

Nervous + Musculoskeletal Systems

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1 Introduction

The nervous system is the control center of your entire body. From coordinating actions that are a conscious choice to coordinating internal bodily actions that you don't even know are going on, the nervous system controls and regulates all of your body's systems.

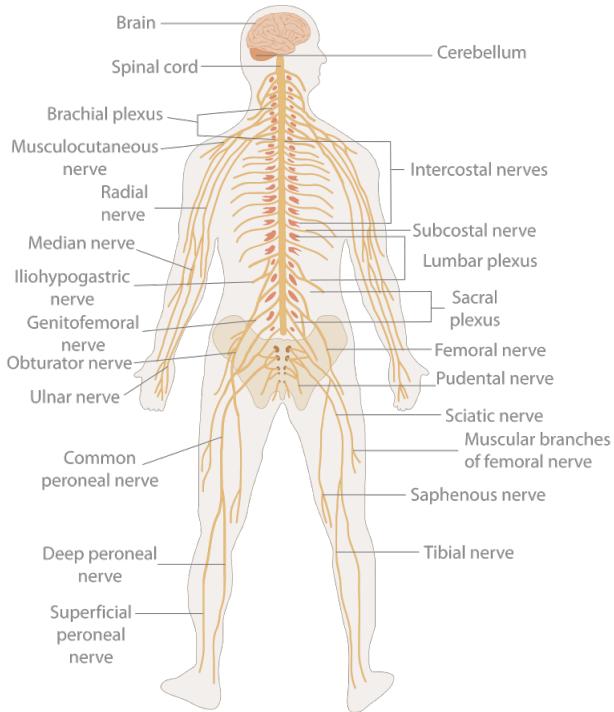


Figure 1: The Nervous System

2 Cells of the Nervous System

The nervous system is split into two main parts: (1) the **central nervous system (CNS)**, composed of the brain and spinal cord; and (2) the **peripheral nervous system (PNS)**, consisting of all the nerves that connect the brain and spinal cord to the rest of the body's muscles, glands, and tissues.

The nervous system as a whole is composed of two main types of cells: (1) **neurons**, which are the functional units of the nervous system that operate by generating electrical signals that transmit information throughout the body; and (2) **glial cells**, which are supportive cells that provide essential support and maintenance for neuronal function.

2.1 Neurons

Neurons are the main functional units of the nervous system. They operate by generating electrical signals in response to a **stimulus**. In most types of neurons, these electrical signals cause the release of chemical messengers called neurotransmitters which communicate with other types of cells.

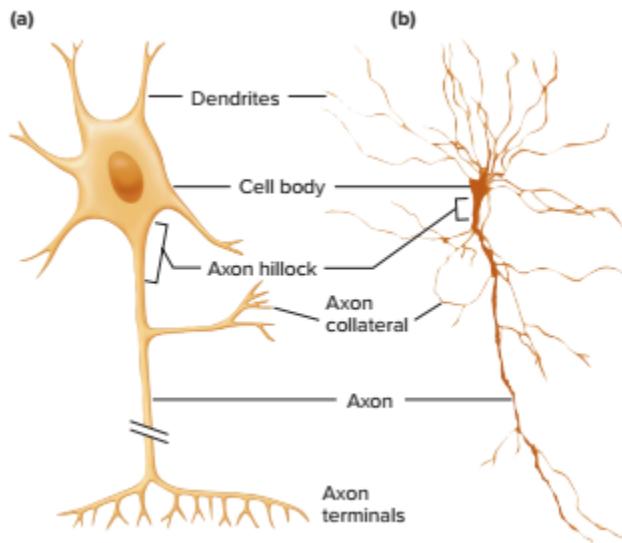


Figure 2: (a) Diagrammatic representation of a neuron (b) Neuron as seen through a microscope

