptor sites specific to the neurotransmitters released by that cell (see Autoreceptor), which provide feedback and mediate excessive neurotransmitter release from it.

There are two major types of neurotransmitter receptors: ionotropic and metabotropic. Ionotropic means that ions can pass through the receptor, whereas metabotropic means that a second messenger inside the cell relays the message (i.e. metabotropic receptors do not have channels). Metabotropic receptors are in fact G protein-coupled receptors. Ionotropic receptors are also called Ligand-gated ion channels and they can be excited by neurotransmitters (ligands) like glutamate and aspartate. These receptors can also be inhibited by neurotransmitters like GABA and glycine. Conversely, G-protein-coupled receptors are neither excitatory nor inhibitory. Rather, they can have a broad number of functions such as modulating the actions of excitatory and inhibitory ion channels or triggering a signalling cascade that releases calcium from stores inside the cell. Most neurotransmitters receptors are G-protein coupled.

Neurotransmitter (NT) receptors are located on the surface of neuronal and glial cells. At a synapse, one neuron sends messages to the other neuron via neurotransmitters. Therefore, the postsynaptic neuron, the one receiving the message, clusters NT receptors at this specific place in its membrane. NT receptors can be inserted into any region of the neuron's membrane such as dendrites, axons, and the cell body. Receptors can be located in different parts of the body to act as either an inhibitor or an excitatory receptor for a specific Neurotransmitter An example of this are the receptors for the neurotransmitter Acetylcholine (ACh), one receptor is located at the neuromuscular junction in skeletal muscle to facilitate muscle contraction (excitation), while the other receptor is located in the heart to slow down heart rate (inhibitory)

Ionotropic receptors: neurotransmitter-gated ion channels

Ligand-gated ion channels (LGICs) are one type of ionotropic receptor or channel-linked receptor. They are a group of transmembrane ion channels that are opened or closed in response to the binding of a chemical messenger (i.e., a ligand), such as a neurotransmitter.

The binding site of endogenous ligands on LGICs protein complexes are normally located on a different portion of the protein (an allosteric binding site) compared to where the ion conduction pore is located. The direct link between ligand binding and opening or closing of the ion channel, which is characteristic of ligand-gated ion channels, is contrasted with the indirect function of metabotropic receptors, which use second messengers. LGICs are also different from voltage-gated ion channels (which open and close depending on membrane potential), and stretch-activated ion channels (which open and close depending on mechanical deformation of the cell membrane).

Metabotropic receptors: G-protein coupled receptors

G protein-coupled receptors (GPCRs), also known as seven-transmembrane domain receptors, 7TM receptors, heptahelical receptors, serpentine receptor, and G protein-linked receptors (GPLR), comprise a large protein family of transmembrane receptors that sense molecules outside the cell and activate inside signal transduction pathways and, ultimately, cellular responses. G protein-coupled receptors are found only in eukaryotes, including yeast, choanoflagellates, and animals. The ligands that bind and activate these receptors include light-sensitive compounds, odors, pheromones, hormones, and neurotransmitters, and vary in size from small molecules to peptides to large proteins. G protein-coupled receptors are involved in many diseases, and are also the target of approximately 30% of all modern medicinal drugs.

There are two principal signal transduction pathways involving the G protein-coupled receptors: the cAMP signal pathway and the phosphatidylinositol signal pathway. When a ligand binds to the GPCR it causes a conformational change in the GPCR, which allows it to act as a guanine nucleotide exchange factor (GEF). The GPCR can then activate an associated G-protein by exchanging its bound GDP for a GTP. The G-protein's subunit, together with the bound GTP, can then dissociate from the and subunits to further affect intracellular signaling proteins or target functional proteins directly depending on the subunit type (G s, G i/o, G q/11, G 12/13).:1160

Neurotransmitter receptors are subject to ligand-induced desensitization: That is, they can become unresponsive upon prolonged exposure to their neurotransmitter. Neurotransmitter receptors are present on both postsynaptic neurons and presynaptic neurons with the former being used to receive neurotransmitters and the latter for the purpose of preventing further release of a given neurotransmitter. In addition to being found in neuron cells, neurotransmitter receptors are also found in various immune and muscle tissues. Many neurotransmitter receptors are categorized as a serpentine receptor or G protein-coupled receptor because they span the cell membrane not once, but seven times. Neurotransmitter receptors are known to become unresponsive to the type of neurotransmitter they receive when exposed for extended periods of time. This phenomenon is known as ligand-induced desensitization or downregulation.

The following are some major classes of neurotransmitter receptors:

- Adrenergic: 1A, 1b, 1c, 1d, 2a, 2b, 2c, 2d, 1, 2, 3
- Dopaminergic: D1, D2, D3, D4, D5
- GABAergic: GABAA, GABAB1a, GABAB1 , GABAB2, GABAC
- Glutaminergic: NMDA, AMPA, kainate, mGluR1, mGluR2, mGluR3, mGluR4, mGluR5, mGluR6, mGluR7
- Histaminergic: H1, H2, H3

- Cholinergic: Muscarinic: M1, M2, M3, M4, M5; Nicotinic: muscle, neuronal (-bungarotoxin-insensitive), neuronal (-bungarotoxin-sensitive)
- Opioid: , 1, 2,
- Serotonergic: 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT4, 5-HT5, 5-HT6, 5-HT7
- Glycinergic: Glycine

Drugs can influence behavior by altering neurotransmitter activity. For instance, drugs can decrease the rate of synthesis of neurotransmitters by affecting the synthetic enzyme(s) for that neurotransmitter. When neurotransmitter syntheses are blocked, the amount of neurotransmitters available for release becomes substantially lower, resulting in a decrease in neurotransmitter activity. Some drugs block or stimulate the release of specific neurotransmitters. Alternatively, drugs can prevent neurotransmitter storage in synaptic vesicles by causing the synaptic vesicle membranes to leak. Drugs that prevent a neurotransmitter from binding to its receptor are called receptor antagonists. For example, drugs used to treat patients with schizophrenia such as haloperidol, chlorpromazine, and clozapine are antagonists at receptors in the brain for dopamine. Other drugs act by binding to a receptor and mimicking the normal neurotransmitter. Such drugs are called receptor agonists. An example of a receptor agonist is morphine, an opiate that mimics effects of the endogenous neurotransmitter -endorphin to relieve pain. Other drugs interfere with the deactivation of a neurotransmitter after it has been released, thereby prolonging the action of a neurotransmitter. This can be accomplished by blocking re-uptake or inhibiting degradative enzymes. Lastly, drugs can also prevent an action potential from occurring, blocking neuronal activity throughout the central and peripheral nervous system. Drugs such as tetrodotoxin that block neural activity are typically lethal.

Drugs targeting the neurotransmitter of major systems affect the whole system, which can explain the complexity of action of some drugs. Cocaine, for example, blocks the re-uptake of dopamine back into the presynaptic neuron, leaving the neurotransmitter molecules in the synaptic gap for an extended period of time. Since the dopamine remains in the synapse longer, the neurotransmitter continues to bind to the receptors on the postsynaptic neuron, eliciting a pleasurable emotional response. Physical addiction to cocaine may result from prolonged exposure to excess dopamine in the synapses, which leads to the downregulation of some post-synaptic receptors. After the effects of the drug wear off, an individual can become depressed due to decreased probability of the neurotransmitter binding to a receptor. Fluoxetine is a selective serotonin re-uptake inhibitor (SSRI), which blocks re-uptake of serotonin by the presynaptic cell which increases the amount of serotonin present at the synapse and furthermore allows it to remain there longer, providing potential for the effect of naturally released serotonin. AMPT prevents the conversion of tyrosine to L-DOPA, the precursor to dopamine; reserpine prevents dopamine storage within vesicles; and deprenyl inhibits monoamine oxidase (MAO)-B and thus increases dopamine levels.

An agonist is a chemical capable of binding to a receptor, such as a neurotransmitter receptor, and initiating the same reaction typically produced by the binding of the endogenous substance. An agonist of a neurotransmitter will thus initiate the same receptor response as the transmitter. In neurons, an agonist drug may activate neurotransmitter receptors either directly or indirectly. Direct-binding agonists can be further characterized as full agonists, partial agonists, inverse agonists.[citation needed]

An antagonist is a chemical that acts within the body to reduce the physiological activity of another chemical substance (as an opiate); especially one that opposes the action on the nervous system of a drug or a substance occurring naturally in the body by combining with and blocking its nervous receptor.

There are two main types of antagonist: direct-acting Antagonist and indirect-acting Antagonists:

- Direct-acting antagonist- which takes up space present on receptors which are otherwise taken up by neurotransmitters themselves. This results in neurotransmitters being blocked from binding to the receptors. The most common is called Atropine.
- Indirect-acting antagonist- drugs that inhibit the release/production of neurotransmitters (e.g., Reserpine).

Chapter 6

The Central Nervous System

The central nervous system (CNS) is the part of the nervous system consisting of the brain and spinal cord. The CNS is so named because it integrates the received information and coordinates and influences the activity of all parts of the bodies of bilaterally symmetric animals—that is, all multicellular animals except sponges and radially symmetric animals such as jellyfish—and it contains the majority of the nervous system. Many consider the retina and the optic nerve (cranial nerve II), as well as the olfactory nerves (cranial nerve I) and olfactory epithelium as parts of the CNS, synapsing directly on brain tissue without intermediate ganglia. As such, the olfactory epithelium is the only central nervous tissue in direct contact with the environment, which opens up for therapeutic treatments. The CNS is contained within the dorsal body cavity, with the brain housed in the cranial cavity and the spinal cord in the spinal canal. In vertebrates, the brain is protected by the skull, while the spinal cord is protected by the vertebrae. The brain and spinal cord are both enclosed in the meninges. Within the CNS, the interneuronal space is filled with a large amount of supporting non-nervous cells called neuroglia or glia from the Greek for "glue".

The CNS consists of the two major structures: the brain and spinal cord. The brain is encased in the skull, and protected by the cranium. The spinal cord is continuous with the brain and lies caudally to the brain. It is protected by the vertebrae. The spinal cord reaches from the base of the skull, continues through or starting below the foramen magnum, and terminates roughly level with the first or second lumbar vertebra, occupying the upper sections of the vertebral canal.

White and gray matter

Microscopically, there are differences between the neurons and tissue of the CNS and the peripheral nervous system (PNS).[citation needed] The CNS is composed of white and gray matter. This can also be seen macroscopically on brain tissue. The white matter consists of axons and oligodendrocytes, while the gray matter consists of neurons and unmyelinated fibers. Both tissues include a number of glial cells (although the white matter contains more), which are often referred to as supporting cells of the CNS. Different forms of glial cells have different functions, some acting almost as scaffolding for neuroblasts to climb during neurogenesis such as bergmann glia, while others such as microglia are a specialized form of macrophage, involved in the immune system of the brain as well as the clearance of various metabolites from the brain tissue. Astrocytes may be involved with both clearance of metabolites as well as transport of fuel and various beneficial substances to neurons from the capillaries of the brain. Upon CNS injury astrocytes will proliferate, causing gliosis, a form of neuronal scar tissue, lacking in functional neurons.

The brain (cerebrum as well as midbrain and hindbrain) consists of a cortex, composed of neuron-bodies constituting gray matter, while internally there is more white matter that form tracts and commissures. Apart from cortical gray matter there is also subcortical gray matter making up a large number of different nuclei.

6.1 The Brain

The shape and size of the brain vary greatly between species, and identifying common features is often difficult. Nevertheless, there are a number of principles of brain architecture that apply across a wide range of species. Some aspects of brain structure are common to almost the entire range of animal species; others distinguish "advanced" brains from more primitive ones, or distinguish vertebrates from invertebrates.

The simplest way to gain information about brain anatomy is by visual inspection, but many more sophisticated techniques have been developed. Brain tissue in its natural state is too soft to work with, but it can be hardened by immersion in alcohol or other fixatives, and then sliced apart for examination of the interior. Visually, the interior of the brain consists of areas of so-called grey matter, with a dark color, separated by areas of white matter, with a lighter color. Further information can be gained by staining slices of brain tissue with a variety of chemicals that bring out areas where specific types of molecules are present in high concentrations. It is also possible to examine the microstructure of brain tissue using a microscope, and to trace the pattern of connections from one brain area to another.

Neurons generate electrical signals that travel along their axons. When a pulse of electricity reaches a junction called a synapse, it causes a neurotransmitter chemical to be released, which binds to receptors on other cells and thereby alters their electrical activity. The brains of all species are composed primarily of two broad classes of cells: neurons and glial cells. Glial cells (also known as glia or neuroglia) come in several types, and perform a number of critical functions, including structural support, metabolic support, insulation, and guidance of development. Neurons, however, are usually considered the most important cells in the brain. The property that makes neurons unique is their ability to send signals to specific target cells over long distances. They send these signals by means of an axon, which is a thin protoplasmic fiber that extends from the cell body and projects, usually with numerous branches, to other areas, sometimes nearby, sometimes in distant parts of the brain or body. The length of an axon can be extraordinary: for example, if a pyramidal cell (an excitatory neuron) of the cerebral cortex were magnified so that its cell body became the size of a human body, its axon, equally magnified, would become a cable a few centimeters in diameter, extending more than a kilometer. These axons transmit signals in the form of electrochemical pulses called action potentials, which last less than a thousandth of a second and travel along the axon at speeds of 1–100 meters per second. Some neurons emit action potentials constantly, at rates of 10–100 per second, usually in irregular patterns; other neurons are quiet most of the time, but occasionally emit a burst of action potentials.

Axons transmit signals to other neurons by means of specialized junctions called synapses. A single axon may make as many as several thousand synaptic connections with other cells. When an action potential, traveling along an axon, arrives at a synapse, it causes a chemical called a neurotransmitter to be released. The neurotransmitter binds to receptor molecules in the membrane of the target cell.

A bright green cell is seen against a red and black background, with long, highly branched, green processes extending out from it in multiple directions. Neurons often have extensive networks of dendrites, which receive synaptic connections. Shown is a pyramidal neuron from the hippocampus, stained for green fluorescent protein. Synapses are the key functional elements of the brain. The essential function of the brain is cell-to-cell communication, and synapses are the points at which communication occurs. The human brain has been estimated to contain approximately 100 trillion synapses; even the brain of a fruit fly contains several million. The functions of these synapses are very diverse: some are excitatory (exciting the target cell); others are inhibitory; others work by activating second messenger systems that change the internal chemistry of their target cells in complex ways. A large number of synapses are dynamically modifiable; that is, they are capable of changing strength in a way that is controlled by the patterns of signals that pass through them. It is widely believed that activity-dependent modification of synapses is the brain's primary mechanism for learning and memory.

Most of the space in the brain is taken up by axons, which are often bundled together in what are called nerve fiber tracts. A myelinated axon is wrapped in a fatty insulating sheath of myelin, which serves to greatly increase the speed of signal propagation. (There are also unmyelinated axons). Myelin is white, making parts of the brain filled exclusively with nerve fibers appear as light-colored white matter, in contrast to the darker-colored grey matter that marks areas with high densities of neuron cell bodies.

Evolution Generic bilaterian nervous system A rod-shaped body contains a digestive system running from the mouth at one end to the anus at the other. Alongside the digestive system is a nerve cord with a brain at the end, near to the mouth. Nervous system of a generic bilaterian animal, in the form of a nerve cord with segmental enlargements, and a "brain" at the front. Except for a few primitive organisms such as sponges (which have no nervous system) and cnidarians (which have a nervous system consisting of a diffuse nerve net), all living multicellular animals are bilaterians, meaning animals with a bilaterally symmetric body shape (that is, left and right sides that are approximate mirror images of each other). All bilaterians are thought to have descended from a common ancestor that appeared early in the Cambrian period, 485-540 million years ago, and it has been hypothesized that this common ancestor had the shape of a simple tubeworm with a segmented body. At a schematic level, that basic worm-shape continues to be reflected in the body and nervous system architecture of all modern bilaterians, including vertebrates. The fundamental bilateral body form is a tube with a hollow gut cavity running from the mouth to the anus, and a nerve cord with an enlargement (a ganglion) for each body segment, with an especially large ganglion at the front, called the brain. The brain is small and simple in some species, such as nematode worms; in other species, including vertebrates, it is the most complex organ in the body. Some types of worms, such as leeches, also have an enlarged ganglion at the back end of the nerve cord, known as a "tail brain".

There are a few types of existing bilaterians that lack a recognizable brain, including echinoderms and tunicates. It has not been definitively established whether the existence of these brainless species indicates that the earliest bilaterians lacked a brain, or whether their ancestors evolved in a way that led to the disappearance of a previously existing brain structure.

Invertebrates A fly resting on a reflective surface. A large, red eye faces the camera. The body appears transparent, apart from black pigment at the end of its abdomen. Fruit flies (Drosophila) have been extensively studied to gain insight into the role of genes in brain development. This category includes tardigrades, arthropods, molluscs, and numerous types of worms. The diversity of invertebrate body plans is matched by an equal diversity in brain structures.

Two groups of invertebrates have notably complex brains: arthropods (insects, crustaceans, arachnids, and others), and cephalopods (octopuses, squids, and similar molluscs). The brains of arthropods and cephalopods arise from twin parallel nerve cords that extend through the body of the animal. Arthropods have a central brain, the supraesophageal ganglion, with three divisions and large optical lobes behind each eye for visual processing. Cephalopods such as the octopus and squid have the largest brains of any invertebrates.

There are several invertebrate species whose brains have been studied intensively because they have properties that make them convenient for experimental work:

Fruit flies (Drosophila), because of the large array of techniques available for studying their genetics, have been a natural subject for studying the role of genes in brain development. In spite of the large evolutionary distance between insects and mammals, many aspects of Drosophila neurogenetics have been shown to be relevant to humans. The first biological clock genes, for example, were identified by examining Drosophila mutants that showed disrupted daily activity cycles. A search in the genomes of vertebrates revealed a set of analogous genes, which were found to play similar roles in the mouse biological clock—and therefore almost certainly in the human biological clock as well. Studies done on Drosophila, also show that most neuropil regions of the brain are continuously reorganized throughout life in response to specific living conditions. The nematode worm Caenorhabditis elegans, like Drosophila, has been studied largely because of its importance in genetics. In the early 1970s, Sydney Brenner chose it as a model organism for studying the way that genes control development. One of the advantages of working with this worm is that the body plan is very stereotyped: the nervous system of the hermaphrodite contains exactly 302 neurons, always in the same places, making identical synaptic connections in every worm. Brenner's team sliced worms into thousands of ultrathin sections and photographed each one under an electron microscope, then visually matched fibers from section to section, to map out every neuron and synapse in the entire body. The complete neuronal wiring diagram of C.elegans – its connectome was achieved. Nothing approaching this level of detail is available for any other organism, and the information gained has enabled a multitude of studies that would otherwise have not been possible. The sea slug Aplysia californica was chosen by Nobel Prize-winning neurophysiologist Eric Kandel as a model for studying the cellular basis of learning and memory, because of the simplicity and accessibility of its nervous system, and it has been examined in hundreds of experiments. Vertebrates A T-shaped object is made up of the cord at the bottom which feeds into a lower central mass. This is topped by a larger central mass with an arm extending from either side. The brain of a shark. The first vertebrates appeared over 500 million years ago (Mya), during the Cambrian period, and may have resembled the modern hagfish in form. Sharks appeared about 450 Mya, amphibians about 400 Mya, reptiles about 350 Mya, and mammals about 200 Mya. Each species has an equally long evolutionary history, but the brains of modern hagfishes, lampreys, sharks, amphibians, reptiles, and mammals show a gradient of size and complexity that roughly follows the evolutionary sequence. All of these brains contain the same set of basic anatomical components, but many are rudimentary in the hagfish, whereas in mammals the foremost part (the telencephalon) is greatly elaborated and expanded.

Brains are most simply compared in terms of their size. The relationship between brain size, body size and other variables has been studied across a wide range of vertebrate species. As a rule, brain size increases with body size, but not in a simple linear proportion. In general, smaller animals tend to have larger brains, measured as a fraction of body size. For mammals, the relationship between brain volume and body mass essentially follows a power law with an exponent of about 0.75. This formula describes the central tendency, but every family of mammals departs from it to some degree, in a way that reflects in part the complexity of their behavior. For example, primates have brains 5 to 10 times larger than the formula predicts. Predators tend to have larger brains than their prey, relative to body size.

The nervous system is shown as a rod with protrusions along its length. The spinal cord at the bottom connects to the hindbrain which widens out before narrowing again. This is connected to the midbrain, which again bulges, and which finally connects to the forebrain which has two large protrusions. The main subdivisions of the embryonic vertebrate brain (left), which later differentiate into structures of the adult brain (right). All vertebrate brains share a common underlying form, which appears most clearly during early stages of embryonic development. In its earliest form, the brain appears as three swellings at the front end of the neural tube; these swellings eventually become the forebrain, midbrain, and hindbrain (the prosencephalon, mesencephalon, and rhombencephalon, respectively). At the earliest stages of brain development, the three areas are roughly equal in size. In many classes of vertebrates, such as fish and amphibians, the three parts remain similar in size in the adult, but in mammals the forebrain becomes much larger than the other parts, and the midbrain becomes very small.

The brains of vertebrates are made of very soft tissue. Living brain tissue is pinkish on the outside and mostly white on the inside, with subtle variations in color. Vertebrate brains are surrounded by a system of connective tissue membranes called meninges that separate the skull from the brain. Blood vessels enter the central nervous system through holes in the meningeal layers. The cells in the blood vessel walls are joined tightly to one another, forming the blood–brain barrier, which blocks the passage of many toxins and pathogens (though at the same time blocking antibodies and some drugs, thereby presenting special challenges in treatment of diseases of the brain).

Neuroanatomists usually divide the vertebrate brain into six main regions: the telencephalon (cerebral hemispheres), diencephalon (thalamus and hypothalamus), mesencephalon (midbrain), cerebellum, pons, and medulla oblongata. Each of these areas has a complex internal structure. Some parts, such as the cerebral cortex and the cerebellar cortex, consist of layers that are folded or convoluted to fit within the available space. Other parts, such as the thalamus and hypothalamus, consist of clusters of many small nuclei. Thousands of distinguishable areas can be identified within the vertebrate brain based on fine distinctions of neural structure, chemistry, and connectivity.

Although the same basic components are present in all vertebrate brains, some branches of vertebrate evolution have led to substantial distortions of brain geometry, especially in the forebrain area. The brain of a shark shows the basic components in a straightforward way, but in teleost fishes (the great majority of existing fish species), the forebrain has become "everted", like a sock turned inside out. In birds, there are also major changes in forebrain structure. These distortions can make it difficult to match brain components from one species with those of another species.

Corresponding regions of human and shark brain are shown. The shark brain is splayed out, while the human brain is more compact. The shark brain starts with the medulla, which is surrounded by various structures, and ends with the telencephalon. The cross-section of the human brain shows the medulla at the bottom surrounded by the same structures, with the telencephalon thickly coating the top of the brain. The main anatomical regions of the vertebrate brain, shown for shark and human. The same parts are present, but they differ greatly in size and shape. Here is a list of some of the most important vertebrate brain components, along with a brief description of their functions as currently understood:

See also: List of regions in the human brain The medulla, along with the spinal cord, contains many small nuclei involved in a wide variety of sensory and involuntary motor functions such as vomiting, heart rate and digestive processes. The pons lies in the brainstem directly above the medulla. Among other things, it contains nuclei that control often voluntary but simple acts such as sleep, respiration, swallowing, bladder function, equilibrium, eye movement, facial expressions, and posture. The hypothalamus is a small region at the base of the forebrain, whose complexity and importance belies its size. It is composed of numerous small nuclei, each with distinct connections and neurochemistry. The hypothalamus is engaged in additional involuntary or partially voluntary acts such as sleep and wake cycles, eating and drinking, and the release of some hormones. The thalamus is a collection of nuclei with diverse functions: some are involved in relaying information to and from the cerebral hemispheres, while others are involved in motivation. The subthalamic area (zona incerta) seems to contain action-generating systems for several types of "consummatory" behaviors such as eating, drinking, defecation, and copulation. The cerebellum modulates the outputs of other brain systems, whether motor related or thought related, to make them certain and precise. Removal of the cerebellum does not prevent an animal from doing anything in particular, but it makes actions hesitant and clumsy. This precision is not built-in, but learned by trial and error. The muscle coordination learned while riding a bicycle is an example of a type of neural plasticity that may take place largely within the cerebellum. 10% of the brain's total volume consists of the cerebellum and 50% of all neurons are held within its structure. The optic tectum allows actions to be directed toward points in space, most commonly in response to visual input. In mammals it is usually referred to as the superior colliculus, and its best-studied function is to direct eye movements. It also directs reaching movements and other object-directed actions. It receives strong visual inputs, but also inputs from other senses that are useful in directing actions, such as auditory input in owls and input from the thermosensitive pit organs in snakes. In some primitive fishes, such as lampreys, this region is the largest part of the brain. The superior colliculus is part of the midbrain. The pallium is a layer of gray matter that lies on the surface of the forebrain and is the most complex and most recent evolutionary development of the brain as an organ. In reptiles and mammals, it is called the cerebral cortex. Multiple functions involve the pallium, including smell and spatial memory. In mammals, where it becomes so large as to dominate the brain, it takes over functions from many other brain areas. In many mammals, the cerebral cortex consists of folded bulges called gyri that create deep furrows or fissures called sulci. The folds increase the surface area of the cortex and therefore increase the amount of gray matter and the amount of information that can be stored and processed. The hippocampus, strictly speaking, is found only in mammals. However, the area it derives from, the medial pallium, has counterparts in all vertebrates. There is evidence that this part of the brain is involved in complex events such as spatial memory and navigation in fishes, birds, reptiles, and mammals. The basal ganglia are a group of interconnected structures in the forebrain. The primary function of the basal ganglia appears to be action selection: they send inhibitory signals to all parts of the brain that can generate motor behaviors, and in the right circumstances can release the inhibition, so that the action-generating systems are able to execute their actions. Reward and punishment exert their most important neural effects by altering connections within the basal ganglia. The olfactory bulb is a special structure that processes olfactory sensory signals and sends its output to the olfactory part of the pallium. It is a major brain component in many vertebrates, but is greatly reduced in humans and other primates (whose senses are dominated by information acquired by sight rather than smell). Mammals The most obvious difference between the brains of mammals and other vertebrates is in terms of size. On average, a mammal has a brain roughly twice as large as that of a bird of the same body size, and ten times as large as that of a reptile of the same body size.

Size, however, is not the only difference: there are also substantial differences in shape. The hindbrain and midbrain of mammals are generally similar to those of other vertebrates, but dramatic differences appear in the forebrain, which is greatly enlarged and also altered in structure. The cerebral cortex is the part of the brain that most strongly distinguishes mammals. In non-mammalian vertebrates, the surface of the cerebrum is lined with a comparatively simple three-layered structure called the pallium. In mammals, the pallium evolves into a complex six-layered structure called neocortex or isocortex. Several areas at the edge of the neocortex, including the hippocampus and amygdala, are also much more extensively developed in mammals than in other vertebrates.

The elaboration of the cerebral cortex carries with it changes to other brain areas. The superior colliculus, which plays a major role in visual control of behavior in most vertebrates, shrinks to a small size in mammals, and many of its functions are taken over by visual areas of the cerebral cortex. The cerebellum of mammals contains a large portion (the neocerebellum) dedicated to supporting the cerebral cortex, which has no counterpart in other vertebrates.

The brains of humans and other primates contain the same structures as the brains of other mammals, but are generally larger in proportion to body size. The encephalization quotient (EQ) is used to compare brain sizes across species. It takes into account the nonlinearity of the brain-to-body relationship. Humans have an average EQ in the 7-to-8 range, while most other primates have an EQ in the 2-to-3 range. Dolphins have values higher than those of primates other than humans, but nearly all other mammals have EQ values that are substantially lower.

Most of the enlargement of the primate brain comes from a massive expansion of the cerebral cortex, especially the prefrontal cortex and the parts of the cortex involved in vision. The visual processing network of primates includes at least 30 distinguishable brain areas, with a complex web of interconnections. It has been estimated that visual processing areas occupy more than half of the total surface of the primate neocortex. The prefrontal cortex carries out functions that include planning, working memory, motivation, attention, and executive control. It takes up a much larger proportion of the brain for primates than for other species, and an especially large fraction of the human brain.

6.2 The Human Brain

The human brain is the central organ of the human nervous system, and with the spinal cord makes up the central nervous system. The brain consists of the cerebrum, the brainstem and the cerebellum. It controls most of the activities of the body, processing, integrating, and coordinating the information it receives from the sense organs, and making decisions as to the instructions sent to the rest of the body. The brain is contained in, and protected by, the skull bones of the head.

The cerebrum is the largest part of the human brain. It is divided into two cerebral hemispheres.

The cerebral cortex is an outer layer of grey matter, covering the core of white matter. The cortex is split into the neocortex and the much smaller allocortex. The neocortex is made up of six neuronal layers, while the allocortex has three or four. Each hemisphere is conventionally divided into four lobes – the frontal, temporal, parietal, and occipital lobes. The frontal lobe is associated with executive functions including self-control, planning, reasoning, and abstract thought, while the occipital lobe is dedicated to vision. Within each lobe, cortical areas are associated with specific functions, such as the sensory, motor and association regions. Although the left and right hemispheres are broadly similar in shape and function, some functions are associated with one side, such as language in the left and visual-spatial ability in the right. The hemispheres are connected by commissural nerve tracts, the largest being the corpus callosum.

The cerebrum is connected by the brainstem to the spinal cord. The brainstem consists of the midbrain, the pons, and the medulla oblongata. The cerebellum is connected to the brainstem by pairs of tracts. Within the cerebrum is the ventricular system, consisting of four interconnected ventricles in which cerebrospinal fluid is produced and circulated. Underneath the cerebral cortex are several important structures, including the thalamus, the epithalamus, the pineal gland, the hypothalamus, the pituitary gland, and the subthalamus; the limbic structures, including the amygdala and the hippocampus; the claustrum, the various nuclei of the basal ganglia; the basal forebrain structures, and the three circumventricular organs. The cells of the brain include neurons and supportive glial cells. There are more than 86 billion neurons in the brain, and a more or less equal number of other cells. Brain activity is made possible by the interconnections of neurons and their release of neurotransmitters in response to nerve impulses. Neurons connect to form neural pathways, neural circuits, and elaborate network systems. The whole circuitry is driven by the process of neurotransmission.

The brain is protected by the skull, suspended in cerebrospinal fluid, and isolated from the bloodstream by the blood–brain barrier. However, the brain is still susceptible to damage, disease, and infection. Damage can be caused by trauma, or a loss of blood supply known as a stroke. The brain is susceptible to degenerative disorders, such as Parkinson's disease, dementias including Alzheimer's disease, and multiple sclerosis. Psychiatric conditions, including schizophrenia and clinical depression, are thought to be associated with brain dysfunctions. The brain can also be the site of tumours, both benign and malignant; these mostly originate from other sites in the body.

The study of the anatomy of the brain is neuroanatomy, while the study of its function is neuroscience. A number of techniques are used to study the brain. Specimens from other animals, which may be examined microscopically, have traditionally provided much information. Medical imaging technologies such as functional neuroimaging, and electroencephalography (EEG) recordings are important in studying the brain. The medical history of people with brain injury has provided insight into the function of each part of the brain. Brain research has evolved over time, with philosophical, experimental, and theoretical phases. The next phase has been predicted to be one of simulating brain activity.

The adult human brain weighs on average about 1.2–1.4 kg (2.6–3.1 lb) which is about 2% of the total body weight, with a volume of around 1260 cm3 in men and 1130 cm3 in women. There is substantial individual variation, with the standard reference range for men being 1,180–1,620 g (2.60–3.57 lb) and for women 1,030–1,400 g (2.27–3.09 lb).

The brain consumes up to 20% of the energy used by the human body, more than any other organ. In humans, blood glucose is the primary source of energy for most cells and is critical for normal function in a number of tissues, including the brain. The human brain consumes approximately 60% of blood glucose in fasted, sedentary individuals. Brain metabolism normally relies upon blood glucose as an energy source, but during times of low glucose (such as fasting, endurance exercise, or limited carbohydrate intake), the brain uses ketone bodies for fuel with a smaller need for glucose. The brain can also utilize lactate during exercise. The brain stores glucose in the form of glycogen, albeit in significantly smaller amounts than that found in the liver or skeletal muscle. Long-chain fatty acids cannot cross the blood–brain barrier, but the liver can break these down to produce ketone bodies. However, short-chain fatty acids (e.g., butyric acid, propionic acid, and acetic acid) and the medium-chain fatty acids, octanoic acid and heptanoic acid, can cross the blood–brain barrier and be metabolized by brain cells.

Although the human brain represents only 2% of the body weight, it receives 15% of the cardiac output, 20% of total body oxygen consumption, and 25% of total body glucose utilization. The brain mostly uses glucose for energy, and deprivation of glucose, as can happen in hypoglycemia, can result in loss of consciousness. The energy consumption of the brain does not vary greatly over time, but active regions of the cortex consume somewhat more energy than inactive regions: this fact forms the basis for the functional brain imaging methods PET and fMRI. These functional imaging techniques provide a three-dimensional image of metabolic activity.

The function of sleep is not fully understood; however, there is evidence that sleep enhances the clearance of metabolic waste products, some of which are potentially neurotoxic, from the brain and may also permit repair. Evidence suggests that the increased clearance of metabolic waste during sleep occurs via increased functioning of the glymphatic system. Sleep may also have an effect on cognitive function by weakening unnecessary connections. Neurological differences between the sexes have not been shown to correlate in any simple way with IQ or other measures of cognitive performance.

The cerebrum, consisting of the cerebral hemispheres, forms the largest part of the brain and overlies the other brain structures. The outer region of the hemispheres, the cerebral cortex, is grey matter, consisting of cortical layers of neurons. Each hemisphere is divided into four main lobes – the frontal lobe, parietal lobe, temporal lobe, and occipital lobe. Three other lobes are included by some sources which are a central lobe, a limbic lobe, and an insular lobe. The central lobe comprises the precentral gyrus and the postcentral gyrus and is included since it forms a distinct functional role.

The brainstem, resembling a stalk, attaches to and leaves the cerebrum at the start of the midbrain area. The brainstem includes the midbrain, the pons, and the medulla oblongata. Behind the brainstem is the cerebellum (Latin: little brain).

The cerebrum, brainstem, cerebellum, and spinal cord are covered by three membranes called meninges. The membranes are the tough dura mater; the middle arachnoid mater and the more delicate inner pia mater. Between the arachnoid mater and the pia mater is the subarachnoid space and subarachnoid cisterns, which contain the cerebrospinal fluid. The outermost membrane of the cerebral cortex is the basement membrane of the pia mater called the glia limitans and is an important part of the blood–brain barrier. The living brain is very soft, having a gel-like consistency similar to soft tofu. The cortical layers of neurons constitute much of the cerebral grey matter, while the deeper subcortical regions of myelinated axons, make up the white matter. he white matter of the brain makes up about half of the total brain volume.

6.3 The Cerebrum

The cerebrum is the largest part of the brain, and is divided into nearly symmetrical left and right hemispheres by a deep groove, the longitudinal fissure. Asymmetry between the lobes is noted as a petalia. The hemispheres are connected by five commissures that span the longitudinal fissure, the largest of these is the corpus callosum. Each hemisphere is conventionally divided into four main lobes; the frontal lobe, parietal lobe, temporal lobe, and occipital lobe, named according to the skull bones that overlie them. Each lobe is associated with one or two specialised functions though there is some functional overlap between them. The surface of the brain is folded into ridges (gyri) and grooves (sulci), many of which are named, usually according to their position, such as the frontal gyrus of the frontal lobe or the central sulcus separating the central regions of the hemispheres. There are many small variations in the secondary and tertiary folds.

The outer part of the cerebrum is the cerebral cortex, made up of grey matter arranged in layers. It is 2 to 4 millimetres (0.079 to 0.157 in) thick, and deeply folded to give a convoluted appearance. Beneath the cortex is the cerebral white matter. The largest part of the cerebral cortex is the neocortex, which has six neuronal layers. The rest of the cortex is of allocortex, which has three or four layers.

The cortex is mapped by divisions into about fifty different functional areas known as Brodmann's areas. These areas are distinctly different when seen under a microscope. The cortex is divided into two main functional areas – a motor cortex and a sensory cortex. The primary motor cortex, which sends axons down to motor neurons in the brainstem and spinal cord, occupies the rear portion of the frontal lobe, directly in front of the somatosensory area. The primary sensory areas receive signals from the sensory nerves and tracts by way of relay nuclei in the thalamus. Primary sensory areas include the visual cortex of the occipital lobe, the auditory cortex in parts of the temporal lobe and insular cortex, and the somatosensory cortex in the parietal lobe. The remaining parts of the cortex, are called the association areas. These areas receive input from the sensory areas and lower parts of the brain and are involved in the complex cognitive processes of perception, thought, and decision-making. The main functions of the frontal lobe are to control attention, abstract thinking, behaviour, problem solving tasks, and physical reactions and personality. The occipital lobe is the smallest lobe; its main functions are visual reception, visual-spatial processing, movement, and colour recognition. There is a smaller occipital lobule in the lobe known as the cuneus. The temporal lobe controls auditory and visual memories, language, and some hearing and speech.

Cortical folds and white matter in horizontal bisection of head The cerebrum contains the ventricles where the cerebrospinal fluid is produced and circulated. Below the corpus callosum is the septum pellucidum, a membrane that separates the lateral ventricles. Beneath the lateral ventricles is the thalamus and to the front and below this is the hypothalamus. The hypothalamus leads on to the pituitary gland. At the back of the thalamus is the brainstem.

The basal ganglia, also called basal nuclei, are a set of structures deep within the hemispheres involved in behaviour and movement regulation. The largest component is the striatum, others are the globus pallidus, the substantia nigra and the subthalamic nucleus. Part of the dorsal striatum, the putamen, and the globus pallidus, lie separated from the lateral ventricles and thalamus by the internal capsule, whereas the caudate nucleus stretches around and abuts the lateral ventricles on their outer sides. At the deepest part of the lateral sulcus between the insular cortex and the striatum is a thin neuronal sheet called the claustrum.

Below and in front of the striatum are a number of basal forebrain structures. These include the nucleus accumbens, nucleus basalis, diagonal band of Broca, substantia innominata, and the medial septal nucleus. These structures are important in producing the neurotransmitter, acetylcholine, which is then distributed widely throughout the brain. The basal forebrain, in particular the nucleus basalis, is considered to be the major cholinergic output of the central nervous system to the striatum and neocortex. The cerebrum or telencephalon is a large part of the brain containing the cerebral cortex (of the two cerebral hemispheres), as well as several subcortical structures, including the hippocampus, basal ganglia, and olfactory bulb. In the human brain, the cerebrum is the uppermost region of the central nervous system. The prosencephalon or forebrain is the embryonic structure from which the cerebrum develops prenatally. In mammals, the dorsal telencephalon, or pallium, develops into the cerebral cortex, and the ventral telencephalon, or subpallium, becomes the basal ganglia. The cerebrum is also divided into approximately symmetric left and right cerebral hemispheres.

With the assistance of the cerebellum, the cerebrum controls all voluntary actions in the human body.

The cerebrum is the largest part of the brain. Depending upon the position of the animal it lies either in front or on top of the brainstem. In humans, the cerebrum is the largest and best-developed of the five major divisions of the brain.

The cerebrum is made up of the two cerebral hemispheres and their cortices, (the outer layers of grey matter), and the underlying regions of white matter. Its subcortical structures include the hippocampus, basal ganglia and olfactory bulb. The cerebrum consists of two C-shaped cerebral hemispheres, separated from each other by a deep fissure called the longitudinal fissure.

Cerebral cortex

Surface of the cerebrum The cerebral cortex, the outer layer of grey matter of the cerebrum, is found only in mammals. In larger mammals, including humans, the surface of the cerebral cortex folds to create gyri (ridges) and sulci (furrows) which increase the surface area.

The cerebral cortex is generally classified into four lobes: the frontal, parietal, occipital and temporal lobes. The lobes are classified based on their overlying neurocranial bones.

Cerebral hemispheres The cerebrum is divided by the medial longitudinal fissure into two cerebral hemispheres, the right and the left. The cerebrum is contralaterally organized, i.e., right hemisphere controls and processes signals from the left side of the body, while the left hemisphere controls and processes signals from the right side of the body. There is a strong but not complete bilateral symmetry between the hemispheres. The lateralization of brain function looks at the known and possible differences between the two.

The diencephalon is a division of the forebrain (embryonic prosencephalon), and is situated between the telencephalon and the midbrain (embryonic mesencephalon). It consists of structures that are on either side of the third ventricle, including the thalamus, the hypothalamus, the epithalamus and the subthalamus.

The diencephalon is the region of the embryonic vertebrate neural tube that gives rise to anterior forebrain structures including the thalamus, hypothalamus, posterior portion of the pituitary gland,

and the pineal gland. The diencephalon encloses a cavity called the third ventricle. The thalamus serves as a relay centre for sensory and motor impulses between the spinal cord and medulla oblongata, and the cerebrum. It recognizes sensory impulses of heat, cold, pain, pressure etc. The floor of the third ventricle is called the hypothalamus. It has control centres for control of eye movement and hearing responses.

The diencephalon is one of the main vesicles of the brain formed during embryogenesis. During the third week of development a neural tube is created from the ectoderm, one of the three primary germ layers. The tube forms three main vesicles during the third week of development: the prosencephalon, the mesencephalon and the rhombencephalon. The prosencephalon gradually divides into the telencephalon and the diencephalon.

6.3.1 Thalamus

The thalamus (from Greek , "chamber") is a large mass of gray matter located in the dorsal part of the diencephalon (a division of the forebrain). Nerve fibers project out of the thalamus to the cerebral cortex in all directions, allowing hub-like exchanges of information. It has several functions, such as relaying of sensory signals, including motor signals to the cerebral cortex,[page needed] and the regulation of consciousness, sleep, and alertness.

Anatomically, it is a midline symmetrical structure of two halves (left and right), within the vertebrate brain, situated between the cerebral cortex and the midbrain. It forms during embryonic development as the main product of the diencephalon, as first recognized by the Swiss embryologist and anatomist Wilhelm His Sr. in 1893.

The thalamus has many connections to the hippocampus via the mammillothalamic tract, this tract comprises the mammillary bodies and fornix.

The thalamus is connected to the cerebral cortex via the thalamocortical radiations.

The spinothalamic tract is a sensory pathway originating in the spinal cord. It transmits information to the thalamus about pain, temperature, itch and crude touch. There are two main parts: the lateral spinothalamic tract, which transmits pain and temperature, and the anterior (or ventral) spinothalamic tract, which transmits crude touch and pressure.

The thalamus has multiple functions, generally believed to act as a relay station, or hub, relaying information between different subcortical areas and the cerebral cortex. In particular, every sensory system (with the exception of the olfactory system) includes a thalamic nucleus that receives sensory signals and sends them to the associated primary cortical area.[citation needed] For the visual system, for example, inputs from the retina are sent to the lateral geniculate nucleus of the thalamus, which in turn projects to the visual cortex in the occipital lobe.[citation needed] The thalamus is believed to both process sensory information as well as relay it—each of the primary sensory relay areas receives strong feedback connections from the cerebral cortex.[citation needed] Similarly the medial geniculate nucleus acts as a key auditory relay between the inferior colliculus of the midbrain and the primary auditory cortex.[citation needed] The ventral posterior nucleus is a key somatosensory relay, which sends touch and proprioceptive information to the primary somatosensory cortex.[citation needed]

The thalamus also plays an important role in regulating states of sleep and wakefulness. Thalamic nuclei have strong reciprocal connections with the cerebral cortex, forming thalamo-corticothalamic circuits that are believed to be involved with consciousness. The thalamus plays a major role in regulating arousal, the level of awareness, and activity. Damage to the thalamus can lead to permanent coma.

The role of the thalamus in the more anterior pallidal and nigral territories in the basal ganglia system disturbances is recognized but still poorly understood. The contribution of the thalamus to vestibular or to tectal functions is almost ignored. The thalamus has been thought of as a "relay" that simply forwards signals to the cerebral cortex. Newer research suggests that thalamic function is more selective. Many different functions are linked to various regions of the thalamus. This is the case for many of the sensory systems (except for the olfactory system), such as the auditory, somatic, visceral, gustatory and visual systems where localized lesions provoke specific sensory deficits. A major role of the thalamus is support of motor and language systems, and much of the circuitry implicated for these systems is shared. The thalamus is functionally connected to the hippocampus as part of the extended hippocampal system at the thalamic anterior nuclei with respect to spatial memory and spatial sensory datum they are crucial for human episodic memory and rodent event memory. There is support for the hypothesis that thalamic regions connection to particular parts of the mesio-temporal lobe provide differentiation of the functioning of recollective and familiarity memory.

The neuronal information processes necessary for motor control were proposed as a network involving the thalamus as a subcortical motor center. Through investigations of the anatomy of the brains of primates the nature of the interconnected tissues of the cerebellum to the multiple motor cortices suggested that the thalamus fulfills a key function in providing the specific channels from the basal ganglia and cerebellum to the cortical motor areas. In an investigation of the saccade and antisaccade motor response in three monkeys, the thalamic regions were found to be involved in the generation of antisaccade eye-movement (that is, the ability to inhibit the reflexive jerking movement of the eyes in the direction of a presented stimulus].

Recent research suggests that the mediodorsal thalamus may play a broader role in cognition. Specifically, the mediodorsal thalamus may "amplify the connectivity (signaling strength) of just the circuits in the cortex appropriate for the current context and thereby contribute to the flexibility (of the mammalian brain) to make complex decisions by wiring the many associations on which decisions depend into weakly connected cortical circuits." Researchers founds that "enhancing MD activity magnified the ability of mice to "think," driving down by more than 25 percent their error rate in deciding which conflicting sensory stimuli to follow to find the reward."

Hypothalamus

The hypothalamus is a portion of the brain that contains a number of small nuclei with a variety of functions. One of the most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland. The hypothalamus is located below the thalamus and is part of the limbic system. In the terminology of neuroanatomy, it forms the ventral part of the diencephalon. All vertebrate brains contain a hypothalamus. In humans, it is the size of an almond. The hypothalamus is responsible for the regulation of certain metabolic processes and other activities of the autonomic nervous system. It synthesizes and secretes certain neurohormones, called releasing hormones or hypothalamic hormones, and these in turn stimulate or inhibit the secretion of hormones from the pituitary gland. The hypothalamus controls body temperature, hunger, important aspects of parenting and attachment behaviours, thirst, fatigue, sleep, and circadian rhythms. The hypothalamus derives its name from Greek , under and , chamber.

The hypothalamus has a central neuroendocrine function, most notably by its control of the anterior pituitary, which in turn regulates various endocrine glands and organs. Releasing hormones (also called releasing factors) are produced in hypothalamic nuclei then transported along axons to either the median eminence or the posterior pituitary, where they are stored and released as needed.

Anterior pituitary In the hypothalamic–adenohypophyseal axis, releasing hormones, also known as hypophysiotropic or hypothalamic hormones, are released from the median eminence, a prolongation of the hypothalamus, into the hypophyseal portal system, which carries them to the anterior pituitary where they exert their regulatory functions on the secretion of adenohypophyseal hormones. These hypophysiotropic hormones are stimulated by parvocellular neurosecretory cells located in the periventricular area of the hypothalamus. After their release into the capillaries of the third ventricle, the hypophysiotropic hormones travel through what is known as the hypothalamo-pituitary portal circulation. Once they reach their destination in the anterior pituitary, these hormones bind to specific receptors located on the surface of pituitary cells. Depending on which cells are activated through this binding, the pituitary will either begin secreting or stop secreting hormones into the rest of the bloodstream.

6.3.2 Cerebellum

The cerebellum is divided into an anterior lobe, a posterior lobe, and the flocculonodular lobe. The anterior and posterior lobes are connected in the middle by the vermis. Compared to the cerebral cortex, the cerebellum has a much thinner outer cortex that is narrowly furrowed into numerous curved transverse fissures. Viewed from underneath between the two lobes is the third lobe the flocculonodular lobe. The cerebellum rests at the back of the cranial cavity, lying beneath the occipital lobes, and is separated from these by the cerebellar tentorium, a sheet of fibre.

It is connected to the midbrain of the brainstem by the superior cerebellar peduncles, to the pons by the middle cerebellar peduncles, and to the medulla by the inferior cerebellar peduncles. The cerebellum consists of an inner medulla of white matter and an outer cortex of richly folded grey matter. The cerebellum's anterior and posterior lobes appear to play a role in the coordination and smoothing of complex motor movements, and the flocculonodular lobe in the maintenance of balance although debate exists as to its cognitive, behavioural and motor functions.

6.3.3 Cerebellum

The cerebellum (Latin for "little brain") is a major feature of the hindbrain of all vertebrates. Although usually smaller than the cerebrum, in some animals such as the mormyrid fishes it may be as large as or even larger. In humans, the cerebellum plays an important role in motor control. It may also be involved in some cognitive functions such as attention and language as well as in regulating fear and pleasure responses, but its movement-related functions are the most solidly established. The human cerebellum does not initiate movement, but contributes to coordination, precision, and accurate timing: it receives input from sensory systems of the spinal cord and from other parts of the brain, and integrates these inputs to fine-tune motor activity. Cerebellar damage produces disorders in fine movement, equilibrium, posture, and motor learning in humans.

Anatomically, the human cerebellum has the appearance of a separate structure attached to the bottom of the brain, tucked underneath the cerebral hemispheres. Its cortical surface is covered with finely spaced parallel grooves, in striking contrast to the broad irregular convolutions of the cerebral cortex. These parallel grooves conceal the fact that the cerebellar cortex is actually a continuous thin layer of tissue tightly folded in the style of an accordion. Within this thin layer are several types of neurons with a highly regular arrangement, the most important being Purkinje cells and granule cells. This complex neural organization gives rise to a massive signal-processing capability, but almost all of the output from the cerebellar cortex passes through a set of small deep nuclei lying in the white matter interior of the cerebellum.

In addition to its direct role in motor control, the cerebellum is necessary for several types of motor learning, most notably learning to adjust to changes in sensorimotor relationships.

At the level of gross anatomy, the cerebellum consists of a tightly folded layer of cortex, with white matter underneath and a fluid-filled ventricle at the base. Four deep cerebellar nuclei are embedded in the white matter. Each part of the cortex consists of the same small set of neuronal elements, laid out in a highly stereotyped geometry. At an intermediate level, the cerebellum and its auxiliary structures can be separated into several hundred or thousand independently functioning modules called "microzones" or "microcompartments".

Gross anatomy

View of the cerebellum from above and behind The cerebellum is located in the posterior cranial fossa. The fourth ventricle, pons and medulla are in front of the cerebellum. It is separated from the overlying cerebrum by a layer of leathery dura mater, the tentorium cerebelli; all of its connections with other parts of the brain travel through the pons. Anatomists classify the cerebellum as part of the metencephalon, which also includes the pons; the metencephalon is the upper part of the rhombencephalon or "hindbrain". Like the cerebral cortex, the cerebellum is divided into two hemispheres; it also contains a narrow midline zone (the vermis). A set of large folds is, by convention, used to divide the overall structure into 10 smaller "lobules". Because of its large number of tiny granule cells, the cerebellum contains more neurons than the total from the rest of the brain, but takes up only 10% of the total brain volume. The number of neurons in the cerebellum is related to the number of neurons in the neocortex. There are about 3.6 times as many neurons in the cerebellum as in the neocortex, a ratio that is conserved across many different mammalian species.

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 gray matter: the cerebellar cortex. Each ridge or gyrus in this layer is called a folium. It is estimated that, if the human cerebellar cortex were completely unfolded, it would give rise to a layer of neural tissue about 1 meter long and averaging 5 centimeters wide—a total surface area of about 500 square cm, packed within a volume of dimensions 6 cm $\times$ 5 cm $\times$ 10 cm. Underneath the gray matter of the cortex lies white matter, made up largely of myelinated nerve fibers running to and from the cortex. Embedded within the white matter—which is sometimes called the arbor vitae (tree of life) because of its branched, tree-like appearance in cross-section—are four deep cerebellar nuclei, composed of gray matter.

Connecting the cerebellum to different parts of the nervous system are three paired cerebellar peduncles. These are the superior cerebellar peduncle, the middle cerebellar peduncle and the inferior cerebellar peduncle, named by their position relative to the vermis. The superior cerebellar peduncle is mainly an output to the cerebral cortex, carrying efferent fibers via thalamic nuclei to upper motor neurons in the cerebral cortex. The fibers arise from the deep cerebellar nuclei. The middle cerebellar peduncle is connected to the pons and receives all of its input from the pons mainly from the pontine nuclei. The input to the pons is from the cerebral cortex and is relayed from the pontine nuclei via transverse pontine fibers to the cerebellum. The middle peduncle is the largest of the three and its afferent fibers are grouped into three separate fascicles taking their inputs to different parts of the cerebellum. The inferior cerebellar peduncle receives input from afferent fibers from the vestibular nuclei, spinal cord and the tegmentum. Output from the inferior peduncle is via efferent fibers to the vestibular nuclei and the reticular formation. The whole of the cerebellum receives modulatory input from the inferior olivary nucleus via the inferior cerebellar peduncle.

Subdivisions

Schematic representation of the major anatomical subdivisions of the cerebellum. Superior view of an "unrolled" cerebellum, placing the vermis in one plane. Based on the surface appearance, three lobes can be distinguished within the cerebellum: the anterior lobe (above the primary fissure), the posterior lobe (below the primary fissure), and the flocculonodular lobe (below the posterior fissure). These lobes divide the cerebellum from rostral to caudal (in humans, top to bottom). In terms of function, however, there is a more important distinction along the medial-to-lateral dimension. Leaving out the flocculonodular lobe, which has distinct connections and functions, the cerebellum can be parsed 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 cerebellar vermis. (Vermis is Latin for "worm".)

The smallest region, the flocculonodular lobe, is often called the vestibulocerebellum. It is the oldest part in evolutionary terms (archicerebellum) 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. Damage to this region causes disturbances of balance and gait.

The medial zone of the anterior and posterior lobes constitutes the spinocerebellum, also known as paleocerebellum. This sector of the cerebellum functions mainly to fine-tune body and limb movements. It receives proprioceptive input from the dorsal columns of the spinal cord (including the spinocerebellar tract) and from the cranial trigeminal nerve, as well as from visual and auditory systems. It sends fibers to deep cerebellar nuclei that, in turn, project to both the cerebral cortex and the brain stem, thus providing modulation of descending motor systems.

The lateral zone, which in humans is by far the largest part, constitutes the cerebrocerebellum, also known as neocerebellum. It receives input exclusively from the cerebral cortex (especially the parietal lobe) via the pontine nuclei (forming cortico-ponto-cerebellar pathways), and sends output mainly to the ventrolateral thalamus (in turn connected to motor areas of the premotor cortex and primary motor area of the cerebral cortex) and to the red nucleus. There is disagreement about the best way to describe the functions of the lateral cerebellum: It is thought to be involved in planning movement that is about to occur, in evaluating sensory information for action, and in a number of purely cognitive functions, such as determining the verb which best fits with a certain noun (as in "sit" for "chair").

Microanatomy Two types of neuron play dominant roles in the cerebellar circuit: Purkinje cells and granule cells. Three types of axons also play dominant roles: mossy fibers and climbing fibers (which enter the cerebellum from outside), and parallel fibers (which are the axons of granule cells). There are two main pathways through the cerebellar circuit, originating from mossy fibers and climbing fibers, both eventually terminating in the deep cerebellar nuclei.

Mossy fibers project directly to the deep nuclei, but also give rise to the following pathway: mossy fibers → granule cells → parallel fibers → Purkinje cells → deep nuclei. Climbing fibers project to Purkinje cells and also send collaterals directly to the deep nuclei. The mossy fiber and climbing fiber inputs each carry fiber-specific information; the cerebellum also receives dopaminergic, serotonergic, noradrenergic, and cholinergic inputs that presumably perform global modulation.

The cerebellar cortex is divided into three layers. At the bottom lies the thick granular layer, densely packed with granule cells, along with interneurons, mainly Golgi cells but also including Lugaro cells and unipolar brush cells. In the middle lies the Purkinje layer, a narrow zone that contains the cell bodies of Purkinje cells and Bergmann glial cells. At the top lies the molecular layer, which contains the flattened dendritic trees of Purkinje cells, along with the huge array of parallel fibers penetrating the Purkinje cell dendritic trees at right angles. This outermost layer of the cerebellar cortex also contains two types of inhibitory interneuron: stellate cells and basket cells. Both stellate and basket cells form GABAergic synapses onto Purkinje cell dendrites.

Purkinje cells

Purkinje cells in the human cerebellum (in orange, from top to bottom 40X, 100X and 200X magnification) stained according to published methods Purkinje cells are among the most distinctive neurons in the brain, and one of the earliest types to be recognized—they were first described by the Czech anatomist Jan Evangelista Purkyně in 1837. They are distinguished by the shape of their dendritic tree: The dendrites branch very profusely, but are severely flattened in a plane perpendicular to the cerebellar folds. Thus, the dendrites of a Purkinje cell form a dense planar net, through which parallel fibers pass at right angles. The dendrites are covered with dendritic spines, each of which receives synaptic input from a parallel fiber. Purkinje cells receive more synaptic inputs than any other type of cell in the brain—estimates of the number of spines on a single human Purkinje cell run as high as 200,000. The large, spherical cell bodies of Purkinje cells are packed into a narrow layer (one cell thick) of the cerebellar cortex, called the Purkinje layer. After emitting collaterals that affect nearby parts of the cortex, their axons travel into the deep cerebellar nuclei, where they make on the order of 1,000 contacts each with several types of nuclear cells, all within a small domain. Purkinje cells use GABA as their neurotransmitter, and therefore exert inhibitory effects on their targets.

Purkinje cells form the heart of the cerebellar circuit, and their large size and distinctive activity patterns have made it relatively easy to study their response patterns in behaving animals using extracellular recording techniques. Purkinje cells normally emit action potentials at a high rate even in the absence of the synaptic input. In awake, behaving animals, mean rates averaging around 40 Hz are typical. The spike trains show a mixture of what are called simple and complex spikes. A simple spike is a single action potential followed by a refractory period of about 10 ms; a complex spike is a stereotyped sequence of action potentials with very short inter-spike intervals and declining amplitudes. Physiological studies have shown that complex spikes (which occur at baseline rates around 1 Hz and never at rates much higher than 10 Hz) are reliably associated with climbing fiber activation, while simple spikes are produced by a combination of baseline activity and parallel fiber input. Complex spikes are often followed by a pause of several hundred milliseconds during which simple spike activity is suppressed.

A specific, recognizable feature of Purkinje neurons is the expression of calbindin. Calbindin staining of rat brain after unilateral chronic sciatic nerve injury suggests that Purkinje neurons may be newly generated in the adult brain, initiating the organization of new cerebellar lobules.

Granule cells

Granule cells (GR, bottom), parallel fibers (horizontal lines, top), and Purkinje cells (P, middle) with flattened dendritic trees Cerebellar granule cells, in contrast to Purkinje cells, are among the smallest neurons in the brain. They are also easily the most numerous neurons in the brain: In humans, estimates of their total number average around 50 billion, which means that about 3/4 of the brain's neurons are cerebellar granule cells. Their cell bodies are packed into a thick layer at the bottom of the cerebellar cortex. A granule cell emits only four to five dendrites, each of which ends in an enlargement called a dendritic claw. These enlargements are sites of excitatory input from mossy fibers and inhibitory input from Golgi cells.

The thin, unmyelinated axons of granule cells rise vertically to the upper (molecular) layer of the cortex, where they split in two, with each branch traveling horizontally to form a parallel fiber; the splitting of the vertical branch into two horizontal branches gives rise to a distinctive "T" shape. A human parallel fiber runs for an average of 3 mm in each direction from the split, for a total length of about 6 mm (about 1/10 of the total width of the cortical layer). As they run along, the parallel fibers pass through the dendritic trees of Purkinje cells, contacting one of every 3–5 that they pass, making a total of 80–100 synaptic connections with Purkinje cell dendritic spines. Granule cells use glutamate as their neurotransmitter, and therefore exert excitatory effects on their targets.

Granule cells receive all of their input from mossy fibers, but outnumber them by 200 to 1 (in humans). Thus, the information in the granule cell population activity state is the same as the information in the mossy fibers, but recoded in a much more expansive way. Because granule cells are so small and so densely packed, it is difficult to record their spike activity in behaving animals, so there is little data to use as a basis for theorizing. The most popular concept of their function was proposed in 1969 by David Marr, who suggested that they could encode combinations of mossy fiber inputs. The idea is that with each granule cell receiving input from only 4–5 mossy fibers, a granule cell would not respond if only a single one of its inputs were active, but would respond if more than one were active. This combinatorial coding scheme would potentially allow the cerebellum to make much finer distinctions between input patterns than the mossy fibers alone would permit.

Mossy fibers Mossy fibers enter the granular layer from their points of origin, many arising from the pontine nuclei, others from the spinal cord, vestibular nuclei etc. In the human cerebellum, the total number of mossy fibers has been estimated at about 200 million. These fibers form excitatory synapses with the granule cells and the cells of the deep cerebellar nuclei. Within the granular layer, a mossy fiber generates a series of enlargements called rosettes. The contacts between mossy fibers and granule cell dendrites take place within structures called glomeruli. Each glomerulus has a mossy fiber rosette at its center, and up to 20 granule cell dendritic claws contacting it. Terminals from Golgi cells infiltrate the structure and make inhibitory synapses onto the granule cell dendrites. The entire assemblage is surrounded by a sheath of glial cells. Each mossy fiber sends collateral branches to several cerebellar folia, generating a total of 20–30 rosettes; thus a single mossy fiber makes contact with an estimated 400–600 granule cells.

Climbing fibers Purkinje cells also receive input from the inferior olivary nucleus on the contralateral side of the brainstem via climbing fibers. Although the inferior olive lies in the medulla oblongata and receives input from the spinal cord, brainstem and cerebral cortex, its output goes entirely to the cerebellum. A climbing fiber gives off collaterals to the deep cerebellar nuclei before entering the cerebellar cortex, where it splits into about 10 terminal branches, each of which gives input to a single Purkinje cell. In striking contrast to the 100,000-plus inputs from parallel fibers, each Purkinje cell receives input from exactly one climbing fiber; but this single fiber "climbs" the dendrites of the Purkinje cell, winding around them and making a total of up to 300 synapses as it goes. The net input is so strong that a single action potential from a climbing fiber is capable of producing an extended complex spike in the Purkinje cell: a burst of several spikes in a row, with diminishing amplitude, followed by a pause during which activity is suppressed. The climbing fiber synapses cover the cell body and proximal dendrites; this zone is devoid of parallel fiber inputs.

Climbing fibers fire at low rates, but a single climbing fiber action potential induces a burst of several action potentials in a target Purkinje cell (a complex spike). The contrast between parallel fiber and climbing fiber inputs to Purkinje cells (over 100,000 of one type versus exactly one of the other type) is perhaps the most provocative feature of cerebellar anatomy, and has motivated much of the theorizing. In fact, the function of climbing fibers is the most controversial topic concerning the cerebellum. There are two schools of thought, one following Marr and Albus in holding that climbing fiber input serves primarily as a teaching signal, the other holding that its function is to shape cerebellar output directly. Both views have been defended in great length in numerous publications. In the words of one review, "In trying to synthesize the various hypotheses on the function of the climbing fibers, one has the sense of looking at a drawing by Escher. Each point of view seems to account for a certain collection of findings, but when one attempts to put the different views together, a coherent picture of what the climbing fibers are doing does not appear. For the majority of researchers, the climbing fibers signal errors in motor performance, either in the usual manner of discharge frequency modulation or as a single announcement of an 'unexpected event'. For other investigators, the message lies in the degree of ensemble synchrony and rhythmicity among a population of climbing fibers."

Deep nuclei Main article: Deep cerebellar nuclei

Sagittal cross-section of human cerebellum, showing the dentate nucleus, as well as the pons and inferior olivary nucleus The deep nuclei of the cerebellum are clusters of gray matter lying within the white matter at the core of the cerebellum. They are, with the minor exception of the nearby vestibular nuclei, the sole sources of output from the cerebellum. These nuclei receive collateral projections from mossy fibers and climbing fibers as well as inhibitory input from the Purkinje cells of the cerebellar cortex. The four nuclei (dentate, globose, emboliform, and fastigial) each communicate with different parts of the brain and cerebellar cortex. (The globose and the emboliform nuclei are also referred to as combined in the interposed nucleus). The fastigial and interposed nuclei belong to the spinocerebellum. The dentate nucleus, which in mammals is much larger than the others, is formed as a thin, convoluted layer of gray matter, and communicates exclusively with the lateral parts of the cerebellar cortex. The flocculonodular lobe is the only part of the cerebellar cortex that does not project to the deep nuclei—its output goes to the vestibular nuclei instead.

The majority of neurons in the deep nuclei have large cell bodies and spherical dendritic trees with a radius of about 400 m, and use glutamate as their neurotransmitter. These cells project to a variety of targets outside the cerebellum. Intermixed with them are a lesser number of small cells, which use GABA as a neurotransmitter and project exclusively to the inferior olivary nucleus, the source of climbing fibers. Thus, the nucleo-olivary projection provides an inhibitory feedback to match the excitatory projection of climbing fibers to the nuclei. There is evidence that each small cluster of nuclear cells projects to the same cluster of olivary cells that send climbing fibers to it; there is strong and matching topography in both directions.

When a Purkinje cell axon enters one of the deep nuclei, it branches to make contact with both large and small nuclear cells, but the total number of cells contacted is only about 35 (in cats). Conversely, a single deep nuclear cell receives input from approximately 860 Purkinje cells (again in cats).

Compartments

Schematic illustration of the structure of zones and microzones in the cerebellar cortex From the viewpoint of gross anatomy, the cerebellar cortex appears to be a homogeneous sheet of tissue, and, from the viewpoint of microanatomy, all parts of this sheet appear to have the same internal structure. There are, however, a number of respects in which the structure of the cerebellum is compartmentalized. There are large compartments that are generally known as zones; these can be divided into smaller compartments known as microzones.

The first indications of compartmental structure came from studies of the receptive fields of cells in various parts of the cerebellar cortex. Each body part maps to specific points in the cerebellum, but there are numerous repetitions of the basic map, forming an arrangement that has been called "fractured somatotopy". A clearer indication of compartmentalization is obtained by immunostaining the cerebellum for certain types of protein. The best-known of these markers are called "zebrins", because staining for them gives rise to a complex pattern reminiscent of the stripes on a zebra. The stripes generated by zebrins and other compartmentalization markers are oriented perpendicular to the cerebellar folds—that is, they are narrow in the mediolateral direction, but much more extended in the longitudinal direction. Different markers generate different sets of stripes, the widths and lengths vary as a function of location, but they all have the same general shape.

Oscarsson in the late 1970s proposed that these cortical zones can be partitioned into smaller units called microzones. A microzone is defined as a group of Purkinje cells all having the same somatotopic receptive field. Microzones were found to contain on the order of 1000 Purkinje cells each, arranged in a long, narrow strip, oriented perpendicular to the cortical folds. Thus, as the adjoining diagram illustrates, Purkinje cell dendrites are flattened in the same direction as the microzones extend, while parallel fibers cross them at right angles.

It is not only receptive fields that define the microzone structure: The climbing fiber input from the inferior olivary nucleus is equally important. The branches of a climbing fiber (usually numbering about 10) usually activate Purkinje cells belonging to the same microzone. Moreover, olivary neurons that send climbing fibers to the same microzone tend to be coupled by gap junctions, which synchronize their activity, causing Purkinje cells within a microzone to show correlated complex spike activity on a millisecond time scale. Also, the Purkinje cells belonging to a microzone all send their axons to the same small cluster of output cells within the deep cerebellar nuclei. Finally, the axons of basket cells are much longer in the longitudinal direction than in the mediolateral direction, causing them to be confined largely to a single microzone. The consequence of all this structure is that cellular interactions within a microzone are much stronger than interactions between different microzones.

In 2005, Richard Apps and Martin Garwicz summarized evidence that microzones themselves form part of a larger entity they call a multizonal microcomplex. Such a microcomplex includes several spatially separated cortical microzones, all of which project to the same group of deep cerebellar neurons, plus a group of coupled olivary neurons that project to all of the included microzones as well as to the deep nuclear area.

Blood supply The cerebellum is provided with blood from three paired major arteries: the superior cerebellar artery (SCA), the anterior inferior cerebellar artery (AICA), and the posterior inferior cerebellar artery (PICA). The SCA supplies the upper region of the cerebellum. It divides at the upper surface and branches into the pia mater where the branches anastomose with those of the anterior and posterior inferior cerebellar arteries. The AICA supplies the front part of the undersurface of the cerebellum. The PICA arrives at the undersurface, where it divides into a medial branch and a lateral branch. The medial branch continues backward to the cerebellar notch between the two hemispheres of the cerebellum; while the lateral branch supplies the under surface of the cerebellum, as far as its lateral border, where it anastomoses with the AICA and the SCA.

Function The strongest clues to the function of the cerebellum have come from examining the consequences of damage to it. Animals and humans with cerebellar dysfunction show, above all, problems with motor control, on the same side of the body as the damaged part of the cerebellum. They continue to be able to generate motor activity but lose precision, producing erratic, uncoordinated, or incorrectly timed movements. A standard test of cerebellar function is to reach with the tip of the finger for a target at arm's length: A healthy person will move the fingertip in a rapid straight trajectory, whereas a person with cerebellar damage will reach slowly and erratically, with many mid-course corrections. Deficits in non-motor functions are more difficult to detect. Thus, the general conclusion reached decades ago is that the basic function of the cerebellum is to calibrate the detailed form of a movement, not to initiate movements or to decide which movements to execute.

Prior to the 1990s the function of the cerebellum was almost universally believed to be purely motor-related, but newer findings have brought that view into question. Functional imaging studies have shown cerebellar activation in relation to language, attention, and mental imagery; correlation studies have shown interactions between the cerebellum and non-motor areas of the cerebral cortex; and a variety of non-motor symptoms have been recognized in people with damage that appears to be confined to the cerebellum. In particular, the cerebellar cognitive affective syndrome or Schmahmann's syndrome has been described in adults and children. Estimates based on functional mapping of the cerebellum using functional MRI suggest that more than half of the cerebellar cortex is interconnected with association zones of the cerebral cortex.

Kenji Doya has argued that the cerebellum's function is best understood not in terms of the behaviors it affects, but the neural computations it performs; the cerebellum consists of a large number of more or less independent modules, all with the same geometrically regular internal structure, and therefore all, it is presumed, performing the same computation. If the input and output connections of a module are with motor areas (as many are), then the module will be involved in motor behavior; but, if the connections are with areas involved in non-motor cognition, the module will show other types of behavioral correlates. Thus the cerebellum has been implicated in the regulation of many differing functional traits such as affection, emotion and behavior. The cerebellum, Doya proposes, is best understood as predictive action selection based on "internal models" of the environment or a device for supervised learning, in contrast to the basal ganglia, which perform reinforcement learning, and the cerebral cortex, which performs unsupervised learning.

Damage to the cerebellum often causes motor-related symptoms, the details of which depend on the part of the cerebellum involved and how it is damaged. Damage to the flocculonodular lobe may show up as a loss of equilibrium and in particular an altered, irregular walking gait, with a wide stance caused by difficulty in balancing. Damage to the lateral zone typically causes problems in skilled voluntary and planned movements which can cause errors in the force, direction, speed and amplitude of movements. Other manifestations include hypotonia (decreased muscle tone), dysarthria (problems with speech articulation), dysmetria (problems judging distances or ranges of movement), dysdiadochokinesia (inability to perform rapid alternating movements such as walking), impaired check reflex or rebound phenomenon, and intention tremor (involuntary movement caused by alternating contractions of opposing muscle groups). Damage to the midline portion may disrupt whole-body movements, whereas damage localized more laterally is more likely to disrupt fine movements of the hands or limbs. Damage to the upper part of the cerebellum tends to cause gait impairments and other problems with leg coordination; damage to the lower part is more likely to cause uncoordinated or poorly aimed movements of the arms and hands, as well as difficulties in speed. This complex of motor symptoms is called ataxia.

6.3.4 Brainstem

The brainstem lies beneath the cerebrum and consists of the midbrain, pons and medulla. It lies in the back part of the skull, resting on the part of the base known as the clivus, and ends at the foramen magnum, a large opening in the occipital bone. The brainstem continues below this as the spinal cord, protected by the vertebral column.

Ten of the twelve pairs of cranial nerves[a] emerge directly from the brainstem. The brainstem also contains many cranial nerve nuclei and nuclei of peripheral nerves, as well as nuclei involved in the regulation of many essential processes including breathing, control of eye movements and balance. The reticular formation, a network of nuclei of ill-defined formation, is present within and along the length of the brainstem. Many nerve tracts, which transmit information to and from the cerebral cortex to the rest of the body, pass through the brainstem.

Cerebrospinal fluid is a clear, colourless transcellular fluid that circulates around the brain in the subarachnoid space, in the ventricular system, and in the central canal of the spinal cord. It also fills some gaps in the subarachnoid space, known as subarachnoid cisterns. The four ventricles, two lateral, a third, and a fourth ventricle, all contain choroid plexus that produces cerebrospinal fluid. The third ventricle lies in the midline and is connected to the lateral ventricles. A single duct, the cerebral aqueduct between the pons and the cerebellum, connects the third ventricle to the fourth ventricle. Three separate openings, the middle and two lateral apertures, drain the cerebrospinal fluid from the fourth ventricle to the cisterna magna one of the major cisterns. From here, cerebrospinal fluid circulates around the brain and spinal cord in the subarachnoid space, between the arachnoid mater and pia mater. At any one time, there is about 150mL of cerebrospinal fluid – most within the subarachnoid space. It is constantly being regenerated and absorbed, and is replaced about once every 5–6 hours.

A glymphatic system has been described as the lymphatic drainage system of the brain. The brain-wide glymphatic pathway includes drainage routes from the cerebrospinal fluid, and from the meningeal lymphatic vessels that are associated with the dural sinuses, and run alongside the cerebral blood vessels. The pathway drains interstitial fluid from the tissue of the brain.

Blood supply

The internal carotid arteries supply oxygenated blood to the front of the brain and the vertebral arteries supply blood to the back of the brain. These two circulations join together in the circle of Willis, a ring of connected arteries that lies in the interpeduncular cistern between the midbrain and pons.

The internal carotid arteries are branches of the common carotid arteries. They enter the cranium through the carotid canal, travel through the cavernous sinus and enter the subarachnoid space. They then enter the circle of Willis, with two branches, the anterior cerebral arteries emerging. These branches travel forward and then upward along the longitudinal fissure, and supply the front and midline parts of the brain. One or more small anterior communicating arteries join the two anterior cerebral arteries shortly after they emerge as branches. The internal carotid arteries continue forward as the middle cerebral arteries. They travel sideways along the sphenoid bone of the eye socket, then upwards through the insula cortex, where final branches arise. The middle cerebral arteries send branches along their length.

The vertebral arteries emerge as branches of the left and right subclavian arteries. They travel upward through transverse foramina which are spaces in the cervical vertebrae. Each side enters the cranial cavity through the foramen magnum along the corresponding side of the medulla. They give off one of the three cerebellar branches. The vertebral arteries join in front of the middle part of the medulla to form the larger basilar artery, which sends multiple branches to supply the medulla and pons, and the two other anterior and superior cerebellar branches. Finally, the basilar artery divides into two posterior cerebral arteries. These travel outwards, around the superior cerebellar peduncles, and along the top of the cerebellar tentorium, where it sends branches to supply the temporal and occipital lobes. Each posterior cerebral artery sends a small posterior communicating artery to join with the internal carotid arteries.

6.4 Spinal cord

The spinal cord is a long, thin, tubular structure made up of nervous tissue, which extends from the medulla oblongata in the brainstem to the lumbar region of the vertebral column. It encloses the central canal of the spinal cord, which contains cerebrospinal fluid. The brain and spinal cord together make up the central nervous system (CNS). In humans, the spinal cord begins at the occipital bone, passing through the foramen magnum and entering the spinal canal at the beginning of the cervical vertebrae. The spinal cord extends down to between the first and second lumbar vertebrae, where it ends. The enclosing bony vertebral column protects the relatively shorter spinal cord. It is around 45 cm (18 in) in men and around 43 cm (17 in) long in women. The diameter of the spinal cord ranges from 13 mm (½ in) in the cervical and lumbar regions to 6.4 mm (¼ in) in the thoracic area.

The spinal cord functions primarily in the transmission of nerve signals from the motor cortex to the body, and from the afferent fibers of the sensory neurons to the sensory cortex. It is also a center for coordinating many reflexes and contains reflex arcs that can independently control reflexes. It is also the location of groups of spinal interneurons that make up the neural circuits known as central pattern generators. These circuits are responsible for controlling motor instructions for rhythmic movements such as walking.

The spinal cord is the main pathway for information connecting the brain and peripheral nervous system. Much shorter than its protecting spinal column, the human spinal cord originates in the brainstem, passes through the foramen magnum, and continues through to the conus medullaris near the second lumbar vertebra before terminating in a fibrous extension known as the filum terminale.

It is about 45 cm (18 in) long in men and around 43 cm (17 in) in women, ovoid-shaped, and is enlarged in the cervical and lumbar regions. The cervical enlargement, stretching from the C5 to T1 vertebrae, is where sensory input comes from and motor output goes to the arms and trunk. The lumbar enlargement, located between L1 and S3, handles sensory input and motor output coming from and going to the legs.

The spinal cord is continuous with the caudal portion of the medulla, running from the base of the skull to the body of the first lumbar vertebra. It does not run the full length of the vertebral column in adults. It is made of 31 segments from which branch one pair of sensory nerve roots and one pair of motor nerve roots. The nerve roots then merge into bilaterally symmetrical pairs of spinal nerves. The peripheral nervous system is made up of these spinal roots, nerves, and ganglia.

The dorsal roots are afferent fascicles, receiving sensory information from the skin, muscles, and visceral organs to be relayed to the brain. The roots terminate in dorsal root ganglia, which are composed of the cell bodies of the corresponding neurons. Ventral roots consist of efferent fibers that arise from motor neurons whose cell bodies are found in the ventral (or anterior) gray horns of the spinal cord.

The spinal cord (and brain) are protected by three layers of tissue or membranes called meninges, that surround the canal . The dura mater is the outermost layer, and it forms a tough protective coating. Between the dura mater and the surrounding bone of the vertebrae is a space called the epidural space. The epidural space is filled with adipose tissue, and it contains a network of blood vessels. The arachnoid mater, the middle protective layer, is named for its open, spiderweb-like appearance. The space between the arachnoid and the underlying pia mater is called the subarachnoid space. The subarachnoid space contains cerebrospinal fluid (CSF), which can be sampled with a lumbar puncture, or "spinal tap" procedure. The delicate pia mater, the innermost protective layer, is tightly associated with the surface of the spinal cord. The cord is stabilized within the dura mater by the connecting denticulate ligaments, which extend from the enveloping pia mater laterally between the dorsal and ventral roots. The dural sac ends at the vertebral level of the second sacral vertebra.

In cross-section, the peripheral region of the cord contains neuronal white matter tracts containing sensory and motor axons. Internal to this peripheral region is the grey matter, which contains the nerve cell bodies arranged in the three grey columns that give the region its butterfly-shape. This central region surrounds the central canal, which is an extension of the fourth ventricle and contains cerebrospinal fluid.

The spinal cord is elliptical in cross section, being compressed dorsolaterally. Two prominent grooves, or sulci, run along its length. The posterior median sulcus is the groove in the dorsal side, and the anterior median fissure is the groove in the ventral side.

Spinal cord segments Gray 111 - Vertebral column-coloured.png The human spinal cord is divided into segments where pairs of spinal nerves (mixed; sensory and motor) form. Six to eight motor nerve rootlets branch out of right and left ventro lateral sulci in a very orderly manner. Nerve rootlets combine to form nerve roots. Likewise, sensory nerve rootlets form off right and left dorsal lateral sulci and form sensory nerve roots. The ventral (motor) and dorsal (sensory) roots combine to form spinal nerves (mixed; motor and sensory), one on each side of the spinal cord. Spinal nerves, with the exception of C1 and C2, form inside the intervertebral foramen (IVF). These rootlets form the demarcation between the central and peripheral nervous systems.

The grey column, (as three regions of grey columns) in the center of the cord, is shaped like a butterfly and consists of cell bodies of interneurons, motor neurons, neuroglia cells and unmyelinated axons. The anterior and posterior grey column present as projections of the grey matter and are also known as the horns of the spinal cord. Together, the grey columns and the gray commissure form the “grey H.”

The white matter is located outside of the grey matter and consists almost totally of myelinated motor and sensory axons. “Columns” of white matter carry information either up or down the spinal cord.

The spinal cord proper terminates in a region called the conus medullaris, while the pia mater continues as an extension called the filum terminale, which anchors the spinal cord to the coccyx. The cauda equina (“horse’s tail”) is a collection of nerves inferior to the conus medullaris that continue to travel through the vertebral column to the coccyx. The cauda equina forms because the spinal cord stops growing in length at about age four, even though the vertebral column continues to lengthen until adulthood. This results in sacral spinal nerves originating in the upper lumbar region.

Within the CNS, nerve cell bodies are generally organized into functional clusters, called nuclei. Axons within the CNS are grouped into tracts.

There are 31 spinal cord nerve segments in a human spinal cord:

- 8 cervical segments forming 8 pairs of cervical nerves (C1 spinal nerves exit the spinal column between the foramen magnum and the C1 vertebra; C2 nerves exit between the posterior arch of the C1 vertebra and the lamina of C2; C3–C8 spinal nerves pass through the IVF above their corresponding cervical vertebrae, with the exception of the C8 pair which exit between the C7 and T1 vertebrae)
- 12 thoracic segments forming 12 pairs of thoracic nerves
- 5 lumbar segments forming 5 pairs of lumbar nerves
- 5 sacral segments forming 5 pairs of sacral nerves
- 1 coccygeal segment

There are two regions where the spinal cord enlarges:

- Cervical enlargement – corresponds roughly to the brachial plexus nerves, which innervate the upper limb. It includes spinal cord segments from about C4 to T1. The vertebral levels of the enlargement are roughly the same (C4 to T1).
- Lumbar enlargement – corresponds to the lumbosacral plexus nerves, which innervate the lower limb. It comprises the spinal cord segments from L2 to S3 and is found about the vertebral levels of T9 to T12.

The spinal cord is made from part of the neural tube during development. There are four stages of the spinal cord that arises from the neural tube: The neural plate, neural fold, neural tube, and the spinal cord. Neural differentiation occurs within the spinal cord portion of the tube. As the neural tube begins to develop, the notochord begins to secrete a factor known as Sonic hedgehog or SHH. As a result, the floor plate then also begins to secrete SHH, and this will induce the basal plate to develop motor neurons. During the maturation of the neural tube, its lateral walls thicken and form a longtitudinal groove called the sulcus limitans. This extends the length of the spinal cord into dorsal and ventral portions as well. Meanwhile, the overlying ectoderm secretes bone morphogenetic protein (BMP). This induces the roof plate to begin to secrete BMP, which will induce the alar plate to develop sensory neurons. Opposing gradients of such morphogens as BMP and SHH form different domains of dividing cells along the dorsal ventral axis. Dorsal root ganglion neurons differentiate from neural crest progenitors. As the dorsal and ventral column cells proliferate, the lumen of the neural tube narrows to form the small central canal of the spinal cord. The alar plate and the basal plate are separated by the sulcus limitans. Additionally, the floor plate also secretes netrins. The netrins act as chemoattractants to decussation of pain and temperature sensory neurons in the alar plate across the anterior white commissure, where they then ascend towards the thalamus. Following the closure of the caudal neuropore and formation of the brain's ventricles that contain the choroid plexus tissue, the central canal of the caudal spinal cord is filled with cerebrospinal fluid.

Earlier findings by Viktor Hamburger and Rita Levi-Montalcini in the chick embryo have been confirmed by more recent studies which have demonstrated that the elimination of neuronal cells by programmed cell death (PCD) is necessary for the correct assembly of the nervous system.

Overall, spontaneous embryonic activity has been shown to play a role in neuron and muscle development but is probably not involved in the initial formation of connections between spinal neurons.

Blood supply The spinal cord is supplied with blood by three arteries that run along its length starting in the brain, and many arteries that approach it through the sides of the spinal column. The three longitudinal arteries are the anterior spinal artery, and the right and left posterior spinal arteries. These travel in the subarachnoid space and send branches into the spinal cord. They form anastamoses (connections) via the anterior and posterior segmental medullary arteries, which enter the spinal cord at various points along its length. The actual blood flow caudally through these arteries, derived from the posterior cerebral circulation, is inadequate to maintain the spinal cord beyond the cervical segments.

The major contribution to the arterial blood supply of the spinal cord below the cervical region comes from the radially arranged posterior and anterior radicular arteries, which run into the spinal cord alongside the dorsal and ventral nerve roots, but with one exception do not connect directly with any of the three longitudinal arteries. These intercostal and lumbar radicular arteries arise from the aorta, provide major anastomoses and supplement the blood flow to the spinal cord. In humans the largest of the anterior radicular arteries is known as the artery of Adamkiewicz, or anterior radicularis magna (ARM) artery, which usually arises between L1 and L2, but can arise anywhere from T9 to L5. Impaired blood flow through these critical radicular arteries, especially during surgical procedures that involve abrupt disruption of blood flow through the aorta for example during aortic aneursym repair, can result in spinal cord infarction and paraplegia.

Somatosensory organization

Spinal cord tracts. Somatosensory organization is divided into the dorsal column-medial lemniscus tract (the touch/proprioception/vibration sensory pathway) and the anterolateral system, or ALS (the pain/temperature sensory pathway). Both sensory pathways use three different neurons to get information from sensory receptors at the periphery to the cerebral cortex. These neurons are designated primary, secondary and tertiary sensory neurons. In both pathways, primary sensory neuron cell bodies are found in the dorsal root ganglia, and their central axons project into the spinal cord.

In the dorsal column-medial leminiscus tract, a primary neuron's axon enters the spinal cord and then enters the dorsal column. 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 level T6, then it travels in the fasciculus cuneatus, which is lateral to the fasciculus gracilis. Either way, the primary axon ascends to the lower medulla, where it leaves its fasciculus and synapses with a secondary neuron in one of the dorsal column nuclei: either the nucleus gracilis or the nucleus cuneatus, depending on the pathway it took. At this point, the secondary axon leaves its nucleus and passes anteriorly and medially. The collection of secondary axons that do this are known as internal arcuate fibers. The internal arcuate fibers decussate and continue ascending as the contralateral medial lemniscus. Secondary axons from the medial lemniscus finally terminate in the ventral posterolateral nucleus (VPLN) of the thalamus, where they synapse with tertiary neurons. From there, tertiary neurons ascend via the posterior limb of the internal capsule and end in the primary sensory cortex.

The proprioception of the lower limbs differs from the upper limbs and upper trunk. There is a four-neuron pathway for lower limb proprioception. This pathway initially follows the dorsal spino-cerebellar pathway. It is arranged as follows: proprioceptive receptors of lower limb $\rightarrow$ peripheral process $\rightarrow$ dorsal root ganglion $\rightarrow$ central process $\rightarrow$ Clarke's column $\rightarrow$ 2nd order neuron $\rightarrow$ medulla oblongata (Caudate nucleus) $\rightarrow$ 3rd order neuron $\rightarrow$ VPLN of thalamus $\rightarrow$ 4th order neuron $\rightarrow$ posterior limb of internal capsule $\rightarrow$ corona radiata $\rightarrow$ sensory area of cerebrum.

The anterolateral system works somewhat differently. Its primary neurons axons 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. After synapsing, secondary axons decussate and ascend in the anterior lateral portion of the spinal cord as the spinothalamic tract. This tract ascends all the way to the VPLN, where it synapses on tertiary neurons. Tertiary neuronal axons then travel to the primary sensory cortex via the posterior limb of the internal capsule.

Some of the "pain fibers" in the ALS deviate from their pathway towards the VPLN. In one such deviation, axons travel towards the reticular formation in the midbrain. The reticular formation then projects to a number of places including the hippocampus (to create memories about the pain), the centromedian nucleus (to cause diffuse, non-specific pain) and various parts of the cortex. Additionally, some ALS axons project to the periaqueductal gray in the pons, and the axons forming the periaqueductal gray then project to the nucleus raphes magnus, which projects back down to where the pain signal is coming from and inhibits it. This helps control the sensation of pain to some degree.

The corticospinal tract serves as the motor pathway for upper motor neuronal signals coming from the cerebral cortex and from primitive brainstem motor nuclei.

Cortical upper motor neurons originate from Brodmann areas 1, 2, 3, 4, and 6 and then descend in the posterior limb of the internal capsule, through the crus cerebri, down through the pons, and to the medullary pyramids, where about 90% of the axons cross to the contralateral side at the decussation of the pyramids. They then descend as the lateral corticospinal tract. These axons synapse with lower motor neurons in the ventral horns of all levels of the spinal cord. The remaining 10% of axons descend on the ipsilateral side as the ventral corticospinal tract. These axons also synapse with lower motor neurons in the ventral horns. Most of them will cross to the contralateral side of the cord (via the anterior white commissure) right before synapsing.

The midbrain nuclei include four motor tracts that send upper motor neuronal axons down the spinal cord to lower motor neurons. These are the rubrospinal tract, the vestibulospinal tract, the tectospinal tract and the reticulospinal tract. The rubrospinal tract descends with the lateral corticospinal tract, and the remaining three descend with the anterior corticospinal tract.

The function of lower motor neurons can be divided into two different groups: the lateral corticospinal tract and the anterior cortical spinal tract. The lateral tract contains upper motor neuronal axons which synapse on dorsal lateral (DL) lower motor neurons. The DL neurons are involved in distal limb control. Therefore, these DL neurons are found specifically only in the cervical and lumbosacral enlargements within the spinal cord. There is no decussation in the lateral corticospinal tract after the decussation at the medullary pyramids.

The anterior corticospinal tract descends ipsilaterally in the anterior column, where the axons emerge and either synapse on lower ventromedial (VM) motor neurons in the ventral horn ipsilaterally or descussate at the anterior white commissure where they synapse on VM lower motor neurons contralaterally . The tectospinal, vestibulospinal and reticulospinal descend ipsilaterally in the anterior column but do not synapse across the anterior white commissure. Rather, they only synapse on VM lower motor neurons ipsilaterally. The VM lower motor neurons control the large, postural muscles of the axial skeleton. These lower motor neurons, unlike those of the DL, are located in the ventral horn all the way throughout the spinal cord.

Spinocerebellar tracts Proprioceptive information in the body travels up the spinal cord via three tracks. Below L2, the proprioceptive information travels up the spinal cord in the ventral spinocerebellar tract. Also known as the anterior spinocerebellar tract, sensory receptors take in the information and travel into the spinal cord. The cell bodies of these primary neurons are located in the dorsal root ganglia. In the spinal cord, the axons synapse and the secondary neuronal axons decussates and then travel up to the superior cerebellar peduncle where they decussate again. From here, the information is brought to deep nuclei of the cerebellum including the fastigial and interposed nuclei.

From the levels of L2 to T1, proprioceptive information enters the spinal cord and ascends ipsilaterally, where it synapses in Clarke's nucleus. The secondary neuronal axons continue to ascend ipsilaterally and then pass into the cerebellum via the inferior cerebellar peduncle. This tract is known as the dorsal spinocerebellar tract.

From above T1, proprioceptive primary axons enter the spinal cord and ascend ipsilaterally until reaching the accessory cuneate nucleus, where they synapse. The secondary axons pass into the cerebellum via the inferior cerebellar peduncle where again, these axons synapse on cerebellar deep nuclei. This tract is known as the cuneocerebellar tract.

Motor information travels from the brain down the spinal cord via descending spinal cord tracts. Descending tracts involve two neurons: the upper motor neuron (UMN) and lower motor neuron

(LMN). A nerve signal travels down the upper motor neuron until it synapses with the lower motor neuron in the spinal cord. Then, the lower motor neuron conducts the nerve signal to the spinal root where efferent nerve fibers carry the motor signal toward the target muscle. The descending tracts are composed of white matter. There are several descending tracts serving different functions. The corticospinal tracts (lateral and anterior) are responsible for coordinated limb movements.

The spinal cord ends at the level of vertebrae L1–L2, while the subarachnoid space —the compartment that contains cerebrospinal fluid— extends down to the lower border of S2. Lumbar punctures in adults are usually performed between L3–L5 (cauda equina level) in order to avoid damage to the spinal cord. In the fetus, the spinal cord extends the full length of the spine and regresses as the body grows.

Chapter 7

The Peripheral Nervous System

The peripheral nervous system (PNS) is one of two components that make up the nervous system of bilateral animals, with the other part being the central nervous system (CNS). The PNS consists of the nerves and ganglia outside the brain and spinal cord. The main function of the PNS is to connect the CNS to the limbs and organs, essentially serving as a relay between the brain and spinal cord and the rest of the body. Unlike the CNS, the PNS is not protected by the vertebral column and skull, or by the blood–brain barrier, which leaves it exposed to toxins and mechanical injuries.

The peripheral nervous system is divided into the somatic nervous system and the autonomic nervous system. In the somatic nervous system, the cranial nerves are part of the PNS with the exception of the optic nerve (cranial nerve II), along with the retina. The second cranial nerve is not a true peripheral nerve but a tract of the diencephalon. Cranial nerve ganglia originated in the CNS. However, the remaining ten cranial nerve axons extend beyond the brain and are therefore considered part of the PNS. The autonomic nervous system exerts involuntary control over smooth muscle and glands. The connection between CNS and organs allows the system to be in two different functional states: sympathetic and parasympathetic.

The peripheral nervous system is divided into the somatic nervous system, and the autonomic nervous system. The somatic nervous system is under voluntary control, and transmits signals from the brain to end organs such as muscles. The sensory nervous system is part of the somatic nervous system and transmits signals from senses such as taste and touch (including fine touch and gross touch) to the spinal cord and brain. The autonomic nervous system is a 'self-regulating' system which influences the function of organs outside voluntary control, such as the heart rate, or the functions of the digestive system.

Somatic nervous system See also: List of nerves of the human body The somatic nervous system includes the sensory nervous system and the somatosensory system and consists of sensory nerves and somatic nerves, and many nerves which hold both functions.

In the head and neck, cranial nerves carry somatosensory data. There are twelve cranial nerves, ten of which originate from the brainstem, and mainly control the functions of the anatomic structures of the head with some exceptions. One unique cranial nerve is the vagus nerve, which receives sensory information from organs in the thorax and abdomen. The accessory nerve is responsible for innervating the sternocleidomastoid and trapezius muscles, neither of which being exclusively in the head.

For the rest of the body, spinal nerves are responsible for somatosensory information. These arise from the spinal cord. Usually these arise as a web ("plexus") of interconnected nerves roots that arrange to form single nerves. These nerves control the functions of the rest of the body. In humans, there are 31 pairs of spinal nerves: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal. These nerve roots are named according to the spinal vertebrata which they are adjacent to. In the cervical region, the spinal nerve roots come out above the corresponding vertebrae (i.e., nerve root between the skull and 1st cervical vertebrae is called spinal nerve C1). From the thoracic region to the coccygeal region, the spinal nerve roots come out below the corresponding vertebrae. It is important to note that this method creates a problem when naming the spinal nerve root between C7 and T1 (so it is called spinal nerve root C8). In the lumbar and sacral region, the spinal nerve roots travel within the dural sac and they travel below the level of L2 as the cauda equina.

Cervical spinal nerves (C1–C4) Further information: Cervical plexus The first 4 cervical spinal nerves, C1 through C4, split and recombine to produce a variety of nerves that serve the neck and back of head.

Spinal nerve C1 is called the suboccipital nerve, which provides motor innervation to muscles at the base of the skull. C2 and C3 form many of the nerves of the neck, providing both sensory and motor control. These include the greater occipital nerve, which provides sensation to the back of the head, the lesser occipital nerve, which provides sensation to the area behind the ears, the greater auricular nerve and the lesser auricular nerve.

The phrenic nerve is a nerve essential for our survival which arises from nerve roots C3, C4 and C5. It supplies the thoracic diaphragm, enabling breathing. If the spinal cord is transected above C3, then spontaneous breathing is not possible.

Brachial plexus (C5–T1) Further information: Brachial plexus The last four cervical spinal nerves, C5 through C8, and the first thoracic spinal nerve, T1, combine to form the brachial plexus, or plexus brachialis, a tangled array of nerves, splitting, combining and recombining, to form the nerves that subserve the upper-limb and upper back. Although the brachial plexus may appear tangled, it is highly organized and predictable, with little variation between people. See brachial plexus injuries.

Lumbosacral plexus (L1–Co1) The anterior divisions of the lumbar nerves, sacral nerves, and coccygeal nerve form the lumbosacral plexus, the first lumbar nerve being frequently joined by a branch from the twelfth thoracic. For descriptive purposes this plexus is usually divided into three parts:

lumbar plexus sacral plexus pudendal plexus Autonomic nervous system The autonomic nervous system (ANS) controls involuntary responses to regulate physiological functions. The brain and spinal cord of the central nervous system are connected with organs that have smooth muscle, such as the heart, bladder, and other cardiac, exocrine, and endocrine related organs, by ganglionic neurons. The most notable physiological effects from autonomic activity are pupil constriction and dilation, and salivation of saliva. The autonomic nervous system is always activated, but is either in the sympathetic or parasympathetic state. Depending on the situation, one state can overshadow the other, resulting in a release of different kinds of neurotransmitters. There is a lesser known division of the autonomic nervous system known as the enteric nervous system. Located only around the digestive tract, this system allows for local control without input from the sympathetic or the parasympathetic branches, though it can still receive and respond to signals from the rest of the body. The enteric system is responsible for various functions related to gastrointestinal system.

Sympathetic nervous system The sympathetic system is activated during a “fight or flight” situation in which mental stress or physical danger is encountered. Neurotransmitters such as norepinephrine, and epinephrine are released, which increases heart rate and blood flow in certain areas like muscle, while simultaneously decreasing activities of non-critical functions for survival, like digestion. The systems are independent to each other, which allows activation of certain parts of the body, while others remain rested.

Parasympathetic nervous system Primarily using the neurotransmitter acetylcholine (ACh) as a mediator, the parasympathetic system allows the body to function in a “rest and digest” state. Consequently, when the parasympathetic system dominates the body, there are increases in salivation and activities in digestion, while heart rate and other sympathetic response decrease. Unlike the sympathetic system, humans have some voluntary controls in the parasympathetic system. The most prominent examples of this control are urination and defecation.

Chapter 8

The Olfactory System

The olfactory system, or sense of smell, is the sensory system used for smelling (olfaction). Olfaction is one of the special senses, that have directly associated specific organs. Most mammals and reptiles have a main olfactory system and an accessory olfactory system. The main olfactory system detects airborne substances, while the accessory system senses fluid-phase stimuli.

Linda B. Buck and Richard Axel won the 2004 Nobel Prize in Physiology or Medicine for their work on the olfactory system.

The peripheral olfactory system consists mainly of the nostrils, ethmoid bone, nasal cavity, and the olfactory epithelium (layers of thin tissue covered in mucus that line the nasal cavity). The primary components of the layers of epithelial tissue are the mucous membranes, olfactory glands, olfactory neurons, and nerve fibers of the olfactory nerves.

Odor molecules can enter the peripheral pathway and reach the nasal cavity either through the nostrils when inhaling (olfaction) or through the throat when the tongue pushes air to the back of the nasal cavity while chewing or swallowing (retro-nasal olfaction). Inside the nasal cavity, mucus lining the walls of the cavity dissolves odor molecules. Mucus also covers the olfactory epithelium, which contains mucous membranes that produce and store mucus and olfactory glands that secrete metabolic enzymes found in the mucus.

Olfactory sensory neurons in the epithelium detect odor molecules dissolved in the mucus and transmit information about the odor to the brain in a process called sensory transduction. Olfactory neurons have cilia (tiny hairs) containing Olfactory receptors that bind to odor molecules, causing an electrical response that spreads through the Sensory neuron to the olfactory nerve fibers at the back of the nasal cavity.

Olfactory nerves and fibers transmit information about odors from the peripheral olfactory system to the central olfactory system of the brain, which is separated from the epithelium by the cribriform plate of the ethmoid bone. Olfactory nerve fibers, which originate in the epithelium, pass through the cribriform plate, connecting the epithelium to the brain's limbic system at the olfactory bulbs.

The main olfactory bulb transmits pulses to both mitral and tufted cells, which help determine odor concentration based off the time certain neuron clusters fire (called 'timing code'). These cells also note differences between highly similar odors and use that data to aid in later recognition. The cells are different with mitral having low firing-rates and being easily inhibited by neighboring cells, while tufted have high rates of firing and are more difficult to inhibit.

The uncus houses the olfactory cortex which includes the piriform cortex (posterior orbitofrontal cortex), amygdala, olfactory tubercle, and parahippocampal gyrus.

The olfactory tubercle connects to numerous areas of the amygdala, thalamus, hypothalamus, hippocampus, brain stem, retina, auditory cortex, and olfactory system. In total it has 27 inputs and 20 outputs. An oversimplification of its role is to state that it: checks to ensure odor signals arose from actual odors rather than villi irritation, regulates motor behavior (primarily social and stereotypical) brought on by odors, integrates auditory and olfactory sensory info to complete the aforementioned tasks, and plays a role in transmitting positive signals to reward sensors (and is thus involved in addiction).

The amygdala (in olfaction) processes pheromone, allomone, and kairomone (same-species, cross-species, and cross-species where the emitter is harmed and the sensor is benefited, respectively) signals. Due to cerebrum evolution this processing is secondary and therefore is largely unnoticed in human interactions. Allomones include flower scents, natural herbicides, and natural toxic plant chemicals. The info for these processes comes from the vomeronasal organ indirectly via the olfactory bulb. The main olfactory bulb's pulses in the amygdala are used to pair odors to names and recognize odor to odor differences.

Stria terminalis, specifically bed nuclei (BNST), act as the information pathway between the amygdala and hypothalamus, as well as the hypothalamus and pituitary gland. BNST abnormalities often lead to sexual confusion and immaturity. BNST also connects to the septal area, rewarding sexual behavior.

Mitral pulses to the hypothalamus promote/discourage feeding, whereas accessory olfactory bulb pulses regulate reproductive and odor-related-reflex processes.

The hippocampus (although minimally connected to the main olfactory bulb) receives almost all of its olfactory information via the amygdala (either directly or via the BNST). The hippocampus forms new and reinforces existing memories.

Similarly, the parahippocampus encodes, recognizes and contextualizes scenes. The parahippocampal gyrus houses the topographical map for olfaction.

The orbitofrontal cortex (OFC) is heavily correlated with the cingulate gyrus and septal area to act out positive/negative reinforcement. The OFC is the expectation of reward/punishment in response to stimuli. The OFC represents the emotion and reward in decision making.

The anterior olfactory nucleus distributes reciprocal signals between the olfactory bulb and piriform cortex. The anterior olfactory nucleus is the memory hub for smell.

The senses of smell and taste (gustatory system) are often referred to together as the chemosensory system, because they both give the brain information about the chemical composition of objects through a process called transduction.

Olfaction is a chemoreception that forms the sense of smell. Olfaction has many purposes, such as the detection of hazards, pheromones, and food. It integrates with other senses to form the sense of flavor.

Olfaction occurs when odorants bind to specific sites on olfactory receptors located in the nasal cavity. Glomeruli aggregate signals from these receptors and transmit them to the olfactory bulb, where the sensory input will start to interact with parts of the brain responsible for smell identification, memory, and emotion.

Often, land organisms will have separate olfaction systems for smell and taste (orthonasal smell and retronasal smell), but water-dwelling organisms usually have only one system.

Olfactory dysfunction arises as the result of many different peripheral and central disturbances, including upper respiratory infections, traumatic brain injury, and neurodegenerative disease.

In vertebrates, smells are sensed by olfactory sensory neurons in the olfactory epithelium. The olfactory epithelium is made up of at least six morphologically and biochemically different cell types. The proportion of olfactory epithelium compared to respiratory epithelium (not innervated, or supplied with nerves) gives an indication of the animal's olfactory sensitivity. Humans have about 10 cm2 (1.6 sq in) of olfactory epithelium, whereas some dogs have 170 cm2 (26 sq in). A dog's olfactory epithelium is also considerably more densely innervated, with a hundred times more receptors per square centimeter.

Molecules of odorants passing through the superior nasal concha of the nasal passages dissolve in the mucus that lines the superior portion of the cavity and are detected by olfactory receptors on the dendrites of the olfactory sensory neurons. This may occur by diffusion or by the binding of the odorant to odorant-binding proteins. The mucus overlying the epithelium contains mucopolysaccharides, salts, enzymes, and antibodies (these are highly important, as the olfactory neurons provide a direct passage for infection to pass to the brain). This mucus acts as a solvent for odor molecules, flows constantly, and is replaced approximately every ten minutes.

In insects, smells are sensed by olfactory sensory neurons in the chemosensory sensilla, which are present in insect antenna, palps, and tarsa, but also on other parts of the insect body. Odorants penetrate into the cuticle pores of chemosensory sensilla and get in contact with insect odorant-binding proteins (OBPs) or Chemosensory proteins (CSPs), before activating the sensory neurons.

Receptor neuron The binding of the ligand (odor molecule or odorant) to the receptor leads to an action potential in the receptor neuron, via a second messenger pathway, depending on the organism. In mammals, the odorants stimulate adenylate cyclase to synthesize cAMP via a G protein called Golf. cAMP, which is the second messenger here, opens a cyclic nucleotide-gated ion channel (CNG), producing an influx of cations (largely Ca2+ with some Na+) into the cell, slightly depolarising it. The Ca2+ in turn opens a Ca2+-activated chloride channel, leading to efflux of Cl−, further depolarizing the cell and triggering an action potential. Ca2+ is then extruded through a sodium-calcium exchanger. A calcium-calmodulin complex also acts to inhibit the binding of cAMP to the cAMP-dependent channel, thus contributing to olfactory adaptation.

The main olfactory system of some mammals also contains small subpopulations of olfactory sensory neurons that detect and transduce odors somewhat differently. Olfactory sensory neurons that use trace amine-associated receptors (TAARs) to detect odors use the same second messenger signaling cascade as do the canonical olfactory sensory neurons. Other subpopulations, such as those that express the receptor guanylyl cyclase GC-D (Gucy2d) or the soluble guanylyl cyclase

Gucy1b2, use a cGMP cascade to transduce their odorant ligands. These distinct subpopulations (olfactory subsystems) appear specialized for the detection of small groups of chemical stimuli.

This mechanism of transduction is somewhat unusual, in that cAMP works by directly binding to the ion channel rather than through activation of protein kinase A. It is similar to the transduction mechanism for photoreceptors, in which the second messenger cGMP works by directly binding to ion channels, suggesting that maybe one of these receptors was evolutionarily adapted into the other. There are also considerable similarities in the immediate processing of stimuli by lateral inhibition.

Averaged activity of the receptor neurons can be measured in several ways. In vertebrates, responses to an odor can be measured by an electro-olfactogram or through calcium imaging of receptor neuron terminals in the olfactory bulb. In insects, one can perform electroantennography or calcium imaging within the olfactory bulb.

Olfactory bulb projections Early Olfactory System Olfactory sensory neurons project axons to the brain within the olfactory nerve, (cranial nerve I). These nerve fibers, lacking myelin sheaths, pass to the olfactory bulb of the brain through perforations in the cribriform plate, which in turn projects olfactory information to the olfactory cortex and other areas. The axons from the olfactory receptors converge in the outer layer of the olfactory bulb within small (50 micrometers in diameter) structures called glomeruli. Mitral cells, located in the inner layer of the olfactory bulb, form synapses with the axons of the sensory neurons within glomeruli and send the information about the odor to other parts of the olfactory system, where multiple signals may be processed to form a synthesized olfactory perception. A large degree of convergence occurs, with 25,000 axons synapsing on 25 or so mitral cells, and with each of these mitral cells projecting to multiple glomeruli. Mitral cells also project to periglomerular cells and granular cells that inhibit the mitral cells surrounding it (lateral inhibition). Granular cells also mediate inhibition and excitation of mitral cells through pathways from centrifugal fibers and the anterior olfactory nuclei. Neuromodulators like acetylcholine, serotonin and norepinephrine all send axons to the olfactory bulb and have been implicated in gain modulation, pattern separation, and memory functions, respectively.

The mitral cells leave the olfactory bulb in the lateral olfactory tract, which synapses on five major regions of the cerebrum: the anterior olfactory nucleus, the olfactory tubercle, the amygdala, the piriform cortex, and the entorhinal cortex. The anterior olfactory nucleus projects, via the anterior commissure, to the contralateral olfactory bulb, inhibiting it. The piriform cortex has two major divisions with anatomically distinct organizations and functions. The anterior piriform cortex (APC) appears to be better at determining the chemical structure of the odorant molecules, and the posterior piriform cortex (PPC) has a strong role in categorizing odors and assessing similarities between odors (e.g. minty, woody, and citrus are odors that can, despite being highly variant chemicals, be distinguished via the PPC in a concentration-independent manner). The piriform cortex projects to the medial dorsal nucleus of the thalamus, which then projects to the orbitofrontal cortex. The orbitofrontal cortex mediates conscious perception of the odor (citation needed). The three-layered piriform cortex projects to a number of thalamic and hypothalamic nuclei, the hippocampus and amygdala and the orbitofrontal cortex, but its function is largely unknown. The entorhinal cortex projects to the amygdala and is involved in emotional and autonomic responses to odor. It also projects to the hippocampus and is involved in motivation and memory. Odor information is stored in long-term memory and has strong connections to emotional memory. This is possibly due to the olfactory system's close anatomical ties to the limbic system and hippocampus, areas of the brain that have long been known to be involved in emotion and place memory, respectively.

Since any one receptor is responsive to various odorants, and there is a great deal of convergence at the level of the olfactory bulb, it may seem strange that human beings are able to distinguish so many different odors. It seems that a highly complex form of processing must be occurring; however, as it can be shown that, while many neurons in the olfactory bulb (and even the pyriform cortex and amygdala) are responsive to many different odors, half the neurons in the orbitofrontal cortex are responsive to only one odor, and the rest to only a few. It has been shown through microelectrode studies that each individual odor gives a particular spatial map of excitation in the olfactory bulb. It is possible that the brain is able to distinguish specific odors through spatial encoding, but temporal coding must also be taken into account. Over time, the spatial maps change, even for one particular odor, and the brain must be able to process these details as well.

Inputs from the two nostrils have separate inputs to the brain, with the result that, when each nostril takes up a different odorant, a person may experience perceptual rivalry in the olfactory sense akin to that of binocular rivalry.

In insects, smells are sensed by sensilla located on the antenna and maxillary palp and first processed by the antennal lobe (analogous to the olfactory bulb), and next by the mushroom bodies and lateral horn.

Accessory olfactory system Many animals, including most mammals and reptiles, but not humans, have two distinct and segregated olfactory systems: a main olfactory system, which detects volatile stimuli, and an accessory olfactory system, which detects fluid-phase stimuli. Behavioral evidence suggests that these fluid-phase stimuli often function as pheromones, although pheromones can also be detected by the main olfactory system. In the accessory olfactory system, stimuli are detected by the vomeronasal organ, located in the vomer, between the nose and the mouth. Snakes use it to smell prey, sticking their tongue out and touching it to the organ. Some mammals make a facial expression called flehmen to direct stimuli to this organ.

The sensory receptors of the accessory olfactory system are located in the vomeronasal organ. As in the main olfactory system, the axons of these sensory neurons project from the vomeronasal organ to the accessory olfactory bulb, which in the mouse is located on the dorsal-posterior portion of the main olfactory bulb. Unlike in the main olfactory system, the axons that leave the accessory olfactory bulb do not project to the brain's cortex but rather to targets in the amygdala and bed nucleus of the stria terminalis, and from there to the hypothalamus, where they may influence aggression and mating behavior.

The process by which olfactory information is coded in the brain to allow for proper perception is still being researched, and is not completely understood. When an odorant is detected by receptors, they in a sense break the odorant down, and then the brain puts the odorant back together for identification and perception. The odorant binds to receptors that recognize only a specific functional group, or feature, of the odorant, which is why the chemical nature of the odorant is important.

After binding the odorant, the receptor is activated and will send a signal to the glomeruli. Each glomerulus receives signals from multiple receptors that detect similar odorant features. Because several receptor types are activated due to the different chemical features of the odorant, several glomeruli are activated as well. All of the signals from the glomeruli are then sent to the brain, where the combination of glomeruli activation encodes the different chemical features of the odorant. The brain then essentially puts the pieces of the activation pattern back together in order to identify and perceive the odorant. This distributed code allows the brain to detect specific odors in mixtures of many background odors.

It is a general idea that the layout of brain structures corresponds to physical features of stimuli (called topographic coding), and similar analogies have been made in olfaction with concepts such as a layout corresponding to chemical features (called chemotopy) or perceptual features. While chemotopy remains a highly controversial concept, evidence exists for perceptual information implemented in the spatial dimensions of olfactory networks.

Although conventional wisdom and lay literature, based on impressionistic findings in the 1920s, have long presented human olfaction as capable of distinguishing between roughly 10,000 unique odors, recent research has suggested that the average individual is capable of distinguishing over one trillion unique odors. Researchers in the most recent study, which tested the psychophysical responses to combinations of over 128 unique odor molecules with combinations composed of up to 30 different component molecules, noted that this estimate is “conservative” and that some subjects of their research might be capable of deciphering between a thousand trillion odorants, adding that their worst performer could probably still distinguish between 80 million scents. Authors of the study concluded, “This is far more than previous estimates of distinguishable olfactory stimuli. It demonstrates that the human olfactory system, with its hundreds of different olfactory receptors, far out performs the other senses in the number of physically different stimuli it can discriminate.” However, it was also noted by the authors that the ability to distinguish between smells is not analogous to being able to consistently identify them, and that subjects were not typically capable of identifying individual odor stimulants from within the odors the researchers had prepared from multiple odor molecules. In November 2014 the study was strongly criticized by Caltech scientist Markus Meister, who wrote that the study’s “extravagant claims are based on errors of mathematical logic”. The logic of his paper has in turn been criticized by the authors of the original paper.

Genetics Different people smell different odors, and most of these differences are caused by genetic differences. Although odorant receptor genes make up one of the largest gene families in the human genome, only a handful of genes have been linked conclusively to particular smells. For instance, the odorant receptor OR5A1 and its genetic variants (alleles) are responsible for our ability (or failure) to smell -ionone, a key aroma in foods and beverages. Similarly, the odorant receptor OR2J3 is associated with the ability to detect the “grassy” odor, cis-3-hexen-1-ol. The preference (or dislike) of cilantro (coriander) has been linked to the olfactory receptor OR6A2.

Chapter 9

The Gustatory System

Taste, gustatory perception, or gustation (Adjectival form: gustatory) is one of the five traditional senses that belongs to the gustatory system.

Taste is the sensation produced or stimulated when a substance in the mouth reacts chemically with taste receptor cells located on taste buds in the oral cavity, mostly on the tongue. Taste, along with smell (olfaction) and trigeminal nerve stimulation (registering texture, pain, and temperature), determines flavors of food and/or other substances. Humans have taste receptors on taste buds (gustatory calyculi) and other areas including the upper surface of the tongue and the epiglottis. The gustatory cortex is responsible for the perception of taste.

The tongue is covered with thousands of small bumps called papillae, which are visible to the naked eye. Within each papilla are hundreds of taste buds. The exception to this is the filiform papillae that do not contain taste buds. There are between 2000 and 5000 taste buds that are located on the back and front of the tongue. Others are located on the roof, sides and back of the mouth, and in the throat. Each taste bud contains 50 to 100 taste receptor cells.

The sensation of taste includes five established basic tastes: sweetness, sourness, saltiness, bitterness, and savoriness (also known as savory or umami). Scientific experiments have demonstrated that these five tastes exist and are distinct from one another. Taste buds are able to distinguish between different tastes through detecting interaction with different molecules or ions. Sweet, savoriness, and bitter tastes are triggered by the binding of molecules to G protein-coupled receptors on the cell membranes of taste buds. Saltiness and sourness are perceived when alkali metal or hydrogen ions enter taste buds, respectively.

The basic tastes contribute only partially to the sensation and flavor of food in the mouth—other factors include smell, detected by the olfactory epithelium of the nose; texture, detected through a variety of mechanoreceptors, muscle nerves, etc.; temperature, detected by thermoreceptors; and "coolness" (such as of menthol) and "hotness" (pungency), through chemesthesis.

As taste senses both harmful and beneficial things, all basic tastes are classified as either aversive or appetitive, depending upon the effect the things they sense have on our bodies. Sweetness helps to identify energy-rich foods, while bitterness serves as a warning sign of poisons.

Among humans, taste perception begins to fade around 50 years of age because of loss of tongue papillae and a general decrease in saliva production. Humans can also have distortion of tastes through dysgeusia. Not all mammals share the same taste senses: some rodents can taste starch (which humans cannot), cats cannot taste sweetness, and several other carnivores including hyenas, dolphins, and sea lions, have lost the ability to sense up to four of their ancestral five taste senses.

Taste in the gustatory system allows humans to distinguish between safe and harmful food, and to gauge foods' nutritional value. Digestive enzymes in saliva begin to dissolve food into base chemicals that are washed over the papillae and detected as tastes by the taste buds. The tongue is covered with thousands of small bumps called papillae, which are visible to the naked eye. Within each papilla are hundreds of taste buds. The exception to this are the filiform papillae that do not contain taste buds. There are between 2000 and 5000 taste buds that are located on the back and front of the tongue. Others are located on the roof, sides and back of the mouth, and in the throat. Each taste bud contains 50 to 100 taste receptor cells.

Bitter foods are generally found unpleasant, while sour, salty, sweet, and umami tasting foods generally provide a pleasurable sensation. The five specific tastes received by taste receptors are saltiness, sweetness, bitterness, sourness, and savoriness, often known by its Japanese term "umami" which translates to 'deliciousness'. As of the early twentieth century, Western physiologists and psychologists believed there were four basic tastes: sweetness, sourness, saltiness, and bitterness. At that time, savoriness was not identified, but now a large number of authorities recognize it as the fifth taste.

One study found that both salt and sour taste mechanisms detect, in different ways, the presence of sodium chloride (salt) in the mouth, however, acids are also detected and perceived as sour. The detection of salt is important to many organisms, but specifically mammals, as it serves a critical role in ion and water homeostasis in the body. It is specifically needed in the mammalian kidney as an osmotically active compound which facilitates passive re-uptake of water into the blood.[citation needed] Because of this, salt elicits a pleasant taste in most humans.

Sour and salt tastes can be pleasant in small quantities, but in larger quantities become more and more unpleasant to taste. For sour taste this is presumably because the sour taste can signal under-ripe fruit, rotten meat, and other spoiled foods, which can be dangerous to the body because of bacteria which grow in such media. Additionally, sour taste signals acids, which can cause serious tissue damage.

Bitter is a generally negative flavor, though its method of action is unknown. It has the characteristic of accustomed enjoyment.

Sweet taste signals the presence of carbohydrates in solution. Since carbohydrates have a very high calorie count (saccharides have many bonds, therefore much energy), they are desirable to the human body, which evolved to seek out the highest calorie intake foods. They are used as direct energy (sugars) and storage of energy (glycogen). However, there are many non-carbohydrate molecules that trigger a sweet response, leading to the development of many artificial sweeteners, including saccharin, sucralose, and aspartame. It is still unclear how these substances activate the sweet receptors and what adaptational significance this has had.

The savory taste (known in Japanese as "umami") was identified by Japanese chemist Kikunae Ikeda of Tokyo Imperial University, which signals the presence of the amino acid L-glutamate, triggers a pleasurable response and thus encourages the intake of peptides and proteins. The amino acids in proteins are used in the body to build muscles and organs, transport molecules (hemoglobin), antibodies, and the organic catalysts known as enzymes. These are all critical molecules, and as such it is important to have a steady supply of amino acids, hence the pleasurable response to their presence in the mouth.

In Asian countries within the sphere of mainly Chinese and Indian cultural influence, pungency (piquancy or hotness) had traditionally been considered a sixth basic taste. In 2015, researchers suggested a new basic taste of fatty acids called fat taste, although oleogustus and pinguis have both been proposed as alternate terms.

Sweetness Main article: Sweetness

Sweetness, usually regarded as a pleasurable sensation, is produced by the presence of sugars and substances that mimic sugar. Sweetness may be connected to aldehydes and ketones, which contain a carbonyl group. Sweetness is detected by a variety of G protein coupled receptors (GPCR) coupled to the G protein gustducin found on the taste buds. At least two different variants of the "sweetness receptors" must be activated for the brain to register sweetness. Compounds the brain senses as sweet are compounds that can bind with varying bond strength to two different sweetness receptors. These receptors are T1R2+3 (heterodimer) and T1R3 (homodimer), which account for all sweet sensing in humans and animals. Taste detection thresholds for sweet substances are rated relative to sucrose, which has an index of 1. The average human detection threshold for sucrose is 10 millimoles per liter. For lactose it is 30 millimoles per liter, with a sweetness index of 0.3, and 5-nitro-2-propoxyaniline 0.002 millimoles per liter. "Natural" sweeteners such as saccharides activate the GPCR, which releases gustducin. The gustducin then activates the molecule adenylate cyclase, which catalyzes the production of the molecule cAMP, or adenosine 3', 5'-cyclic monophosphate. This molecule closes potassium ion channels, leading to depolarization and neurotransmitter release. Synthetic sweeteners such as saccharin activate different GPCRs and induce taste receptor cell depolarization by an alternate pathway.

Sourness "Sour" redirects here. For other uses, see Sour (disambiguation).

Sourness is the taste that detects acidity. The sourness of substances is rated relative to dilute hydrochloric acid, which has a sourness index of 1. By comparison, tartaric acid has a sourness index of 0.7, citric acid an index of 0.46, and carbonic acid an index of 0.06.

Sour taste is detected by a small subset of cells that are distributed across all taste buds in the tongue. Sour taste cells can be identified by expression of the protein PKD2L1, although this gene is not required for sour responses. There is evidence that the protons that are abundant in sour substances can directly enter the sour taste cells through apically located ion channels. In 2018, the proton-elective ion channel otopetrin 1 (Otop1) was implicated as the primary mediator of this proton influx. This transfer of positive charge into the cell can itself trigger an electrical response. It has also been proposed that weak acids such as acetic acid, which is not fully dissociated at physiological pH values, can penetrate taste cells and thereby elicit an electrical response. According to this mechanism, intracellular hydrogen ions inhibit potassium channels, which normally function to hyperpolarize the cell. By a combination of direct intake of hydrogen ions (which itself depolarizes the cell) and the inhibition of the hyperpolarizing channel, sourness causes the taste cell to fire action potentials and release neurotransmitter.

The most common foods with natural sourness are fruits, such as lemon, grape, orange, tamarind, and bitter melon. Fermented foods, such as wine, vinegar or yogurt, may have sour taste. Children in the US and UK show a greater enjoyment of sour flavors than adults, and sour candy containing citric acid or malic acid is common.

Saltiness "Saltiness" redirects here. For the saltiness in the water, see Salinity. The simplest receptor found in the mouth is the sodium chloride (salt) receptor. Saltiness is a taste produced primarily by the presence of sodium ions. Other ions of the alkali metals group also taste salty, but the further from sodium, the less salty the sensation is. A sodium channel in the taste cell wall allows sodium cations to enter the cell. This on its own depolarizes the cell, and opens voltage-dependent calcium channels, flooding the cell with positive calcium ions and leading to neurotransmitter release. This sodium channel is known as an epithelial sodium channel (ENaC) and is composed of three subunits. An ENaC can be blocked by the drug amiloride in many mammals, especially rats. The sensitivity of the salt taste to amiloride in humans, however, is much less pronounced, leading to conjecture that there may be additional receptor proteins besides ENaC to be discovered.

The size of lithium and potassium ions most closely resemble those of sodium, and thus the saltiness is most similar. In contrast, rubidium and caesium ions are far larger, so their salty taste differs accordingly.[citation needed] The saltiness of substances is rated relative to sodium chloride (NaCl), which has an index of 1. Potassium, as potassium chloride (KCl), is the principal ingredient in salt substitutes and has a saltiness index of 0.6.

Other monovalent cations, e.g. ammonium (NH4+), and divalent cations of the alkali earth metal group of the periodic table, e.g. calcium (Ca2+), ions generally elicit a bitter rather than a salty taste even though they, too, can pass directly through ion channels in the tongue, generating an action potential. But the chloride of calcium is saltier and less bitter than potassium chloride, and is commonly used in pickle brine instead of KCl.

Bitterness See also: Bitter taste evolution

Bitterness is one of the most sensitive of the tastes, and many perceive it as unpleasant, sharp, or disagreeable, but it is sometimes desirable and intentionally added via various bittering agents. Common bitter foods and beverages include coffee, unsweetened cocoa, South American mate, coca tea, bitter gourd, uncured olives, citrus peel, many plants in the family Brassicaceae, dandelion greens, horehound, wild chicory, and escarole. The ethanol in alcoholic beverages tastes bitter, as do the additional bitter ingredients found in some alcoholic beverages including hops in beer and gentiana in bitters. Quinine is also known for its bitter taste and is found in tonic water.

Bitterness is of interest to those who study evolution, as well as various health researchers since a large number of natural bitter compounds are known to be toxic. The ability to detect bitter-tasting, toxic compounds at low thresholds is considered to provide an important protective function. Plant leaves often contain toxic compounds, and among leaf-eating primates there is a tendency to prefer immature leaves, which tend to be higher in protein and lower in fiber and poisons than mature leaves. Amongst humans, various food processing techniques are used worldwide to detoxify otherwise inedible foods and make them palatable. Furthermore, the use of fire, changes in diet, and avoidance of toxins has led to neutral evolution in human bitter sensitivity. This has allowed several loss of function mutations that has led to a reduced sensory capacity towards bitterness in humans when compared to other species.

The threshold for stimulation of bitter taste by quinine averages a concentration of 8 M (8 micromolar). The taste thresholds of other bitter substances are rated relative to quinine, which is thus given a reference index of 1. For example, brucine has an index of 11, is thus perceived as intensely more bitter than quinine, and is detected at a much lower solution threshold. The most bitter natural substance is amarogentin a compound present in the roots of the plant gentiana lutea and the most bitter substance known is the synthetic chemical denatonium, which has an index of 1,000. It is used as an aversive agent (a bitterant) that is added to toxic substances to prevent accidental ingestion. It was discovered accidentally in 1958 during research on a local anesthetic, by MacFarlan Smith of Gorgie, Edinburgh, Scotland.

Research has shown that TAS2Rs (taste receptors, type 2, also known as T2Rs) such as TAS2R38 coupled to the G protein gustducin are responsible for the human ability to taste bitter substances. They are identified not only by their ability to taste for certain "bitter" ligands, but also by the morphology of the receptor itself (surface bound, monomeric). The TAS2R family in humans is thought to comprise about 25 different taste receptors, some of which can recognize a wide variety of bitter-tasting compounds. Over 670 bitter-tasting compounds have been identified, on a bitter database, of which over 200 have been assigned to one or more specific receptors. Recently it is speculated that the selective constraints on the TAS2R family have been weakened due to the relatively high rate of mutation and pseudogenization. Researchers use two synthetic substances, phenylthiocarbamide (PTC) and 6-n-propylthiouracil (PROP) to study the genetics of bitter perception. These two substances taste bitter to some people, but are virtually tasteless to others. Among the tasters, some are so-called "supertasters" to whom PTC and PROP are extremely bitter. The variation in sensitivity is determined by two common alleles at the TAS2R38 locus. This genetic variation in the ability to taste a substance has been a source of great interest to those who study genetics.

Gustducin is made of three subunits. When it is activated by the GPCR, its subunits break apart and activate phosphodiesterase, a nearby enzyme, which in turn converts a precursor within the cell into a secondary messenger, which closes potassium ion channels.[citation needed] Also, this secondary messenger can stimulate the endoplasmic reticulum to release Ca2+ which contributes to depolarization. This leads to a build-up of potassium ions in the cell, depolarization, and neurotransmitter release. It is also possible for some bitter tastants to interact directly with the G protein, because of a structural similarity to the relevant GPCR.

Savoriness Main article: Umami Savory, or savoriness is an appetitive taste and is occasionally described by its Japanese name, umami or "meaty". It can be tasted in cheese and soy sauce. A loanword from Japanese meaning "good flavor" or "good taste", umami ( ) is considered fundamental to many Asian cuisines and dates back to the Romans' deliberate use of fermented fish sauce (also called garum).

Umami was first studied in 1907 by isolating its dashi taste called ajinomoto, Japanese for "at the origin of flavor", later identified as the chemical monosodium glutamate (MSG). MSG is a sodium salt that produces a strong savory taste, especially combined with foods rich in nucleotides such as meats, fish, nuts, and mushrooms.

Some savory taste buds respond specifically to glutamate in the same way that "sweet" ones respond to sugar. Glutamate binds to a variant of G protein coupled glutamate receptors. L-glutamate may bond to a type of GPCR known as a metabotropic glutamate receptor (mGluR4) which causes the G-protein complex to activate the sensation of umami.

In the human body a stimulus refers to a form of energy which elicits a physiological or psychological action or response. Sensory receptors are the structures in the body which change the stimulus from one form of energy to another. This can mean changing the presence of a chemical, sound wave, source of heat, or touch to the skin into an electrical action potential which can be understood by the brain, the body's control center. Sensory receptors are modified ends of sensory neurons; modified to deal with specific types of stimulus, thus there are many different types of sensory receptors in the body. The neuron is the primary component of the nervous system, which transmits messages from sensory receptors all over the body.

Taste is a form of chemoreception which occurs in the specialised taste receptors in the mouth. To date, there are five different types of taste these receptors can detect which are recognized: salt, sweet, sour, bitter, and umami. Each type of receptor has a different manner of sensory transduction: that is, of detecting the presence of a certain compound and starting an action potential which alerts the brain. It is a matter of debate whether each taste cell is tuned to one specific tastant or to several; Smith and Margolskee claim that "gustatory neurons typically respond to more than one kind of stimulus, [a]lthough each neuron responds most strongly to one tastant". Researchers[who?] believe that the brain interprets complex tastes by examining patterns from a large set of neuron responses. This enables the body to make "keep or spit out" decisions when there is more than one tastant present. "No single neuron type alone is capable of discriminating among stimuli or different qualities, because a given cell can respond the same way to disparate stimuli."[citation needed] As well, serotonin is thought to act as an intermediary hormone which communicates with taste cells within a taste bud, mediating the signals being sent to the brain. Receptor molecules are found on the top of microvilli of the taste cells.

Sweetness Sweetness is produced by the presence of sugars, some proteins, and other substances such as alcohols like anethol, glycerol and propylene glycol, saponins such as glycyrrhizin, artificial sweeteners (organic compounds with a variety of structures), and lead compounds such as lead acetate.[citation needed] It is often connected to aldehydes and ketones, which contain a carbonyl group.[citation needed] Many foods can be perceived as sweet despite of the sugar content, alcoholic drinks can taste sweet despite of having sugar or not, some plants such as liquorice, anise or stevia are sometimes used as sweeteners. Rebaudioside A is a steviol glycoside coming from stevia that is 200 times sweeter than sugar. Lead acetate and other lead compounds were used as sweeteners, mostly for wine, until lead poisoning became known. Romans used to deliberately boil the must inside of lead vessels to make a sweeter wine. Sweetness is detected by a variety of G protein-coupled receptors coupled to a G protein that acts as an intermediary in the communication between taste bud and brain, gustducin. These receptors are T1R2+3 (heterodimer) and T1R3 (homodimer), which account for sweet sensing in humans and other animals.

Saltiness Saltiness is a taste produced best by the presence of cations (such as Na+ , K+ or Li+) and is directly detected by cation influx into glial like cells via leak channels causing depolarisation of the cell.

Other monovalent cations, e.g., ammonium, NH+ 4, and divalent cations of the alkali earth metal group of the periodic table, e.g., calcium, Ca2+ , ions, in general, elicit a bitter rather than a salty taste even though they, too, can pass directly through ion channels in the tongue.[citation needed]

Sourness Sourness is acidity, and, like salt, it is a taste sensed using ion channels. Undissociated acid diffuses across the plasma membrane of a presynaptic cell, where it dissociates in accordance with Le Chatelier's principle. The protons that are released then block potassium channels, which depolarise the cell and cause calcium influx. In addition, the taste receptor PKD2L1 has been found to be involved in tasting sour.

Bitterness Research has shown that TAS2Rs (taste receptors, type 2, also known as T2Rs) such as TAS2R38 are responsible for the human ability to taste bitter substances. They are identified not only by their ability to taste certain bitter ligands, but also by the morphology of the receptor itself (surface bound, monomeric).

Savoriness The amino acid glutamic acid is responsible for savoriness, but some nucleotides (inosinic acid and guanylic acid) can act as complements, enhancing the taste.

Glutamic acid binds to a variant of the G protein-coupled receptor, producing a savory taste.

Further sensations and transmission The tongue can also feel other sensations not generally included in the basic tastes. These are largely detected by the somatosensory system. In humans, the sense of taste is conveyed via three of the twelve cranial nerves. The facial nerve (VII) carries taste sensations from the anterior two thirds of the tongue, the glossopharyngeal nerve (IX) carries taste sensations from the posterior one third of the tongue while a branch of the vagus nerve (X) carries some taste sensations from the back of the oral cavity.

The trigeminal nerve (cranial nerve V) provides information concerning the general texture of food as well as the taste-related sensations of peppery or hot (from spices).

The glossopharyngeal nerve innervates a third of the tongue including the circumvallate papillae. The facial nerve innervates the other two thirds of the tongue and the cheek via the chorda tympani.

The pterygopalatine ganglia are ganglia (one on each side) of the soft palate. The greater petrosal, lesser palatine and zygomatic nerves all synapse here. The greater petrosal, carries soft palate taste signals to the facial nerve. The lesser palatine sends signals to the nasal cavity; which is why spicy foods cause nasal drip. The zygomatic sends signals to the lacrimal nerve that activate the lacrimal gland; which is the reason that spicy foods can cause tears. Both the lesser palatine and the zygomatic are maxillary nerves (from the trigeminal nerve).

The special visceral afferents of the vagus nerve carry taste from the epiglottal region of the tongue.

The lingual nerve (trigeminal, not shown in diagram) is deeply interconnected with chorda tympani in that it provides all other sensory info from the of the tongue. This info is processed separately (nearby) in rostal lateral subdivision of nucleus of the solitary tract (NST).

NST receives input from the amygdala (regulates oculomotor nuclei output), bed nuclei of stria terminalis, hypothalamus, and prefrontal cortex. NST is the topographical map that processes gustatory and sensory (temp, texture, etc.) info.

Reticular formation (includes Raphe nuclei responsible for serotonin production) is signaled to release serotonin during and after a meal to suppress appetite. Similarly, salivary nuclei are signaled to decrease saliva secretion.

Hypoglossal and thalamic connections aid in oral-related movements.

Hypothalamus connections hormonally regulate hunger and the digestive system.

Substantia innominata connects the thalamus, temporal lobe, and insula.

Edinger-Westphal nucleus reacts to taste stimuli by dilating and constricting the pupils.

Spinal ganglion are involved in movement.

The frontal operculum is speculated to be the memory and association hub for taste.[citation needed]

The insula cortex aids in swallowing and gastric motility.

Chapter 10

The Auditory and Vestibular Systems

The ear is the organ of hearing and, in mammals, balance. In mammals, the ear is usually described as having three parts—the outer ear, the middle ear and the inner ear. The outer ear consists of the pinna and the ear canal. Since the outer ear is the only visible portion of the ear in most animals, the word "ear" often refers to the external part alone. The middle ear includes the tympanic cavity and the three ossicles. The inner ear sits in the bony labyrinth, and contains structures which are key to several senses: the semicircular canals, which enable balance and eye tracking when moving; the utricle and saccule, which enable balance when stationary; and the cochlea, which enables hearing. The ears of vertebrates are placed somewhat symmetrically on either side of the head, an arrangement that aids sound localisation.

The ear develops from the first pharyngeal pouch and six small swellings that develop in the early embryo called otic placodes, which are derived from ectoderm.

The human ear consists of three parts—the outer ear, middle ear and inner ear. The ear canal of the outer ear is separated from the air-filled tympanic cavity of the middle ear by the eardrum. The middle ear contains the three small bones—the ossicles—involved in the transmission of sound, and is connected to the throat at the nasopharynx, via the pharyngeal opening of the Eustachian tube. The inner ear contains the otolith organs—the utricle and saccule—and the semicircular canals belonging to the vestibular system, as well as the cochlea of the auditory system.

10.1 The Auditory System

Hearing, or auditory perception, is the ability to perceive sounds by detecting vibrations, changes in the pressure of the surrounding medium through time, through an organ such as the ear. The academic field concerned with hearing is auditory science.

Sound may be heard through solid, liquid, or gaseous matter. It is one of the traditional five senses; partial or total inability to hear is called hearing loss.

In humans and other vertebrates, hearing is performed primarily by the auditory system: mechanical waves, known as vibrations, are detected by the ear and transduced into nerve impulses that are perceived by the brain (primarily in the temporal lobe). Like touch, audition requires sensitivity to the movement of molecules in the world outside the organism. Both hearing and touch are types of mechanosensation.

The outer ear funnels sound vibrations to the eardrum, increasing the sound pressure in the middle frequency range. The middle-ear ossicles further amplify the vibration pressure roughly 20 times. The base of the stapes couples vibrations into the cochlea via the oval window, which vibrates the perilymph liquid (present throughout the inner ear) and causes the round window to bulb out as the oval window bulges in.

Vestibular and tympanic ducts are filled with perilymph, and the smaller cochlear duct between them is filled with endolymph, a fluid with a very different ion concentration and voltage. Vestibular duct perilymph vibrations bend organ of Corti outer cells (4 lines) causing prestin to be released in cell tips. This causes the cells to be chemically elongated and shrunk (somatic motor), and hair bundles to shift which, in turn, electrically affects the basilar membrane's movement (hair-bundle motor). These motors (outer hair cells) amplify the traveling wave amplitudes over 40-fold. The outer hair cells (OHC) are minimally innervated by spiral ganglion in slow (unmyelinated) reciprocal communicative bundles (30+ hairs per nerve fiber); this contrasts inner hair cells (IHC) that have only afferent innervation (30+ nerve fibers per one hair) but are heavily connected. There are three to four times as many OHCs as IHCs. The basilar membrane (BM) is a barrier between scalae, along the edge of which the IHCs and OHCs sit. Basilar membrane width and stiffness vary to control the frequencies best sensed by the IHC. At the cochlear base the BM is at its narrowest and most stiff (high-frequencies), while at the cochlear apex it is at its widest and least stiff (low-frequencies). The tectorial membrane (TM) helps facilitate cochlear amplification by stimulating OHC (direct) and IHC (via endolymph vibrations). TM width and stiffness parallels BM's and similarly aids in frequency differentiation.

The superior olivary complex (SOC), in pons, is the first convergence of the left and right cochlear pulses. SOC has 14 described nuclei; their abbreviation are used here (see Superior olivary complex for their full names). MSO determines the angle the sound came from by measuring time differences in left and right info. LSO normalizes sound levels between the ears; it uses the sound intensities to help determine sound angle. LSO innervates the IHC. VNTB innervate OHC. MNTB inhibit LSO via glycine. LNTB are glycine-immune, used for fast signalling. DPO are high-frequency and tonotopical. DLPO are low-frequency and tonotopical. VLPO have the same function as DPO, but act in a different area. PVO, CPO, RPO, VMPO, ALPO and SPON (inhibited by glycine) are various signalling and inhibiting nuclei.

The trapezoid body is where most of the cochlear nucleus (CN) fibers decussate (cross left to right and vice versa); this cross aids in sound localization. The CN breaks into ventral (VCN) and dorsal (DCN) regions. The VCN has three nuclei.[clarification needed] Bushy cells transmit timing info, their shape averages timing jitters. Stellate (chopper) cells encode sound spectra (peaks and valleys) by spatial neural firing rates based on auditory input strength (rather than frequency). Octopus cells have close to the best temporal precision while firing, they decode the auditory timing code. The DCN has 2 nuclei. DCN also receives info from VCN. Fusiform cells integrate information to determine spectral cues to locations (for example, whether a sound originated from in front or behind). Cochlear nerve fibers (30,000+) each have a most sensitive frequency and respond over a wide range of levels.

Simplified, nerve fibers' signals are transported by bushy cells to the binaural areas in the olivary complex, while signal peaks and valleys are noted by stellate cells, and signal timing is extracted by octopus cells. The lateral lemniscus has three nuclei: dorsal nuclei respond best to bilateral input and have complexity tuned responses; intermediate nuclei have broad tuning responses; and ventral nuclei have broad and moderately complex tuning curves. Ventral nuclei of lateral lemniscus help the inferior colliculus (IC) decode amplitude modulated sounds by giving both phasic and tonic responses (short and long notes, respectively). IC receives inputs not shown, including visual (pretectal area: moves eyes to sound. superior colliculus: orientation and behavior toward objects, as well as eye movements (saccade)) areas, pons (superior cerebellar peduncle: thalamus to cerebellum connection/hear sound and learn behavioral response), spinal cord (periaqueductal grey: hear sound and instinctually move), and thalamus. The above are what implicate IC in the 'startle response' and ocular reflexes. Beyond multi-sensory integration IC responds to specific amplitude modulation frequencies, allowing for the detection of pitch. IC also determines time differences in binaural hearing. The medial geniculate nucleus divides into ventral (relay and relay-inhibitory cells: frequency, intensity, and binaural info topographically relayed), dorsal (broad and complex tuned nuclei: connection to somatosensory info), and medial (broad, complex, and narrow tuned nuclei: relay intensity and sound duration). The auditory cortex (AC) brings sound into awareness/perception. AC identifies sounds (sound-name recognition) and also identifies the sound's origin location. AC is a topographical frequency map with bundles reacting to different harmonies, timing and pitch. Right-hand-side AC is more sensitive to tonality, left-hand-side AC is more sensitive to minute sequential differences in sound. Rostromedial and ventrolateral prefrontal cortices are involved in activation during tonal space and storing short-term memories, respectively. The Heschl's gyrus/transverse temporal gyrus includes Wernicke's area and functionality, it is heavily involved in emotion-sound, emotion-facial-expression, and sound-memory processes. The entorhinal cortex is the part of the 'hippocampus system' that aids and stores visual and auditory memories. The supramarginal gyrus (SMG) aids in language comprehension and is responsible for compassionate responses. SMG links sounds to words with the angular gyrus and aids in word choice. SMG integrates tactile, visual, and auditory info.

The folds of cartilage surrounding the ear canal are called the pinna. Sound waves are reflected and attenuated when they hit the pinna, and these changes provide additional information that will help the brain determine the sound direction.

The sound waves enter the auditory canal, a deceptively simple tube. The ear canal amplifies sounds that are between 3 and 12 kHz. The tympanic membrane, at the far end of the ear canal marks the beginning of the middle ear.

Middle ear Main article: Middle ear

Auditory ossicles from a deep dissection of the tympanic cavity Sound waves travel through the ear canal and hit the tympanic membrane, or eardrum. This wave information travels across the air-filled middle ear cavity via a series of delicate bones: the malleus (hammer), incus (anvil) and stapes (stirrup). These ossicles act as a lever, converting the lower-pressure eardrum sound vibrations into higher-pressure sound vibrations at another, smaller membrane called the oval window or vestibular window. The manubrium (handle) of the malleus articulates with the tympanic membrane, while the footplate (base) of the stapes articulates with the oval window. Higher pressure is necessary at the oval window than at the typanic membrane because the inner ear beyond the oval window contains liquid rather than air. The stapedius reflex of the middle ear muscles helps protect the inner ear from damage by reducing the transmission of sound energy when the stapedius muscle is activated in response to sound. The middle ear still contains the sound information in wave form; it is converted to nerve impulses in the cochlea.

Inner ear Cochlea Gray928.png Diagrammatic longitudinal section of the cochlea. The cochlear duct, or scala media, is labeled as ductus cochlearis at right. Anatomical terminology [edit on Wikidata] Main article: Inner ear The inner ear consists of the cochlea and several non-auditory structures. The cochlea has three fluid-filled sections (i.e. the scala media, scala tympani and scala vestibuli), and supports a fluid wave driven by pressure across the basilar membrane separating two of the sections. Strikingly, one section, called the cochlear duct or scala media, contains endolymph. Endolymph is a fluid similar in composition to the intracellular fluid found inside cells. The organ of Corti is located in this duct on the basilar membrane, and transforms mechanical waves to electric signals in neurons. The other two sections are known as the scala tympani and the scala vestibuli. These are located within the bony labyrinth, which is filled with fluid called perilymph, similar in composition to cerebrospinal fluid. The chemical difference between the fluids endolymph and perilymph fluids is important for the function of the inner ear due to electrical potential differences between potassium and calcium ions.

The plan view of the human cochlea (typical of all mammalian and most vertebrates) shows where specific frequencies occur along its length. The frequency is an approximately exponential function of the length of the cochlea within the Organ of Corti. In some species, such as bats and dolphins, the relationship is expanded in specific areas to support their active sonar capability.

10.2 Organ of Corti

The organ of Corti, or spiral organ, is the receptor organ for hearing and is located in the mammalian cochlea. This highly varied strip of epithelial cells allows for transduction of auditory signals into nerve impulses' action potential. Transduction occurs through vibrations of structures in the inner ear causing displacement of cochlear fluid and movement of hair cells at the organ of Corti to produce electrochemical signals.

Italian anatomist Alfonso Giacomo Gaspare Corti (1822–1876) discovered the organ of Corti in 1851. The structure evolved from the basilar papilla and is crucial for mechanotransduction in mammals.

The organ of Corti is located in the scala media of the cochlea of the inner ear between the vestibular duct and the tympanic duct and is composed of mechanosensory cells, known as hair cells. Strategically positioned on the basilar membrane of the organ of Corti are three rows of outer hair cells (OHCs) and one row of inner hair cells (IHCs). Separating these hair cells are supporting cells: Deiters cells, also called phalangeal cells, which separate and support both the OHCs and the IHCs.

Projecting from the tips of the hair cells are tiny finger like projections called stereocilia, which are arranged in a graduated fashion with the shortest stereocilia on the outer rows and the longest in the center. This gradation is thought to be the most important anatomic feature of the organ of Corti because this allows the sensory cells superior tuning capability.

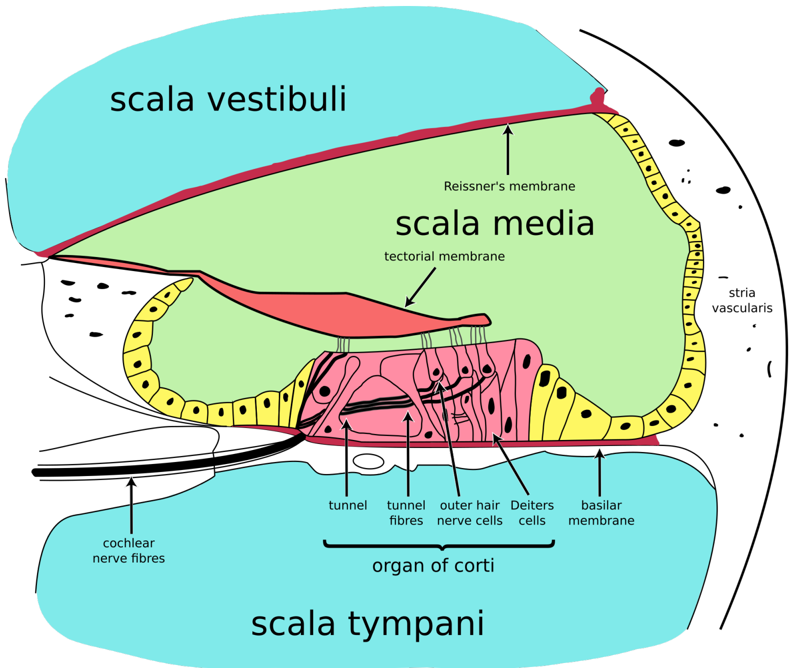


Figure 10.1: A cross section of the cochlea illustrating the organ of Corti.[1]

If the cochlea were uncoiled it would roll out to be about 33 mm long in women and 34 mm in men, with about 2.28 mm of standard deviation for the population. The cochlea is also tonotopically organized, meaning that different frequencies of sound waves interact with different locations on the structure. The base of the cochlea, closest to the outer ear, is the most stiff and narrow and is where the high frequency sounds are transduced. The apex, or top, of the cochlea is wider and much more flexible and loose and functions as the transduction site for low frequency sounds.

Function The function of the organ of Corti is to transduce auditory signals and minimise the hair cells' extraction of sound energy. It is the auricle and middle ear that act as mechanical transformers and amplifiers so that the sound waves end up with amplitudes 22 times greater than when they entered the ear.

Auditory transduction In normal hearing subjects, the majority of the auditory signals that reach the organ of Corti in the first place come from the outer ear. Sound waves enter through the auditory canal and vibrate the tympanic membrane, also known as the eardrum, which vibrates three small bones called the ossicles. As a result, the attached oval window moves and causes movement of the round window, which leads to displacement of the cochlear fluid. However, the stimulation can happen also via direct vibration of the cochlea from the skull. The latter is referred to as Bone Conduction (or BC) hearing, as complementary to the first one described, which is instead called Air Conduction (or AC) hearing. Both AC and BC stimulate the basilar membrane in the same way (Békésy, G.v., Experiments in Hearing. 1960).

The basilar membrane on the tympanic duct presses against the hair cells of the organ as perilymphatic pressure waves pass. The stereocilia atop the IHCs move with this fluid displacement and in response their cation, or positive ion selective, channels are pulled open by cadherin structures called tip links that connect adjacent stereocilia. The organ of Corti, surrounded in potassium rich fluid endolymph, lies on the basilar membrane at the base of the scala media. Under the organ of Corti is the scala tympani and above it, the scala vestibuli. Both structures exist in a low potassium fluid called perilymph. Because those stereocilia are in the midst of a high concentration of potassium, once their cation channels are pulled open, potassium ions as well as calcium ions flow into the top of the hair cell. With this influx of positive ions the IHC becomes depolarized, opening voltage-gated calcium channels at the basolateral region of the hair cells and triggering the release of the neurotransmitter glutamate. An electrical signal is then sent through the auditory nerve and into the auditory cortex of the brain as a neural message.

Cochlear amplification The organ of Corti is also capable of modulating the auditory signal. The outer hair cells (OHCs) can amplify the signal through a process called electromotility where they increase movement of the basilar and tectorial membranes and therefore increase deflection of stereocilia in the IHCs.

A crucial piece to this cochlear amplification is the motor protein prestin, which changes shape based on the voltage potential inside of the hair cell. When the cell is depolarized, prestin shortens, and because it is located on the membrane of OHCs it then pulls on the basilar membrane and increasing how much the membrane is deflected, creating a more intense effect on the inner hair cells (IHCs). When the cell hyperpolarizes prestin lengthens and eases tension on the IHCs, which decreases the neural impulses to the brain. In this way, the hair cell itself is able to modify the auditory signal before it even reaches the brain.

The organ of Corti forms a ribbon of sensory epithelium which runs lengthwise down the cochlea's entire scala media. Its hair cells transform the fluid waves into nerve signals. The journey of countless nerves begins with this first step; from here, further processing leads to a panoply of auditory reactions and sensations.

Hair cell

Hair cells are columnar cells, each with a bundle of 100–200 specialized cilia at the top, for which they are named. There are two types of hair cells; inner and outer hair cells. Inner hair cells are the mechanoreceptors for hearing: they transduce the vibration of sound into electrical activity in nerve fibers, which is transmitted to the brain. Outer hair cells are a motor structure. Sound energy causes changes in the shape of these cells, which serves to amplify sound vibrations in a frequency specific manner. Lightly resting atop the longest cilia of the inner hair cells is the tectorial membrane, which moves back and forth with each cycle of sound, tilting the cilia, which is what elicits the hair cells' electrical responses.

Inner hair cells, like the photoreceptor cells of the eye, show a graded response, instead of the spikes typical of other neurons. These graded potentials are not bound by the "all or none" properties of an action potential.

At this point, one may ask how such a wiggle of a hair bundle triggers a difference in membrane potential. The current model is that cilia are attached to one another by "tip links", structures which link the tips of one cilium to another. Stretching and compressing, the tip links may open an ion channel and produce the receptor potential in the hair cell. Recently it has been shown that cadherin-23 CDH23 and protocadherin-15 PCDH15 are the adhesion molecules associated with these tip links. It is thought that a calcium driven motor causes a shortening of these links to regenerate tensions. This regeneration of tension allows for apprehension of prolonged auditory stimulation.

Afferent neurons innervate cochlear inner hair cells, at synapses where the neurotransmitter glutamate communicates signals from the hair cells to the dendrites of the primary auditory neurons.

There are far fewer inner hair cells in the cochlea than afferent nerve fibers – many auditory nerve fibers innervate each hair cell. The neural dendrites belong to neurons of the auditory nerve, which in turn joins the vestibular nerve to form the vestibulocochlear nerve, or cranial nerve number VIII. The region of the basilar membrane supplying the inputs to a particular afferent nerve fibre can be considered to be its receptive field.

Efferent projections from the brain to the cochlea also play a role in the perception of sound, although this is not well understood. Efferent synapses occur on outer hair cells and on afferent (towards the brain) dendrites under inner hair cells

Cochlear nucleus

The cochlear nucleus is the first site of the neuronal processing of the newly converted "digital" data from the inner ear (see also binaural fusion). In mammals, this region is anatomically and physiologically split into two regions, the dorsal cochlear nucleus (DCN), and ventral cochlear nucleus (VCN). The VCN is further divided by the nerve root into the posteroventral cochlear nucleus (PVCN) and the anteroventral cochlear nucleus (AVCN).

Trapezoid body

The trapezoid body is a bundle of decussating fibers in the ventral pons that carry information used for binaural computations in the brainstem. Some of these axons come from the cochlear nucleus and cross over to the other side before traveling on to the superior olivary nucleus. This is believed to help with localization of sound.

Superior olivary complex

The superior olivary complex is located in the pons, and receives projections predominantly from the ventral cochlear nucleus, although the dorsal cochlear nucleus projects there as well, via the ventral acoustic stria. Within the superior olivary complex lies the lateral superior olive (LSO) and the medial superior olive (MSO). The former is important in detecting interaural level differences while the latter is important in distinguishing interaural time difference.

Lateral lemniscus in red, as it connects the cochlear nucleus, superior olivary nucleus and the inferior colliculus, seen from behind

Lateral lemniscus 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.

Inferior colliculi The inferior colliculi (IC) are located just below the visual processing centers known as the superior colliculi. The central nucleus of the IC is a nearly obligatory relay in the ascending auditory system, and most likely acts to integrate information (specifically regarding sound source localization from the superior olivary complex and dorsal cochlear nucleus) before sending it to the thalamus and cortex.

Medial geniculate nucleus Main article: Medial geniculate nucleus The medial geniculate nucleus is part of the thalamic relay system.

10.3 Primary auditory cortex

The primary auditory cortex is the first region of cerebral cortex to receive auditory input.

Perception of sound is associated with the left posterior superior temporal gyrus (STG). The superior temporal gyrus contains several important structures of the brain, including Brodmann areas 41 and 42, marking the location of the primary auditory cortex, the cortical region responsible for the sensation of basic characteristics of sound such as pitch and rhythm. We know from research in nonhuman primates that the primary auditory cortex can probably be divided further into functionally differentiable subregions. The neurons of the primary auditory cortex can be considered to have receptive fields covering a range of auditory frequencies and have selective responses to harmonic pitches. Neurons integrating information from the two ears have receptive fields covering a particular region of auditory space.

The primary auditory cortex is surrounded by secondary auditory cortex, and interconnects with it. These secondary areas interconnect with further processing areas in the superior temporal gyrus, in the dorsal bank of the superior temporal sulcus, and in the frontal lobe. In humans, connections of these regions with the middle temporal gyrus are probably important for speech perception. The frontotemporal system underlying auditory perception allows us to distinguish sounds as speech, music, or noise.

From the primary auditory cortex emerge two separate pathways: the auditory ventral stream and auditory dorsal stream. The auditory ventral stream includes the anterior superior temporal gyrus, anterior superior temporal sulcus, middle temporal gyrus and temporal pole. Neurons in these areas are responsible for sound recognition, and extraction of meaning from sentences. The auditory dorsal stream includes the posterior superior temporal gyrus and sulcus, inferior parietal lobule and intra-parietal sulcus. Both pathways project in humans to the inferior frontal gyrus. The most established role of the auditory dorsal stream in primates is sound localization. In humans, the auditory dorsal stream in the left hemisphere is also responsible for speech repetition and articulation, phonological long-term encoding of word names, and verbal working memory.

10.4 The Vestibular System

Providing balance, when moving or stationary, is also a central function of the ear. The ear facilitates two types of balance: static balance, which allows a person to feel the effects of gravity, and dynamic balance, which allows a person to sense acceleration.

Static balance is provided by two ventricles, the utricle and the saccule. Cells lining the walls of these ventricles contain fine filaments, and the cells are covered with a fine gelatinous layer. Each cell has 50–70 small filaments, and one large filament, the kinocilium. Within the gelatinous layer lie otoliths, tiny formations of calcium carbonate. When a person moves, these otoliths shift position. This shift alters the positions of the filaments, which opens ion channels within the cell membranes, creating depolarisation and an action potential that is transmitted to the brain along the vestibulocochlear nerve.

Dynamic balance is provided through the three semicircular canals. These three canals are orthogonal (at right angles) to each other. At the end of each canal is a slight enlargement, known as the ampulla, which contains numerous cells with filaments in a central area called the cupula. The fluid in these canals rotates according to the momentum of the head. When a person changes acceleration, the inertia of the fluid changes. This affects the pressure on the cupula, and results in the opening of ion channels. This causes depolarisation, which is passed as a signal to the brain along the vestibulocochlear nerve. Dynamic balance also helps maintain eye tracking when moving, via the vestibulo–ocular reflex. The vestibular system, in vertebrates, is part of the inner ear. In most mammals, the vestibular system is the sensory system that provides the leading contribution to the sense of balance and spatial orientation for the purpose of coordinating movement with balance. Together with the cochlea, a part of the auditory system, it constitutes the labyrinth of the inner ear in most mammals. As movements consist of rotations and translations, the vestibular system comprises two components: the semicircular canals which indicate rotational movements; and the otoliths which indicate linear accelerations. The vestibular system sends signals primarily to the neural structures that control eye movements, and to the muscles that keep an animal upright and in general control posture. The projections to the former provide the anatomical basis of the vestibulo-ocular reflex, which is required for clear vision; while the projections to the latter provide the anatomical means required to enable an animal to maintain its desired position in space.

The brain uses information from the vestibular system in the head and from proprioception throughout the body to enable the animal to understand its body's dynamics and kinematics (including its position and acceleration) from moment to moment. How these two perceptive sources are integrated to provide the underlying structure of the sensorium is unknown.

Semicircular canal system

Cochlea and vestibular system The semicircular canal system detects rotational movements. The semicircular canals are its main tools to achieve this detection.

Since the world is three-dimensional, the vestibular system contains three semicircular canals in each labyrinth. They are approximately orthogonal (at right angles) to each other, and are the horizontal (or lateral), the anterior semicircular canal (or superior), and the posterior (or inferior) semicircular canal. Anterior and posterior canals may collectively be called vertical semicircular canals.

Movement of fluid within the horizontal semicircular canal corresponds to rotation of the head around a vertical axis (i.e. the neck), as when doing a pirouette. The anterior and posterior semicircular canals detect rotations of the head in the sagittal plane (as when nodding), and in the frontal plane, as when cartwheeling. Both anterior and posterior canals are orientated at approximately 45° between frontal and sagittal planes. The movement of fluid pushes on a structure called the cupula which contains hair cells that transduce the mechanical movement to electrical signals.

The semicircular canals are a component of the bony labyrinth that are at right angles from each other. At one end of each of the semicircular canals is a dilated sac called an osseous ampulla which is more than twice the diameter of the canal. Each ampulla contains an ampulla crest, the crista ampullaris which consists of a thick gelatinous cap called a cupula and many hair cells. The superior and posterior semicircular canals are oriented vertically at right angles to each other. The lateral semicircular canal is about a 30-degree angle from the horizontal plane. The orientations of the canals cause a different canal to be stimulated by movement of the head in different planes, and more than one canal is stimulated at once if the movement is off those planes. The horizontal canal detects angular acceleration of the head when the head is turned and the superior and posterior canals detect vertical head movements when the head is moved up or down. When the head changes position, the endolymph in the canals lags behind due to inertia and this acts on the cupula which bends the cilia of the hair cells. The stimulation of the hair cells sends the message to the brain that acceleration is taking place. The ampullae open into the vestibule by five orifices, one of the apertures being common to two of the canals.

Among species of mammals, the size of the semicircular canals is correlated with their type of locomotion. Specifically, species that are agile and have fast, jerky locomotion have larger canals relative to their body size than those that move more cautiously.

Horizontal semicircular canal The lateral or horizontal canal (external semicircular canal) is the shortest of the three canals. Movement of fluid within this canal corresponds to rotation of the head around a vertical axis (i.e. the neck), or in other words rotation in the transverse plane. This occurs, for example, when you turn your head to the left and right- hand sides before crossing a road

It measures from 12 to 15 mm., and its arch is directed horizontally backward and laterally; thus each semicircular canal stands at right angles to the other two. Its ampullated end corresponds to the upper and lateral angle of the vestibule, just above the oval window, where it opens close to the ampullated end of the superior canal; its opposite end opens at the upper and back part of the vestibule. The lateral canal of one ear is very nearly in the same plane as that of the other.

Superior semicircular canal The superior or anterior semicircular canal is a part of the vestibular system and detects rotations of the head in around the lateral axis, or in other words rotation in the sagittal plane. This occurs, for example, when nodding your head.

It is 15 to 20 mm in length, is vertical in direction, and is placed transversely to the long axis of the petrous part of the temporal bone, on the anterior surface of which its arch forms a round projection. It describes about two-thirds of a circle. Its lateral extremity is ampullated, and opens into the upper part of the vestibule; the opposite end joins with the upper part of the posterior canal to form the crus commune, which opens into the upper and medial part of the vestibule.

Posterior semicircular canal The posterior semicircular canal is a part of the vestibular system that detects rotation of the head around the antero-posterior (sagittal) axis, or in other words rotation in the coronal plane. This occurs, for example, when you move your head to touch your shoulders, or when doing a cartwheel.

It is directed superiorly, as per its nomenclature, and posteriorly, nearly parallel to the posterior surface of the petrous bone. The vestibular aqueduct is immediately medial to it. The posterior canal is part of the bony labyrinth and is used by the vestibular system to detect rotations of the head in the coronal plane. It is the longest of the three canals, measuring from 18 to 22 mm. Its lower or ampullated end opens into the lower and back part of the vestibule, its upper into the crus commune.

Development Findings from a 2009 study demonstrated a critical late role for BMP 2b in the morphogenesis of semicircular canals in the zebrafish inner ear. It is suspected that the role of bmp2 in semicircular canal duct outgrowth is likely to be conserved between different vertebrate species.

Additionally, it has been found that the two semicircular canals found in the lamprey inner ear are developmentally similar to the superior and posterior canals found in humans, as the canals of both organisms arise from two depressions in the otic vesicle during early development. These depressions first form in lampreys between the 11 and 42 millimeter larval stages and form in zebrafish 57 hours post-fertilization

Function

Cochlea and vestibular system See also: Balance (ability) and Equilibrioception The semicircular ducts provide sensory input for experiences of rotary movements. They are oriented along the pitch, roll, and yaw axes.

Each canal is filled with a fluid called endolymph and contains motion sensors within the fluids. At the base of each canal, the bony region of the canal is enlarged which opens into the utricle and has a dilated sac at one end called the osseous ampullae. Within the ampulla is a mound of hair cells and supporting cells called crista ampullaris. These hair cells have many cytoplasmic projections on the apical surface called stereocilia which are embedded in a gelatinous structure called the cupula. As the head rotates the duct moves but the endolymph lags behind owing to inertia. This deflects the cupula and bends the stereocilia within. The bending of these stereocilia alters an electric signal that is transmitted to the brain. Within approximately 10 seconds of achieving constant motion, the endolymph catches up with the movement of the duct and the cupula is no longer affected, stopping the sensation of acceleration. The specific gravity of the cupula is comparable to that of the surrounding endolymph. Consequently, the cupula is not displaced by gravity, unlike the otolithic membranes of the utricle and saccule. As with macular hair cells, hair cells of the crista ampullaris will depolarise when the stereocilia deflect towards the kinocilium. Deflection in the opposite direction results in hyperpolarisation and inhibition. In the horizontal canal, ampullopetal flow is necessary for hair-cell stimulation, whereas ampullofugal flow is necessary for the anterior and posterior canals.

This adjustment period is in part the cause of an illusion known as "the leans" often experienced by pilots. As a pilot enters a turn, hair cells in the semicircular canals are stimulated, telling the brain that the aircraft, and the pilot, are no longer moving in a straight line but rather making a banked turn. If the pilot were to sustain a constant rate turn, the endolymph would eventually catch up with the ducts and cease to deflect the cupula. The pilot would no longer feel as if the aircraft was in a turn. As the pilot exits the turn, the semicircular canals are stimulated to make the pilot think that they are now turning in the opposite direction rather than flying straight and level. In response to this, the pilot will often lean in the direction of the original turn in an attempt to compensate for this illusion. A more serious form of this is called a graveyard spiral. Rather than the pilot leaning in the direction of the original turn, they may actually reenter the turn. As the endolymph stabilizes, the semicircular canals stop registering the gradual turn and the aircraft slowly loses altitude until impact with the ground. Push-pull systems

Push-pull system of the semicircular canals, for a horizontal head movement to the right. The canals are arranged in such a way that each canal on the left side has an almost parallel counterpart on the right side. Each of these three pairs works in a push-pull fashion: when one canal is stimulated, its corresponding partner on the other side is inhibited, and vice versa.

This push-pull system makes it possible to sense all directions of rotation: while the right horizontal canal gets stimulated during head rotations to the right (Fig 2), the left horizontal canal gets stimulated (and thus predominantly signals) by head rotations to the left.

Vertical canals are coupled in a crossed fashion, i.e. stimulations that are excitatory for an anterior canal are also inhibitory for the contralateral posterior, and vice versa.

Otolithic organs While the semicircular canals respond to rotations, the otolithic organs sense linear accelerations. Humans have two otolithic organs on each side, one called the utricle, the other called the saccule. The utricle contains a patch of hair cells and supporting cells called a macula. Similarly, the saccule contains a patch of hair cells and a macula. Each hair cell of a macula has 40-70 stereocilia and one true cilium called a kinocilium. The tips of these cilia are embedded in an otolithic membrane. This membrane is weighted down with protein-calcium carbonate granules called otoconia. These otoconia add to the weight and inertia of the membrane and enhance the sense of gravity and motion. With the head erect, the otolithic membrane bears directly down on the hair cells and stimulation is minimal. When the head is tilted, however, the otolithic membrane sags and bends the stereocilia, stimulating the hair cells. Any orientation of the head causes a combination of stimulation to the utricles and saccules of the two ears. The brain interprets head orientation by comparing these inputs to each other and to other input from the eyes and stretch receptors in the neck, thereby detecting whether the head is tilted or the entire body is tipping. Essentially, these otolithic organs sense how quickly you are accelerating forward or backward, left or right, or up or down. Most of the utricular signals elicit eye movements, while the majority of the saccular signals projects to muscles that control our posture.

While the interpretation of the rotation signals from the semicircular canals is straightforward, the interpretation of otolith signals is more difficult: since gravity is equivalent to a constant linear acceleration, one somehow has to distinguish otolith signals that are caused by linear movements from those caused by gravity. Humans can do that quite well, but the neural mechanisms underlying this separation are not yet fully understood. Humans can sense head tilting and linear acceleration even in dark environments because of the orientation of two groups of hair cell bundles on either side of the striola. Hair cells on opposite sides move with mirror symmetry, so when one side is moved, the other is inhibited. The opposing effects caused by a tilt of the head cause differential sensory inputs from the hair cell bundles allow humans to tell which way the head is tilting, Sensory information is then sent to the brain, which can respond with appropriate corrective actions to the nervous and muscular systems to ensure that balance and awareness are maintained.

Chapter 11

The Visual System

Visual perception is the ability to interpret the surrounding environment using light in the visible spectrum reflected by the objects in the environment. This is different from visual acuity, which refers to how clearly a person sees (for example "20/20 vision"). A person can have problems with visual perceptual processing even if they have 20/20 vision.

The resulting perception is also known as visual perception, eyesight, sight, or vision (adjectival form: visual, optical, or ocular). The various physiological components involved in vision are referred to collectively as the visual system, and are the focus of much research in linguistics, psychology, cognitive science, neuroscience, and molecular biology, collectively referred to as vision science.

Different species are able to see different parts of the light spectrum; for example, bees can see into the ultraviolet, while pit vipers can accurately target prey with their pit organs, which are sensitive to infrared radiation. The mantis shrimp possesses arguably the most complex visual system in any species. The eye of the mantis shrimp holds 16 color receptive cones, whereas humans only have three. The variety of cones enables them to perceive an enhanced array of colors as a mechanism for mate selection, avoidance of predators, and detection of prey. Swordfish also possess an impressive visual system. The eye of a swordfish can generate heat to better cope with detecting their prey at depths of 2000 feet. Certain one-celled micro-organisms, the warnowiid dinoflagellates have eye-like ocelloids, with analogous structures for the lens and retina of the multi-cellular eye. The armored shell of the chiton Acanthopleura granulata is also covered with hundreds of aragonite crystalline eyes, named ocelli, which can form images.

Many fan worms, such as Acromegalomma interruptum which live in tubes on the sea floor of the Great Barrier Reef, have evolved compound eyes on their tentacles, which they use to detect encroaching movement. If movement is detected the fan worms will rapidly withdraw their tentacles. Bok, et al, have discovered opsins and G proteins in the fan worm's eyes, which were previously only seen in simple ciliary photoreceptors in the brains of some invertebrates, as opposed to the rhabdomeric receptors in the eyes of most invertebrates.

Only higher primate Old World (African) monkeys and apes (macaques, apes, orangutans) have the same kind of three-cone photoreceptor color vision humans have, while lower primate New World

(South American) monkeys (spider monkeys, squirrel monkeys, cebus monkeys) have a two-cone photoreceptor kind of color vision.

11.1 The Visual System

The visual system is the part of the central nervous system which gives organisms the ability to process visual detail as sight, as well as enabling the formation of several non-image photo response functions. It detects and interprets information from visible light to build a representation of the surrounding environment. The visual system carries out a number of complex tasks, including the reception of light and the formation of monocular representations; the buildup of a nuclear binocular perception from a pair of two dimensional projections; the identification and categorization of visual objects; assessing distances to and between objects; and guiding body movements in relation to the objects seen. The psychological process of visual information is known as visual perception, a lack of which is called blindness. Non-image forming visual functions, independent of visual perception, include the pupillary light reflex (PLR) and circadian photoentrainment.

Together the cornea and lens refract light into a small image and shine it on the retina. The retina transduces this image into electrical pulses using rods and cones. The optic nerve then carries these pulses through the optic canal. Upon reaching the optic chiasm the nerve fibers decussate (left becomes right). The fibers then branch and terminate in three places.

Most of the optic nerve fibers end in the lateral geniculate nucleus (LGN). Before the LGN forwards the pulses to V1 of the visual cortex (primary) it gauges the range of objects and tags every major object with a velocity tag. These tags predict object movement.

The LGN also sends some fibers to V2 and V3.

V1 performs edge-detection to understand spatial organization (initially, 40 milliseconds in, focusing on even small spatial and color changes. Then, 100 milliseconds in, upon receiving the translated LGN, V2, and V3 info, also begins focusing on global organization). V1 also creates a bottom-up saliency map to guide attention or gaze shft .

V2 both forwards (direct and via pulvinar) pulses to V1 and receives them. Pulvinar is responsible for saccade and visual attention. V2 serves much the same function as V1, however, it also handles illusory contours, determining depth by comparing left and right pulses (2D images), and foreground distinguishment. V2 connects to V1 - V5.

V3 helps process 'global motion' (direction and speed) of objects. V3 connects to V1 (weak), V2, and the inferior temporal cortex.

V4 recognizes simple shapes, gets input from V1 (strong), V2, V3, LGN, and pulvinar. V5's outputs include V4 and its surrounding area, and eye-movement motor cortices (frontal eye-field and lateral intraparietal area).

V5's functionality is similar to that of the other V's, however, it integrates local object motion into global motion on a complex level. V6 works in conjunction with V5 on motion analysis. V5 analyzes self-motion, whereas V6 analyzes motion of objects relative to the background. V6's primary input is V1, with V5 additions. V6 houses the topographical map for vision. V6 outputs to the region directly around it (V6A). V6A has direct connections to arm-moving cortices, including the premotor cortex.

The inferior temporal gyrus recognizes complex shapes, objects, and faces or, in conjunction with the hippocampus, creates new memories. The pretectal area is seven unique nuclei. Anterior, posterior and medial pretectal nuclei inhibit pain (indirectly), aid in REM, and aid the accommodation reflex, respectively. The Edinger-Westphal nucleus moderates pupil dilation and aids (since it provides parasympathetic fibers) in convergence of the eyes and lens adjustment. Nuclei of the optic tract are involved in smooth pursuit eye movement and the accommodation reflex, as well as REM.

The suprachiasmatic nucleus is the region of the hypothalamus that halts production of melatonin (indirectly) at first light.

Eye Main articles: Eye and Anterior segment of eyeball Light entering the eye is refracted as it passes through the cornea. It then passes through the pupil (controlled by the iris) and is further refracted by the lens. The cornea and lens act together as a compound lens to project an inverted image onto the retina.

Retina

S. Ramón y Cajal, Structure of the Mammalian Retina, 1900 Main article: Retina The retina consists of a large number of photoreceptor cells which contain particular protein molecules called opsins. In humans, two types of opsins are involved in conscious vision: rod opsins and cone opsins. (A third type, melanopsin in some of the retinal ganglion cells (RGC), part of the body clock mechanism, is probably not involved in conscious vision, as these RGC do not project to the lateral geniculate nucleus but to the pretectal olivary nucleus.) An opsin absorbs a photon (a particle of light) and transmits a signal to the cell through a signal transduction pathway, resulting in hyper-polarization of the photoreceptor.

Rods and cones differ in function. Rods are found primarily in the periphery of the retina and are used to see at low levels of light. Cones are found primarily in the center (or fovea) of the retina. There are three types of cones that differ in the wavelengths of light they absorb; they are usually called short or blue, middle or green, and long or red. Cones are used primarily to distinguish color and other features of the visual world at normal levels of light.

In the retina, the 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 significant amount of visual processing arises from the patterns of communication between neurons in the retina. About 130 million photo-receptors absorb light, yet roughly 1.2 million axons of ganglion cells transmit information from the retina to the brain. The processing in the retina includes the formation of center-surround receptive fields of bipolar and ganglion cells in the retina, as well as convergence and divergence from photoreceptor to bipolar cell. In addition, other neurons in the retina, particularly horizontal and amacrine cells, transmit information laterally (from a neuron in one layer to an adjacent neuron in the same layer), resulting in more complex receptive fields that can be either indifferent to color and sensitive to motion or sensitive to color and indifferent to motion.

Mechanism of generating visual signals: The retina adapts to change in light through the use of the rods. In the dark, the chromophore retinal has a bent shape called cis-retinal (referring to a cis conformation in one of the double bonds). When light interacts with the retinal, it changes conformation to a straight form called trans-retinal and breaks away from the opsin. This is called bleaching because the purified rhodopsin changes from violet to colorless in the light. At baseline in the dark, the rhodopsin absorbs no light and releases glutamate which inhibits the bipolar cell. This inhibits the release of neurotransmitters from the bipolar cells to the ganglion cell. When there is light present, glutamate secretion ceases thus no longer inhibiting the bipolar cell from releasing neurotransmitters to the ganglion cell and therefore an image can be detected.

The final result of all this processing is five different populations of ganglion cells that send visual (image-forming and non-image-forming) information to the brain:

M cells, with large center-surround receptive fields that are sensitive to depth, indifferent to color, and rapidly adapt to a stimulus; P cells, with smaller center-surround receptive fields that are sensitive to color and shape; K cells, with very large center-only receptive fields that are sensitive to color and indifferent to shape or depth; another population that is intrinsically photosensitive; and a final population that is used for eye movements. A 2006 University of Pennsylvania study calculated the approximate bandwidth of human retinas to be about 8960 kilobits per second, whereas guinea pig retinas transfer at about 875 kilobits.

In 2007 Zaidi and co-researchers on both sides of the Atlantic studying patients without rods and cones, discovered that the novel photoreceptive ganglion cell in humans also has a role in conscious and unconscious visual perception. The peak spectral sensitivity was 481 nm. This shows that there are two pathways for sight in the retina – one based on classic photoreceptors (rods and cones) and the other, newly discovered, based on photo-receptive ganglion cells which act as rudimentary visual brightness detectors.

Photochemistry Main article: Visual cycle The functioning of a camera is often compared with the workings of the eye, mostly since both focus light from external objects in the field of view onto a light-sensitive medium. In the case of the camera, this medium is film or an electronic sensor; in the case of the eye, it is an array of visual receptors. With this simple geometrical similarity, based on the laws of optics, the eye functions as a transducer, as does a CCD camera.

In the visual system, retinal, technically called retinene1 or "retinaldehyde", is a light-sensitive molecule found in the rods and cones of the retina. Retinal is the fundamental structure involved in the transduction of light into visual signals, i.e. nerve impulses in the ocular system of the central nervous system. In the presence of light, the retinal molecule changes configuration and as a result a nerve impulse is generated.

Optic nerve Main article: Optic nerve

Information flow from the eyes (top), crossing at the optic chiasma, joining left and right eye information in the optic tract, and layering left and right visual stimuli in the lateral geniculate nucleus. V1 in red at bottom of image. (1543 image from Andreas Vesalius' Fabrica) The information about the image via the eye is transmitted to the brain along the optic nerve. Different populations of ganglion cells in the retina send information to the brain through the optic nerve. About 90% of the axons in the optic nerve go to the lateral geniculate nucleus in the thalamus. These axons originate from the M, P, and K ganglion cells in the retina, see above. This parallel processing is important for reconstructing the visual world; each type of information will go through a different route to perception. Another population sends information to the superior colliculus in the midbrain, which assists in controlling eye movements (saccades) as well as other motor responses.

A final population of photosensitive ganglion cells, containing melanopsin for photosensitivity, sends information via the retinohypothalamic tract (RHT) to the pretectum (pupillary reflex), to several structures involved in the control of circadian rhythms and sleep such as the suprachiasmatic nucleus (SCN, the biological clock), and to the ventrolateral preoptic nucleus (VLPO, a region involved in sleep regulation). A recently discovered role for photoreceptive ganglion cells is that they mediate conscious and unconscious vision – acting as rudimentary visual brightness detectors as shown in rodless coneless eyes.

Optic chiasm Main article: Optic chiasm The optic nerves from both eyes meet and cross at the optic chiasm, at the base of the hypothalamus of the brain. At this point the information coming from both eyes is combined and then splits according to the visual field. The corresponding halves of the field of view (right and left) are sent to the left and right halves of the brain, respectively, to be processed. That is, the right side of primary visual cortex deals with the left half of the field of view from both eyes, and similarly for the left brain. A small region in the center of the field of view is processed redundantly by both halves of the brain.

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

Six layers in the LGN Lateral geniculate nucleus Main article: Lateral geniculate nucleus The lateral geniculate nucleus (LGN) is a sensory relay nucleus in the thalamus of the brain. The LGN consists of six layers in humans and other primates starting from catarhinians, including cercopithecidae and apes. Layers 1, 4, and 6 correspond to information from the contralateral (crossed) fibers of the nasal retina (temporal visual field); layers 2, 3, and 5 correspond to information from the ipsilateral (uncrossed) fibers of the temporal retina (nasal visual field). Layer one (1) contains M cells which correspond to the M (magnocellular) cells of the optic nerve of the opposite eye and are concerned with depth or motion. Layers four and six (4 & 6) of the LGN also connect to the opposite eye, but to the P cells (color and edges) of the optic nerve. By contrast, layers two, three and five (2, 3, & 5) of the LGN connect to the M cells and P (parvocellular) cells of the optic nerve for the same side of the brain as its respective LGN. Spread out, the six layers of the LGN are the area of a credit card and about three times its thickness. The LGN is rolled up into two ellipsoids about the size and shape of two small birds' eggs. In between the six layers are smaller cells that receive information from the K cells (color) in the retina. The neurons of the LGN then relay the visual image to the primary visual cortex (V1) which is located at the back of the brain (posterior end) in the occipital lobe in and close to the calcarine sulcus. The LGN is not just a simple relay station but it is also a center for processing; it receives reciprocal input from the cortical and subcortical layers and reciprocal innervation from the visual cortex.

Scheme of the optic tract with image being decomposed on the way, up to simple cortical cells (simplified). Optic radiation Main article: Optic radiation The optic radiations, one on each side of the brain, carry information from the thalamic lateral geniculate nucleus to layer 4 of the visual cortex. The P layer neurons of the LGN relay to V1 layer 4C . The M layer neurons relay to V1 layer 4C . The K layer neurons in the LGN relay to large neurons called blobs in layers 2 and 3 of V1.

There is a direct correspondence from an angular position in the visual field of the eye, all the way through the optic tract to a nerve position in V1 (up to V4, i.e. the primary visual areas. After that, the visual pathway is roughly separated into a ventral and dorsal pathway).

Visual cortex Main article: Visual cortex

Visual cortex: V1; V2; V3; V4; V5 (also called MT) The visual cortex is the largest system in the human brain and is responsible for processing the visual image. It lies at the rear of the brain (highlighted in the image), above the cerebellum. The region that receives information directly from the LGN 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/MT (the exact connectivity depends on the species of the animal). These secondary visual areas (collectively termed the extrastriate visual cortex) process a wide variety of visual primitives. Neurons in V1 and V2 respond selectively to bars of specific orientations, or combinations of bars. These are believed to support edge and corner detection. Similarly, basic information about color and motion is processed here.

Heider, et al. (2002) have found that neurons involving V1, V2, and V3 can detect stereoscopic illusory contours; they found that stereoscopic stimuli subtending up to 8° can activate these neurons.

Visual cortex is active even during resting state fMRI. Visual association cortex Main article: Two Streams hypothesis As visual information passes forward through the visual hierarchy, the complexity of the neural representations increases. Whereas a V1 neuron may respond selectively to a line segment of a particular orientation in a particular retinotopic location, neurons in the lateral occipital complex respond selectively to complete object (e.g., a figure drawing), and neurons in visual association cortex may respond selectively to human faces, or to a particular object.

Along with this increasing complexity of neural representation may come a level of specialization of processing into two distinct pathways: the dorsal stream and the ventral stream (the Two Streams hypothesis, first proposed by Ungerleider and Mishkin in 1982). The dorsal stream, commonly referred to as the "where" stream, is involved in spatial attention (covert and overt), and communicates with regions that control eye movements and hand movements. More recently, this area has been called the "how" stream to emphasize its role in guiding behaviors to spatial locations. The ventral stream, commonly referred as the "what" stream, is involved in the recognition, identification and categorization of visual stimuli.

Intraparietal sulcus (red) However, there is still much debate about the degree of specialization within these two pathways, since they are in fact heavily interconnected.

Horace Barlow proposed the efficient coding hypothesis in 1961 as a theoretical model of sensory coding in the brain.

The default mode network is a network of brain regions that are active when an individual is awake and at rest. The visual system's default mode can be monitored during resting state fMRI: Fox, et al. (2005) have found that "The human brain is intrinsically organized into dynamic, anticorrelated functional networks"', in which the visual system switches from resting state to attention.

In the parietal lobe, the lateral and ventral intraparietal cortex are involved in visual attention and saccadic eye movements. These regions are in the Intraparietal sulcus (marked in red in the adjacent image).

Proper function of the visual system is required for sensing, processing, and understanding the surrounding environment. Difficulty in sensing, processing and understanding light input has the potential to adversely impact an individual's ability to communicate, learn and effectively complete routine tasks on a daily basis.

In children, early diagnosis and treatment of impaired visual system function is an important factor in ensuring that key social, academic and speech/language developmental milestones are met.

Cataract is clouding of the lens, which in turn affects vision. Although it may be accompanied by yellowing, clouding and yellowing can occur separately. This is typically a result of ageing, disease, or drug use.

Presbyopia is a visual condition that causes farsightedness. The eye's lens becomes too inflexible to accommodate to normal reading distance, focus tending to remain fixed at long distance.

Glaucoma is a type of blindness that begins at the edge of the visual field and progresses inward. It may result in tunnel vision. This typically involves the outer layers of the optic nerve, sometimes as a result of buildup of fluid and excessive pressure in the eye.

Scotoma is a type of blindness that produces a small blind spot in the visual field typically caused by injury in the primary visual cortex.

Homonymous hemianopia is a type of blindness that destroys one entire side of the visual field typically caused by injury in the primary visual cortex.

Quadrantanopia is a type of blindness that destroys only a part of the visual field typically caused by partial injury in the primary visual cortex. This is very similar to homonymous hemianopia, but to a lesser degree.

Prosopagnosia, or face blindness, is a brain disorder that produces an inability to recognize faces. This disorder often arises after damage to the fusiform face area (FFA).

Visual agnosia, or visual-form agnosia, is a brain disorder that produces an inability to recognize objects. This disorder often arises after damage to the ventral stream.

Chapter 12

The Somatic Nervous System

The somatic nervous system (SNS or voluntary nervous system) is the part of the peripheral nervous system associated with the voluntary control of body movements via skeletal muscles.

The somatic nervous system consists of afferent nerves or sensory nerves, and efferent nerves or motor nerves. Afferent nerves are responsible for relaying sensation from the body to the central nervous system; efferent nerves are responsible for sending out commands from the CNS to the body, stimulating muscle contraction; they include all the non-sensory neurons connected with skeletal muscles and skin. The a- of afferent and the e- of efferent correspond to the prefixes ad- (to, toward) and ex- (out of).

Peripheral structures of the somatic motor system include skeletal muscles and neural connections with muscle tissues. Central structures include cerebral cortex, brainstem, spinal cord, pyramidal system including the upper motor neurons, extrapyramidal system, cerebellum, and the lower motor neurons in the brainstem and the spinal cord.

12.1 Pyramidal motor system

The pyramidal motor system, also called the pyramidal tract or the corticospinal tract, start in the motor center of the cerebral cortex. There are upper and lower motor neurons in the corticospinal tract. The motor impulses originate in the giant pyramidal cells or Betz cells of the motor area; i.e., precentral gyrus of cerebral cortex. These are the upper motor neurons (UMN) of the corticospinal tract. The axons of these cells pass in the depth of the cerebral cortex to the corona radiata and then to the internal capsule passing through the posterior branch of internal capsule and continue to descend in the midbrain and the medulla oblongata. In the lower part of Medulla oblongata 80 to 85% of these fibers decussate (pass to the opposite side) and descend in the white matter of the lateral funiculus of the spinal cord on the opposite side. The remaining 15 to 20% pass to the same side. Fibers for the extremities (limbs) pass 100% to the opposite side. The fibers of the corticospinal tract terminate at different levels in the anterior horn of the grey matter of the spinal cord. Here the lower motor neurons (LMN) of the corticospinal cord are located. Peripheral motor nerves carry the motor impulses from the anterior horn to the voluntary muscles.

The pyramidal tracts include both the corticobulbar tract and the corticospinal tract. These are aggregations of efferent nerve fibers from the upper motor neurons that travel from the cerebral cortex and terminate either in the brainstem (corticobulbar) or spinal cord (corticospinal) and are involved in the control of motor functions of the body.

The corticobulbar tract conducts impulses from the brain to the cranial nerves. These nerves control the muscles of the face and neck and are involved in facial expression, mastication, swallowing, and other functions.

The corticospinal tract conducts impulses from the brain to the spinal cord. It is made up of a lateral and anterior tract. The corticospinal tract is involved in voluntary movement. The majority of fibres of the corticospinal tract cross over in the medulla oblongata, resulting in muscles being controlled by the opposite side of the brain. The corticospinal tract also contains the axons of Betz cells (the largest pyramidal cells) located in the primary motor cortex.

The pyramidal tracts are named because they pass through the pyramids of the medulla oblongata. The corticospinal fibers when descending from the internal capsule to the brain stem, converge to a point from multiple directions giving the impression of an inverted pyramid.

The myelination of the pyramidal fibres is incomplete at birth and gradually progresses in cranio-caudal direction and thereby progressively gaining functionality. Most of the myelination is complete by two years of age and thereafter it progresses very slowly in cranio-caudal direction up to twelve years of age.

The term pyramidal tracts refers to upper motor neurons that originate in the cerebral cortex and terminate in the spinal cord (corticospinal) or brainstem (corticobulbar). Nerves emerge in the cerebral cortex, pass down and may cross sides in the medulla oblongata, and travel as part of the spinal cord until they synapse with interneurons in the grey column of the spinal cord.

There is some variation in terminology. The pyramidal tracts definitively encompass the corticospinal tracts, and many authors also include the corticobulbar tracts.

Corticospinal tract Further information: Corticospinal tract Nerve fibres in the corticospinal tract originate from pyramidal cells in layer V of the cerebral cortex. Fibres arise from the primary motor cortex (about 30%), supplementary motor area and the premotor cortex (together also about 30%), and the somatosensory cortex, parietal lobe, and cingulate gyrus supplies the rest. The cells have their bodies in the cerebral cortex, and the axons form the bulk of the pyramidal tracts. The nerve axons travel from the cortex through the posterior limb of internal capsule, through the cerebral peduncle and into the brainstem and anterior medulla oblongata. Here they form two prominences called the medulla oblongatary pyramids. Below the prominences, the majority of axons cross over to the opposite side from which they originated, known as decussation. The axons that cross over move to the outer part of the medulla oblongata and form the lateral corticospinal tract, whereas the fibres that remain form the anterior corticospinal tract. About 80% of axons cross over and form the lateral corticospinal tract; 10% do not cross over and join the tract, and 10% of fibres travel in the anterior corticospinal tract.[citation needed]

The nerve axons traveling down the tract are the efferent nerve fibers of the upper motor neurons. These axons travel down the tracts in the white matter of the spinal cord until they reach the vertebral level of the muscle that they will innervate. At this point, the axons synapse with lower motor neurons. The majority of axons do not directly synapse with lower motor neurons, but instead synapse with an interneuron that then synapses with a lower motor neuron. This generally occurs in the anterior grey column. Nerve axons of the lateral corticospinal tract that did not cross over in the medulla oblongata do so at the level of the spinal cord they terminate in.

These tracts contain more than 1 million axons and the majority of the axons are myelinated. The corticospinal tracts myelinate largely during the first and second years after birth. The majority of nerve axons are small (<4 m) in diameter. About 3% of nerve axons have a much larger diameter (16 m) and arise from Betz cells, mostly in the leg area of the primary motor cortex. These cells are notable because of their rapid conduction rate, over 70m/sec, the fastest conduction of any signals from the brain to the spinal cord.

Horizontal section through the lower part of the pons, showing the fibers of the corticospinal tract (#19) passing through the pontine nuclei Corticobulbar tract Further information: Corticobulbar tract Fibres from the ventral motor cortex travel with the corticospinal tract through the internal capsule, but terminate in a number of locations in the midbrain (cortico-mesencephalic tract), pons (Corticopontine tract), and medulla oblongata (cortico-bulbar tract). The upper motor neurons of the corticobulbar tract synapse with interneurons or directly with the lower motor neurons located in the motor cranial nerve nuclei, namely oculomotor, trochlear, motor nucleus of the trigeminal nerve, abducens, facial nerve and accessory and in the nucleus ambiguus to the hypoglossal, vagus and accessory nerves. These nuclei are supplied by nerves from both sides of the brain, with the exception of the parts of the facial nerve that control muscles of the lower face. These muscles are only innervated by nerves from the contralateral (opposite) side of the cortex.

Function The nerves within the corticospinal tract are involved in movement of muscles of the body. Because of the crossing-over of fibres, muscles are supplied by the side of the brain opposite to that of the muscle. The nerves within the corticobulbar tract are involved in movement in muscles of the head. They are involved in swallowing, phonation, and movements of the tongue. By virtue of involvement with the facial nerve, the corticobulbar tract is also responsible for transmitting facial expression. With the exception of lower muscles of facial expression, all functions of the corticobulbar tract involve inputs from both sides of the brain.

12.2 Extrapyramidal motor system

The extrapyramidal motor system consists of motor-modulation systems, particularly the basal ganglia and cerebellum. The system is called extrapyramidal to distinguish it from the tracts of the motor cortex that reach their targets by traveling through the pyramids of the medulla. The pyramidal tracts (corticospinal tract and corticobulbar tracts) may directly innervate motor neurons of the spinal cord or brainstem (anterior (ventral) horn cells or certain cranial nerve nuclei), whereas the extrapyramidal system centers on the modulation and regulation (indirect control) of anterior (ventral) horn cells.

Extrapyramidal tracts are chiefly found in the reticular formation of the pons and medulla, and target lower motor neurons in the spinal cord that are involved in reflexes, locomotion, complex movements, and postural control. These tracts are in turn modulated by various parts of the central nervous system, including the nigrostriatal pathway, the basal ganglia, the cerebellum, the vestibular nuclei, and different sensory areas of the cerebral cortex. All of these regulatory components can be considered part of the extrapyramidal system, in that they modulate motor activity without directly innervating motor neurons.

The extrapyramidal tracts include parts of the following:

- rubrospinal tract
- pontine reticulospinal tract
- medullary reticulospinal tract
- lateral vestibulospinal tract
- tectospinal tract

12.3 The Basal Ganglia

The basal ganglia (or basal nuclei) are a group of subcortical nuclei, of varied origin, in the brains of vertebrates, including humans, which are situated at the base of the forebrain and top of the midbrain. There are some differences in the basal ganglia of primates. Basal ganglia are strongly interconnected with the cerebral cortex, thalamus, and brainstem, as well as several other brain areas. The basal ganglia are associated with a variety of functions, including control of voluntary motor movements, procedural learning, habit learning, eye movements, cognition, and emotion.

The nomenclature of the basal ganglia system and its components has always been problematic. Early anatomists, seeing the macroscopic anatomical structure but knowing nothing of the cellular architecture or neurochemistry, grouped together components that are now believed to have distinct functions (such as the internal and external segments of the globus pallidus), and gave distinct names to components that are now thought to be functionally parts of a single structure (such as the caudate nucleus and putamen).

The term "basal" comes from the fact that most of its elements are located in the basal part of the forebrain. The term ganglia is a misnomer: In modern usage, neural clusters are called "ganglia" only in the peripheral nervous system; in the central nervous system they are called "nuclei". For this reason, the basal ganglia are also occasionally known as the "basal nuclei".

The main components of the basal ganglia – as defined functionally – are the striatum; both dorsal striatum (caudate nucleus and putamen) and ventral striatum (nucleus accumbens and olfactory tubercle), globus pallidus, ventral pallidum, substantia nigra, and subthalamic nucleus. Each of these components has a complex internal anatomical and neurochemical organization. The largest component, the striatum (dorsal and ventral), receives input from many brain areas beyond the basal ganglia, but only sends output to other components of the basal ganglia. The pallidum receives input from the striatum, and sends inhibitory output to a number of motor-related areas. The substantia nigra is the source of the striatal input of the neurotransmitter dopamine, which plays an important role in basal ganglia function. The subthalamic nucleus receives input mainly from the striatum and cerebral cortex, and projects to the globus pallidus.

Popular theories implicate the basal ganglia primarily in action selection – in helping to decide which of several possible behaviors to execute at any given time. In more specific terms, the basal ganglia's primary function is likely to control and regulate activities of the motor and premotor cortical areas so that voluntary movements can be performed smoothly. Experimental studies show that the basal ganglia exert an inhibitory influence on a number of motor systems, and that a release of this inhibition permits a motor system to become active. The "behavior switching" that takes place within the basal ganglia is influenced by signals from many parts of the brain, including the prefrontal cortex, which plays a key role in executive functions.

The basal ganglia are of major importance for normal brain function and behaviour. Their dysfunction results in a wide range of neurological conditions including disorders of behaviour control and movement. Those of behaviour include Tourette syndrome, obsessive–compulsive disorder, and addiction. Movement disorders include, most notably Parkinson's disease, which involves degeneration of the dopamine-producing cells in the substantia nigra, Huntington's disease, which primarily involves damage to the striatum, dystonia, and more rarely hemiballismus. The basal ganglia have a limbic sector whose components are assigned distinct names: the nucleus accumbens, ventral pallidum, and ventral tegmental area (VTA). There is considerable evidence that this limbic part plays a central role in reward learning as well as cognition and frontal lobe functioning, via the mesolimbic pathway from the VTA to the nucleus accumbens that uses the neurotransmitter dopamine, and the mesocortical pathway. A number of highly addictive drugs, including cocaine, amphetamine, specific medications that are prescribed by a doctor, and nicotine, are thought to work by increasing the efficacy of this dopamine signal. There is also evidence implicating overactivity of the VTA dopaminergic projection in schizophrenia.

The basal ganglia form a fundamental component of the cerebrum. In contrast to the cortical layer that lines the surface of the forebrain, the basal ganglia are a collection of distinct masses of gray matter lying deep in the brain not far from the junction of the thalamus. They lie to the side of and surround the thalamus. Like most parts of the brain, the basal ganglia consist of left and right sides that are virtual mirror images of each other.

In terms of anatomy, the basal ganglia are divided into four distinct structures, depending on how superior or rostral they are (in other words depending on how close to the top of the head they are): Two of them, the striatum and the pallidum, are relatively large; the other two, the substantia nigra and the subthalamic nucleus, are smaller. In the illustration to the right, two coronal sections of the human brain show the location of the basal ganglia components. Of note, and not seen in this section, the subthalamic nucleus and substantia nigra lie farther back (posteriorly) in the brain than the striatum and pallidum.

12.3.1 Striatum

The striatum is a subcortical structure generally divided into the dorsal striatum and ventral striatum, although a medial lateral classification has been suggested to be more relevant behaviorally and is being more widely used.

The striatum is composed mostly of medium spiny neurons. These GABAergic neurons project to the external (lateral) globus pallidus and internal (medial) globus pallidus as well as the substantia nigra pars reticulata. The projections into the globus pallidus and substantia nigra are primarily dopaminergic, although enkephalin, dynorphin and substance P are expressed. The striatum also contains interneurons that are classified into nitrergic neurons (due to use of nitric oxide as a neurotransmitter), tonically active[clarification needed] cholinergic interneurons, parvalbumin-expressing neurons and calretinin-expressing neurons. The dorsal striatum receives significant glutamatergic inputs from the cortex, as well as dopaminergic inputs from the substantia nigra pars compacta. The dorsal striatum is generally considered to be involved in sensorimotor activities. The ventral striatum receives glutamatergic inputs from the limbic areas as well as dopaminergic inputs from the VTA, via the mesolimbic pathway. The ventral striatum is believed to play a role in reward and other limbic functions. The dorsal striatum is divided into the caudate and putamen by the internal capsule while the ventral striatum is composed of the nucleus accumbens and olfactory tubercle. The caudate has three primary regions of connectivity, with the head of the caudate demonstrating connectivity to the prefrontal cortex, cingulate cortex and amygdala. The body and tail show differentiation between the dorsolateral rim and ventral caudate, projecting to the sensorimotor and limbic regions of the striatum respectively. Striatopallidal fibres connect the striatum to the pallidus.

12.3.2 Pallidum

The pallidum consists of a large structure called the globus pallidus ("pale globe") together with a smaller ventral extension called the ventral pallidum. The globus pallidus appears as a single neural mass, but can be divided into two functionally distinct parts, called the internal (or medial) and external (lateral) segments, abbreviated GPi and GPe. Both segments contain primarily GABAergic neurons, which therefore have inhibitory effects on their targets. The two segments participate in distinct neural circuits. The GPe receives input mainly from the striatum, and projects to the subthalamic nucleus. The GPi receives signals from the striatum via the "direct" and "indirect" pathways. Pallidal neurons operate using a disinhibition principle. These neurons fire at steady high rates in the absence of input, and signals from the striatum cause them to pause or reduce their rate of firing. Because pallidal neurons themselves have inhibitory effects on their targets, the net effect of striatal input to the pallidum is a reduction of the tonic inhibition exerted by pallidal cells on their targets (disinhibition) with an increased rate of firing in the targets.

12.3.3 Substantia nigra

The substantia nigra is a midbrain gray matter portion of the basal ganglia that has two parts – the pars compacta (SNc) and the pars reticulata (SNr). SNr often works in unison with GPi, and the SNr-GPi complex inhibits the thalamus. Substantia nigra pars compacta (SNc) however, produces the neurotransmitter dopamine, which is very significant in maintaining balance in the striatal pathway. The circuit portion below explains the role and circuit connections of each of the components of the basal ganglia.

The substantia nigra (SN) is a basal ganglia structure located in the midbrain that plays an important role in reward and movement. Substantia nigra is Latin for "black substance", reflecting the fact that parts of the substantia nigra appear darker than neighboring areas due to high levels of neuromelanin in dopaminergic neurons. It was discovered in 1784 by Félix Vicq-d'Azyr, and Samuel Thomas von Sömmerring alluded to this structure in 1791. Parkinson's disease is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta.

Although the substantia nigra appears as a continuous band in brain sections, anatomical studies have found that it actually consists of two parts with very different connections and functions: the pars compacta (SNpc) and the pars reticulata (SNpr). This classification was first proposed by Sano in 1910. The pars compacta serves mainly as an output to the basal ganglia circuit, supplying the striatum with dopamine. The pars reticulata, though, serves mainly as an input, conveying signals from the basal ganglia to numerous other brain structures.

The substantia nigra is an important player in brain function, in particular, in eye movement, motor planning, reward-seeking, learning, and addiction. Many of the substantia nigra's effects are mediated through the striatum. The nigral dopaminergic input to the striatum via the nigrostriatal pathway is intimately linked with the striatum's function. The co-dependence between the striatum and substantia nigra can be seen in this way: when the substantia nigra is electrically stimulated, no movement occurs; however, the symptoms of nigral degeneration due to Parkinson's is a poignant example of the substantia nigra's influence on movement. In addition to striatum-mediated functions, the substantia nigra also serves as a major source of GABAergic inhibition to various brain targets.

The substantia nigra is critical in the development of many diseases and syndromes, including parkinsonism and Parkinson's disease. Parkinson's disease is a neurodegenerative disease characterized, in part, by the death of dopaminergic neurons in the SNpc. The major symptoms of Parkinson's disease include tremor, akinesia, bradykinesia, and stiffness. Other symptoms include disturbances to posture, fatigue, sleep abnormalities, and depressed mood. The cause of death of dopaminergic neurons in the SNpc is unknown. The substantia nigra is the target of chemical therapeutics for the treatment of Parkinson's disease. Levodopa (commonly referred to as L-DOPA), the dopamine precursor, is the most commonly prescribed medication for Parkinson's disease, despite controversy concerning the neurotoxicity of dopamine and L-DOPA. The drug is especially effective in treating patients in the early stages of Parkinson's, although it does lose its efficacy over time. Levodopa can cross the blood–brain barrier and increases dopamine levels in the substantia nigra, thus alleviating the symptoms of Parkinson's disease. The drawback of levodopa treatment is that it treats the symptoms of Parkinson's (low dopamine levels), rather than the cause (the death of dopaminergic neurons in the substantia nigra).

12.3.4 Subthalamic nucleus

The subthalamic nucleus is a diencephalic gray matter portion of the basal ganglia, and the only portion of the ganglia that produces an excitatory neurotransmitter, glutamate. The role of the subthalamic nucleus is to stimulate the SNr-GPi complex and it is part of the indirect pathway. The subthalamic nucleus receives inhibitory input from the external part of the globus pallidus and sends excitatory input to the GPi.

Chapter 13

The Autonomic Nervous System

The autonomic nervous system (ANS), formerly the vegetative nervous system, is a division of the peripheral nervous system that supplies smooth muscle and glands, and thus influences the function of internal organs. The autonomic nervous system is a control system that acts largely unconsciously and regulates bodily functions such as the heart rate, digestion, respiratory rate, pupillary response, urination, and sexual arousal. This system is the primary mechanism in control of the fight-or-flight response.

Within the brain, the autonomic nervous system is regulated by the hypothalamus. Autonomic functions include control of respiration, cardiac regulation (the cardiac control center), vasomotor activity (the vasomotor center), and certain reflex actions such as coughing, sneezing, swallowing and vomiting. Those are then subdivided into other areas and are also linked to ANS subsystems and nervous systems external to the brain. The hypothalamus, just above the brain stem, acts as an integrator for autonomic functions, receiving ANS regulatory input from the limbic system to do so.

The autonomic nervous system has three branches: the sympathetic nervous system, the parasympathetic nervous system and the enteric nervous system. Some textbooks do not include the enteric nervous system as part of this system. The sympathetic nervous system is often considered the “fight or flight” system, while the parasympathetic nervous system is often considered the “rest and digest” or “feed and breed” system. In many cases, both of these systems have “opposite” actions where one system activates a physiological response and the other inhibits it. An older simplification of the sympathetic and parasympathetic nervous systems as “excitatory” and “inhibitory” was overturned due to the many exceptions found. A more modern characterization is that the sympathetic nervous system is a “quick response mobilizing system” and the parasympathetic is a “more slowly activated dampening system”, but even this has exceptions, such as in sexual arousal and orgasm, wherein both play a role.

There are inhibitory and excitatory synapses between neurons. Relatively recently, a third subsystem of neurons that have been named non-noradrenergic, non-cholinergic transmitters (because they use nitric oxide as a neurotransmitter) have been described and found to be integral in autonomic function, in particular in the gut and the lungs.

Although the ANS is also known as the visceral nervous system, the ANS is only connected with the motor side. Most autonomous functions are involuntary but they can often work in conjunction with the somatic nervous system which provides voluntary control.

The autonomic nervous system is divided into the sympathetic nervous system and parasympathetic nervous system. The sympathetic division emerges from the spinal cord in the thoracic and lumbar areas, terminating around L2-3. The parasympathetic division has craniosacral "outflow", meaning that the neurons begin at the cranial nerves (specifically the oculomotor nerve, facial nerve, glossopharyngeal nerve and vagus nerve) and sacral (S2-S4) spinal cord.

The autonomic nervous system is unique in that it requires a sequential two-neuron efferent pathway; the preganglionic neuron must first synapse onto a postganglionic neuron before innervating the target organ. The preganglionic, or first, neuron will begin at the "outflow" and will synapse at the postganglionic, or second, neuron's cell body. The postganglionic neuron will then synapse at the target organ.

Table 13.1: Effects of the parasympathetic and sympathetic branches of the autonomic system on their target organs.

Target organ/system	Parasympathetic	Sympathetic
		The most abundant type of macroglial cell in the CNS, astrocytes (also called astrog have numerous projections that link neurons to their blood supply while forming the blood-brain barrier. They regulate the external chemicalenvironment of neurons removing excess potassium ions, and recycling neurotransmitters released during synaptic transmission. Astrocytes may regulate vasoconstriction and vasodila by producing substances such as arachidonic acid, whose metabolites are vasoactive.
		Astrocytes signal each other using ATP. The gap junctions (also known as electrical synapses) between astrocytes allow the messenger molecule IP3 to diffuse from one astrocyte to another. IP3 activates calcium channels on cellular organelles, releasing calcium into the cytoplasm. This calcium may stimulate the production of IP3 and cause release of ATP through channels in the membrane made of pannexins. net effect is a calcium wave that propagates from cell to cell. Extracellular release of and consequent activation of purinergic receptors on other astrocytes, may also medi calcium waves in some cases.
	Astrocytes	In general, there are two types of astrocytes, protoplasmic and fibrous, similar in fun but distinct in morphology and distribution. Protoplasmic astrocytes have short, thic highly branched processes and are typically found in gray matter. Fibrous astrocytes long, thin, less branched processes and are more commonly found in white matter.
		It has recently been shown that astrocyte activity is linked to blood flow in the brain that this is what is actually being measured in fMRI. They also have been involved i neuronal circuits playing an inhibitory role after sensing changes in extracellular calc
	Oligodendroc	Oligodendrocytes are cells that coat axons in the central nervous system (CNS) wit cell membrane, forming a specialized membrane differentiation called myelin, produc the myelin sheath. The myelin sheath provides insulation to the axon that allows electrical signals to propagate more efficiently.

CNS	Ependymal cells	Ependymal cells, also named ependymocytes, line the spinal cord and the ventricular system of the brain. These cells are involved in the creation and secretion of cerebrospinal fluid (CSF) and beat their cilia to help circulate the CSF and make up the blood-CSF barrier. They are also thought to act as neural stem cells.
	Radial glia	Radial glia cells arise from neuroepithelial cells after the onset of neurogenesis. Their differentiation abilities are more restricted than those of neuroepithelial cells. In the developing nervous system, radial glia function both as neuronal progenitors and as a scaffold upon which newborn neurons migrate. In the mature brain, the cerebellum and retina retain characteristic radial glial cells. In the cerebellum, these are Bergmann glia, which regulate synaptic plasticity. In the retina, the radial Müller cell is the glial cell that spans the thickness of the retina and, in addition to astroglial cells,[14] participates in a bidirectional communication with neurons.
	Schwann cells	Similar in function to oligodendrocytes, Schwann cells provide myelination to axons in the peripheral nervous system(PNS). They also have phagocytotic activity and clear cellular debris that allows for regrowth of PNS neurons.
PNS	Satellite cells	Satellite glial cells are small cells that surround neurons in sensory, sympathetic, and parasympathetic ganglia.[17]These cells help regulate the external chemical environment. Like astrocytes, they are interconnected by gap junctions and respond to ATP by elevating intracellular concentration of calcium ions. They are highly sensitive to injury and inflammation, and appear to contribute to pathological states, such as chronic pain.
	Enteric glial cells	Are found in the intrinsic ganglia of the digestive system. They are thought to have many roles in the enteric system, some related to homeostasis and muscular digestive processes.

13.1 Sympathetic division

There are two kinds of neurons involved in the transmission of any signal through the sympathetic system: pre-ganglionic and post-ganglionic. The shorter preganglionic neurons originate in the thoracolumbar division of the spinal cord specifically at T1 to L2~L3, and travel to a ganglion, often one of the paravertebral ganglia, where they synapse with a postganglionic neuron. From there, the long postganglionic neurons extend across most of the body.

At the synapses within the ganglia, preganglionic neurons release acetylcholine, a neurotransmitter that activates nicotinic acetylcholine receptors on postganglionic neurons. In response to this stimulus, the postganglionic neurons release norepinephrine, which activates adrenergic receptors that are present on the peripheral target tissues. The activation of target tissue receptors causes the effects associated with the sympathetic system. However, there are three important exceptions:

Postganglionic neurons of sweat glands release acetylcholine for the activation of muscarinic receptors, except for areas of thick skin, the palms and the plantar surfaces of the feet, where norepinephrine is released and acts on adrenergic receptors. Chromaffin cells of the adrenal medulla are analogous to post-ganglionic neurons; the adrenal medulla develops in tandem with the sympathetic nervous system and acts as a modified sympathetic ganglion. Within this endocrine gland, pre-ganglionic neurons synapse with chromaffin cells, triggering the release of two transmitters: a small proportion of norepinephrine, and more substantially, epinephrine. The synthesis and release of epinephrine as opposed to norepinephrine is another distinguishing feature of chromaffin cells compared to postganglionic sympathetic neurons. Postganglionic sympathetic nerves terminating in the kidney release dopamine, which acts on dopamine D1 receptors of blood vessels to control how much blood the kidney filters. Dopamine is the immediate metabolic precursor to norepinephrine, but is nonetheless a distinct signaling molecule. Organization

The sympathetic nervous system extends from the thoracic to lumbar vertebrae and has connections with the thoracic, abdominal, and pelvic plexuses. Sympathetic nerves arise from near the middle of the spinal cord in the intermediolateral nucleus of the lateral grey column, beginning at the first thoracic vertebra of the vertebral column and are thought to extend to the second or third lumbar vertebra. Because its cells begin in the thoracolumbar division – the thoracic and lumbar regions of the spinal cord, the sympathetic nervous system is said to have a thoracolumbar outflow. Axons of these nerves leave the spinal cord through the anterior root. They pass near the spinal (sensory) ganglion, where they enter the anterior rami of the spinal nerves. However, unlike somatic innervation, they quickly separate out through white rami connectors (so called from the shiny white sheaths of myelin around each axon) that connect to either the paravertebral (which lie near the vertebral column) or prevertebral (which lie near the aortic bifurcation) ganglia extending alongside the spinal column.

To reach target organs and glands, the axons must travel long distances in the body, and, to accomplish this, many axons relay their message to a second cell through synaptic transmission. The ends of the axons link across a space, the synapse, to the dendrites of the second cell. The first cell (the presynaptic cell) sends a neurotransmitter across the synaptic cleft where it activates the second cell (the postsynaptic cell). The message is then carried to the final destination.

Presynaptic nerves' axons terminate in either the paravertebral ganglia or prevertebral ganglia. There are four different paths an axon can take before reaching its terminal. In all cases, the axon enters the paravertebral ganglion at the level of its originating spinal nerve. After this, it can then either synapse in this ganglion, ascend to a more superior or descend to a more inferior paravertebral ganglion and synapse there, or it can descend to a prevertebral ganglion and synapse there with the postsynaptic cell.

The postsynaptic cell then goes on to innervate the targeted end effector (i.e. gland, smooth muscle, etc.). Because paravertebral and prevertebral ganglia are relatively close to the spinal cord, presynaptic neurons are generally much shorter than their postsynaptic counterparts, which must extend throughout the body to reach their destinations.

A notable exception to the routes mentioned above is the sympathetic innervation of the suprarenal (adrenal) medulla. In this case, presynaptic neurons pass through paravertebral ganglia, on through prevertebral ganglia and then synapse directly with suprarenal tissue. This tissue consists of cells that have pseudo-neuron like qualities in that when activated by the presynaptic neuron, they will release their neurotransmitter (epinephrine) directly into the bloodstream.

In the sympathetic nervous system and other components of the peripheral nervous system, these synapses are made at sites called ganglia. The cell that sends its fiber is called a preganglionic cell, while the cell whose fiber leaves the ganglion is called a postganglionic cell. As mentioned previously, the preganglionic cells of the sympathetic nervous system are located between the first thoracic segment and third lumbar segments of the spinal cord. Postganglionic cells have their cell bodies in the ganglia and send their axons to target organs or glands.

The ganglia include not just the sympathetic trunks but also the cervical ganglia (superior, middle and inferior), which send sympathetic nerve fibers to the head and thorax organs, and the celiac and mesenteric ganglia, which send sympathetic fibers to the gut.

13.2 Parasympathetic division

The parasympathetic nerves are autonomic or visceral branches of the peripheral nervous system (PNS). Parasympathetic nerve supply arises through three primary areas:

Certain cranial nerves in the cranium, namely the preganglionic parasympathetic nerves (CN III, CN VII, and CN IX) usually arise from specific nuclei in the central nervous system (CNS) and synapse at one of four parasympathetic ganglia: ciliary, pterygopalatine, otic, or submandibular. From these four ganglia the parasympathetic nerves complete their journey to target tissues via trigeminal branches (ophthalmic nerve, maxillary nerve, mandibular nerve). The vagus nerve does not participate in these cranial ganglia as most of its parasympathetic fibers are destined for a broad array of ganglia on or near thoracic viscera (esophagus, trachea, heart, lungs) and abdominal viscera (stomach, pancreas, liver, kidneys, small intestine, and about half of the large intestine). The vagus innervation ends at the junction between the midgut and hindgut, just before the splenic flexure of the transverse colon. The pelvic splanchnic efferent preganglionic nerve cell bodies reside in the lateral gray horn of the spinal cord at the T12-L1 vertebral levels (the spinal cord terminates at the L1-L2 vertebrae with the conus medullaris), and their axons exit the vertebral column as S2-S4 spinal nerves through the sacral foramina. Their axons continue away from the CNS to synapse at an autonomic ganglion. The parasympathetic ganglion where these preganglionic neurons synapse will be close to the organ of innervation. This differs from the sympathetic nervous system, where synapses between pre- and post-ganglionic efferent nerves in general occur at ganglia that are farther away from the target organ. As in the sympathetic nervous system, efferent parasympathetic nerve signals are carried from the central nervous system to their targets by a system of two neurons. The first neuron in this pathway is referred to as the preganglionic or presynaptic neuron. Its cell body sits in the central nervous system and its axon usually extends to synapse with the dendrites of a postganglionic neuron somewhere else in the body. The axons of presynaptic parasympathetic neurons are usually long, extending from the CNS into a ganglion that is either very close to or embedded in their target organ. As a result, the postsynaptic parasympathetic nerve fibers are very short.:42

Cranial nerves The oculomotor nerve is responsible for a number of parasympathetic functions related to the eye. The oculomotor PNS fibers originate in the Edinger-Westphal nucleus in the central nervous system and travel through the superior orbital fissure to synapse in the ciliary ganglion located just behind the orbit (eye). From the ciliary ganglion the postganglionic parasympathetic fibers leave via short ciliary nerve fibers, a continuation of the nasociliary nerve (a branch of ophthalmic division of the trigeminal nerve (CN V1)). The short ciliary nerves innervate the orbit to control the ciliary muscle (responsible for accommodation) and the iris sphincter muscle, which is responsible for miosis or constriction of the pupil (in response to light or accommodation). There are two motors that are part of the oculomotor nerve known as the somatic motor and visceral motor. The somatic motor is responsible for moving the eye in precise motions and for keeping the eye fixated on an object. The visceral motor helps constrict the pupil.

The parasympathetic aspect of the facial nerve controls secretion of the sublingual and submandibular salivary glands, the lacrimal gland, and the glands associated with the nasal cavity. The preganglionic fibers originate within the CNS in the superior salivatory nucleus and leave as the intermediate nerve (which some consider a separate cranial nerve altogether) to connect with the facial nerve just distal (further out) to it surfacing the central nervous system. Just after the facial nerve geniculate ganglion (general sensory ganglion) in the temporal bone, the facial nerve gives off two separate parasympathetic nerves. The first is the greater petrosal nerve and the second is the chorda tympani. The greater petrosal nerve travels through the middle ear and eventually combines with the deep petrosal nerve (sympathetic fibers) to form the nerve of the pterygoid canal. The parasympathetic fibers of the nerve of the pterygoid canal synapse at the pterygopalatine ganglion, which is closely associated with the maxillary division of the trigeminal nerve (CN V2). The postganglionic parasympathetic fibers leave the pterygopalatine ganglion in several directions. One division leaves on the zygomatic division of CN V2 and travels on a communicating branch to unite with the lacrimal nerve (branch of the ophthalmic nerve of CN V1) before synapsing at the lacrimal gland. These parasympathetic to the lacrimal gland control tear production.

A separate group of parasympathetic leaving from the pterygopalatine ganglion are the descending palatine nerves (CN V2 branch), which include the greater and lesser palatine nerves. The greater palatine parasympathetic synapse on the hard palate and regulate mucus glands located there. The lesser palatine nerve synapses at the soft palate and controls sparse taste receptors and mucus glands. Yet another set of divisions from the pterygopalatine ganglion are the posterior, superior, and inferior lateral nasal nerves; and the nasopalatine nerves (all branches of CN V2, maxillary division of the trigeminal nerve) that bring parasympathetic innervation to glands of the nasal mucosa. The second parasympathetic branch that leaves the facial nerve is the chorda tympani. This nerve carries secretomotor fibers to the submandibular and sublingual glands. The chorda tympani travels through the middle ear and attaches to the lingual nerve (mandibular division of trigeminal, CN V3). After joining the lingual nerve, the preganglionic fibers synapse at the submandibular ganglion and send postganglionic fibers to the sublingual and submandibular salivary glands.

The glossopharyngeal nerve has parasympathetic fibers that innervate the parotid salivary gland. The preganglionic fibers depart CN IX as the tympanic nerve and continue to the middle ear where they make up a tympanic plexus on the cochlear promontory of the mesotympanum. The tympanic plexus of nerves rejoin and form the lesser petrosal nerve and exit through the foramen ovale to synapse at the otic ganglion. From the otic ganglion postganglionic parasympathetic fibers travel with the auriculotemporal nerve (mandibular branch of trigeminal, CN V3) to the parotid salivary gland.

Vagus nerve The vagus nerve, named after the Latin word vagus (because the nerve controls such a broad range of target tissues – vagus in Latin literally means "wandering"), has parasympathetic functions that originate in the dorsal nucleus of the vagus nerve and the nucleus ambiguus in the CNS. The vagus nerve is an unusual cranial parasympathetic in that it doesn't join the trigeminal nerve in order to get to its target tissues. Another peculiarity is that the vagus has an autonomic ganglion associated with it at approximately the level of C1 vertebra. The vagus gives no parasympathetic to the cranium. The vagus nerve is hard to track definitively due to its ubiquitous nature in the thorax and abdomen so the major contributions will be discussed. Several parasympathetic nerves come off the vagus nerve as it enters the thorax. One nerve is the recurrent laryngeal nerve, which becomes the inferior laryngeal nerve. From the left vagus nerve the recurrent laryngeal nerve hooks around the aorta to travel back up to the larynx and proximal esophagus while, from the right vagus nerve, the recurrent laryngeal nerve hooks around the right subclavian artery to travel back up to the same location as its counterpart. These different paths are a direct result of embryological development of the circulatory system. Each recurrent laryngeal nerve supplies the trachea and the esophagus with parasympathetic secretomotor innervation for glands associated with them (and other fibers that are not PN).

Another nerve that comes off the vagus nerves approximately at the level of entering the thorax are the cardiac nerves. These cardiac nerves go on to form cardiac and pulmonary plexuses around the heart and lungs. As the main vagus nerves continue into the thorax they become intimately linked with the esophagus and sympathetic nerves from the sympathetic trunks to form the esophageal plexus. This is very efficient as the major function of the vagus nerve from there on will be control of the gut smooth muscles and glands. As the esophageal plexus enter the abdomen through the esophageal hiatus anterior and posterior vagus trunks form. The vagus trunks then join with preaortic sympathetic ganglion around the aorta to disperse with the blood vessels and sympathetic nerves throughout the abdomen. The extent of the parasympathetic in the abdomen include the pancreas, kidneys, liver, gall bladder, stomach and gut tube. The vagus contribution of parasympathetic continues down the gut tube until the end of the midgut. The midgut ends two thirds of the way across the transverse colon near the splenic flexure.

Pelvic splanchnic nerves The pelvic splanchnic nerves, S2-4, work in tandem to innervate the pelvic viscera. Unlike in the cranium, where one parasympathetic is in charge of one particular tissue or region, for the most part the pelvic splanchnics each contribute fibers to pelvic viscera by traveling to one or more plexuses before being dispersed to the target tissue. These plexuses are composed of mixed autonomic nerve fibers (parasympathetic and sympathetic) and include the vesical, prostatic, rectal, uterovaginal, and inferior hypogastric plexuses. The preganglionic neurons in the pathway do not synapse in a ganglion as in the cranium but rather in the walls of the tissues or organs that they innervate. The fiber paths are variable and each individual's autonomic nervous system in the pelvis is unique. The visceral tissues in the pelvis that the parasympathetic nerve pathway controls include those of the urinary bladder, ureters, urinary sphincter, anal sphincter, uterus, prostate, glands, vagina, and penis. Unconsciously, the parasympathetic will cause peristaltic movements of the ureters and intestines, moving urine from the kidneys into the bladder and food down the intestinal tract and, upon necessity, the parasympathetic will assist in excreting urine from the bladder or defecation. Stimulation of the parasympathetic will cause the detrusor muscle (urinary bladder wall) to contract and simultaneously relax the internal sphincter muscle between the bladder and the urethra, allowing the bladder to void. Also, parasympathetic stimulation of the internal anal sphincter will relax this muscle to allow defecation. There are other skeletal muscles involved with these processes but the parasympathetic plays a huge role in continence and bowel retention.

A study published in 2016, suggests that all sacral autonomic output may be sympathetic; indicating that the rectum, bladder and reproductive organs may only be innervated by the sympathetic nervous system. This suggestion is based on detailed analysis of 15 phenotypic and ontogenetic factors differentiating sympathetic from parasympathetic neurons in the mouse. Assuming that the reported findings most likely applies to other mammals as well, this perspective suggests a simplified, bipartite architecture of the autonomic nervous system, in which the parasympathetic nervous system receives input from cranial nerves exclusively and the sympathetic nervous system from thoracic to sacral spinal nerves.

The parasympathetic nervous system consists of cells with bodies in one of two locations: the brainstem (Cranial Nerves III, VII, IX, X) or the sacral spinal cord (S2, S3, S4). These are the preganglionic neurons, which synapse with postganglionic neurons in these locations:

Parasympathetic ganglia of the head: Ciliary (Cranial nerve III), Submandibular (Cranial nerve VII), Pterygopalatine (Cranial nerve VII), and Otic (Cranial nerve IX) In or near the wall of an organ innervated by the Vagus (Cranial nerve X) or Sacral nerves (S2, S3, S4) These ganglia provide the postganglionic neurons from which innervations of target organs follows. Examples are:

The postganglionic parasympathetic splanchnic (visceral) nerves The vagus nerve, which passes through the thorax and abdominal regions innervating, among other organs, the heart, lungs, liver and stomach

The sensory arm is composed of primary visceral sensory neurons found in the peripheral nervous system (PNS), in cranial sensory ganglia: the geniculate, petrosal and nodose ganglia, appended respectively to cranial nerves VII, IX and X. These sensory neurons monitor the levels of carbon dioxide, oxygen and sugar in the blood, arterial pressure and the chemical composition of the stomach and gut content. They also convey the sense of taste and smell, which, unlike most functions of the ANS, is a conscious perception. Blood oxygen and carbon dioxide are in fact directly sensed by the carotid body, a small collection of chemosensors at the bifurcation of the carotid artery, innervated by the petrosal (IXth) ganglion. Primary sensory neurons project (synapse) onto "second order" visceral sensory neurons located in the medulla oblongata, forming the nucleus of the solitary tract (nTS), that integrates all visceral information. The nTS also receives input from a nearby chemosensory center, the area postrema, that detects toxins in the blood and the cerebrospinal fluid and is essential for chemically induced vomiting or conditional taste aversion (the memory that ensures that an animal that has been poisoned by a food never touches it again). All this visceral sensory information constantly and unconsciously modulates the activity of the motor neurons of the ANS.

Motor neurons of the autonomic nervous system are found in ''autonomic ganglia". Those of the parasympathetic branch are located close to the target organ whilst the ganglia of the sympathetic branch are located close to the spinal cord.

The sympathetic ganglia here, are found in two chains: the pre-vertebral and pre-aortic chains. The activity of autonomic ganglionic neurons is modulated by "preganglionic neurons" located in the central nervous system. Preganglionic sympathetic neurons are located in the spinal cord, at the thorax and upper lumbar levels. Preganglionic parasympathetic neurons are found in the medulla oblongata where they form visceral motor nuclei; the dorsal motor nucleus of the vagus nerve; the nucleus ambiguus, the salivatory nuclei, and in the sacral region of the spinal cord.

Function

Function of the autonomic nervous system Sympathetic and parasympathetic divisions typically function in opposition to each other. But this opposition is better termed complementary in nature rather than antagonistic. For an analogy, one may think of the sympathetic division as the accelerator and the parasympathetic division as the brake. The sympathetic division typically functions in actions requiring quick responses. The parasympathetic division functions with actions that do not require immediate reaction. The sympathetic system is often considered the "fight or flight" system, while the parasympathetic system is often considered the "rest and digest" or "feed and breed" system.

However, many instances of sympathetic and parasympathetic activity cannot be ascribed to "fight" or "rest" situations. For example, standing up from a reclining or sitting position would entail an unsustainable drop in blood pressure if not for a compensatory increase in the arterial sympathetic tonus. Another example is the constant, second-to-second, modulation of heart rate by sympathetic and parasympathetic influences, as a function of the respiratory cycles. In general, these two systems should be seen as permanently modulating vital functions, in usually antagonistic fashion, to achieve homeostasis. Higher organisms maintain their integrity via homeostasis which relies on negative feedback regulation which, in turn, typically depends on the autonomic nervous system. Some typical actions of the sympathetic and parasympathetic nervous systems are listed below.

Innervation Autonomic nerves travel to organs throughout the body. Most organs receive parasympathetic supply by the vagus nerve and sympathetic supply by splanchnic nerves. The sensory part of the latter reaches the spinal column at certain spinal segments. Pain in any internal organ is perceived as referred pain, more specifically as pain from the dermatome corresponding to the spinal segment.

Sympathetic nervous system Main article: Sympathetic nervous system Promotes a fight-or-flight response, corresponds with arousal and energy generation, and inhibits digestion

Diverts blood flow away from the gastro-intestinal (GI) tract and skin via vasoconstriction Blood flow to skeletal muscles and the lungs is enhanced (by as much as 1200% in the case of skeletal muscles) Dilates bronchioles of the lung through circulating epinephrine, which allows for greater alveolar oxygen exchange Increases heart rate and the contractility of cardiac cells (myocytes), thereby providing a mechanism for enhanced blood flow to skeletal muscles Dilates pupils and relaxes the ciliary muscle to the lens, allowing more light to enter the eye and enhances far vision Provides vasodilation for the coronary vessels of the heart Constricts all the intestinal sphincters and the urinary sphincter Inhibits peristalsis Stimulates orgasm Parasympathetic nervous system Main article: Parasympathetic nervous system The parasympathetic nervous system has been said to promote a “rest and digest” response, promotes calming of the nerves return to regular function, and enhancing digestion. Functions of nerves within the parasympathetic nervous system include:[citation needed]

Dilating blood vessels leading to the GI tract, increasing the blood flow. Constricting the bronchiolar diameter when the need for oxygen has diminished Dedicated cardiac branches of the vagus and thoracic spinal accessory nerves impart parasympathetic control of the heart (myocardium) Constriction of the pupil and contraction of the ciliary muscles, facilitating accommodation and allowing for closer vision Stimulating salivary gland secretion, and accelerates peristalsis, mediating digestion of food and, indirectly, the absorption of nutrients Sexual. Nerves of the peripheral nervous system are involved in the erection of genital tissues via the pelvic splanchnic nerves 2–4. They are also responsible for stimulating sexual arousal. Enteric nervous system Main article: Enteric nervous system The enteric nervous system is the intrinsic nervous system of the gastrointestinal system. It has been described as “the Second Brain of the Human Body”. Its functions include:

Sensing chemical and mechanical changes in the gut Regulating secretions in the gut Controlling peristalsis and some other movements Neurotransmitters Main articles: Table of neurotransmitter actions in the ANS and Non-noradrenergic, non-cholinergic transmitter

A flow diagram showing the process of stimulation of adrenal medulla that makes it release adrenaline, that further acts on adrenoreceptors, indirectly mediating or mimicking sympathetic activity. At the effector organs, sympathetic ganglionic neurons release noradrenaline (norepinephrine), along with other cotransmitters such as ATP, to act on adrenergic receptors, with the exception of the sweat glands and the adrenal medulla:

Acetylcholine is the preganglionic neurotransmitter for both divisions of the ANS, as well as the postganglionic neurotransmitter of parasympathetic neurons. Nerves that release acetylcholine are said to be cholinergic. In the parasympathetic system, ganglionic neurons use acetylcholine as a neurotransmitter to stimulate muscarinic receptors. At the adrenal medulla, there is no postsynaptic neuron. Instead the presynaptic neuron releases acetylcholine to act on nicotinic receptors. Stimulation of the adrenal medulla releases adrenaline (epinephrine) into the bloodstream, which acts on adrenoceptors, thereby indirectly mediating or mimicking sympathetic activity.