- **Dendrites:** Outgrowths from the cell body that receive signals from other neurons. Certain dendritic outgrowths called **dendritic spines** increase the surface area of dendrites so that they can receive signals from many neurons. Additionally, **thin dendritic spines** enable neuronal plasticity and learning with their dynamic structures. In diseases such as Alzheimer's, these thin spines are less plastic and retract as the disease progresses.
- **Cell Body (Soma):** Contains the nucleus and ribosomes, has the genetic information and machinery necessary for protein synthesis. Neurons also have a specialized rough endoplasmic reticulum known as **Nissl Substance/Body**.
- **Axon:** The long extension from the cell body that carries signals to its target cells. Axons can be really long or really short, depending on the type of neuron and its location. The cell membrane of an axon is referred to as the *axolemma*.
- **Axon terminals:** The end of the axon, where the neurotransmitters are released. In addition, certain neurons release neurotransmitters or other chemical messengers from areas along the axon (that bulge) called **varicosities**.
- **Axon Hillock:** The part of the axon that initially arises from the cell body. This is the location where signals are generated in most neurons.
- **Axon Collaterals:** Branches and regions that branch out from the axon.

Because the axon has such a small diameter, it has high **capacitance**, which is the ability of a system to store electric charge. As a consequence, the conduction velocity of nerve impulses is reduced, resulting in slower transmission of signals along the axon. This can lead to delayed neural responses and reduced efficiency in the communication between neurons. On the other hand, when the axon has a large diameter, such as a giant squid axon, it has a low capacitance.

The solution to this problem are **myelin sheathes** which will be explained in more detail in section 2.2.

In order to maintain the structure and function of neurons, organelles and other cellular materials move along the cell in a process known as **axonal transport**. Axonal Transport depends on the movement across microtubules using specialized motor proteins called **kinesins** and **dyneins** (you would have already heard about dyneins in cilia and flagella movement). These motor proteins work like **myosin** across **actin filaments**, they use energy derived from the hydrolysis of ATP to move along the microtubules.

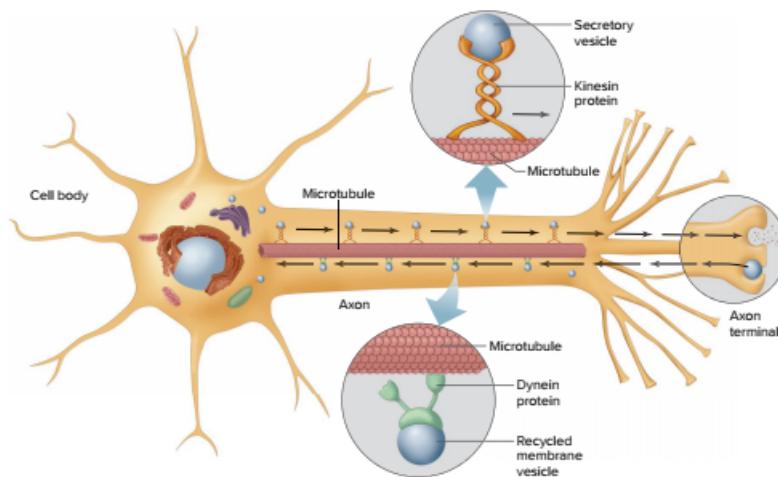


Figure 3: Axonal Transport

- **Kinesin:** Kinesin transport happens from the cell body toward the axon terminals (**anterograde transport**) and is most important in moving nutrients, enzymes, mitochondria, vesicles filled with neurotransmitters, and other organelles
- **Dynein:** Dynein transport moves recycled vesicles, growth factors, and other chemical figures towards the soma (**retrograde transport**). Harmful agents invade the CNS through retrograde transport such as the **polio virus**.

Neurons can be divided into three main classes based on function:

- **Afferent Neurons:** Carry information from tissues and organs of the body *toward* the CNS. The ends of afferent neuron axons have **sensory receptors** that detect stimuli and changes in the environment by electrical signals in the neuron. Afferent neurons have 1 axon coming out of the cell body, but shortly after, the axon divides into two branches. One branch, the **peripheral process**, is on the right side in Figure 4 and connects the sensory receptors to the cell body. The other branch which is called the **central process** enters the CNS to form junctions with interneurons. In afferent neurons, only the end of the central process is in the CNS, the rest of the neuron is in the PNS.

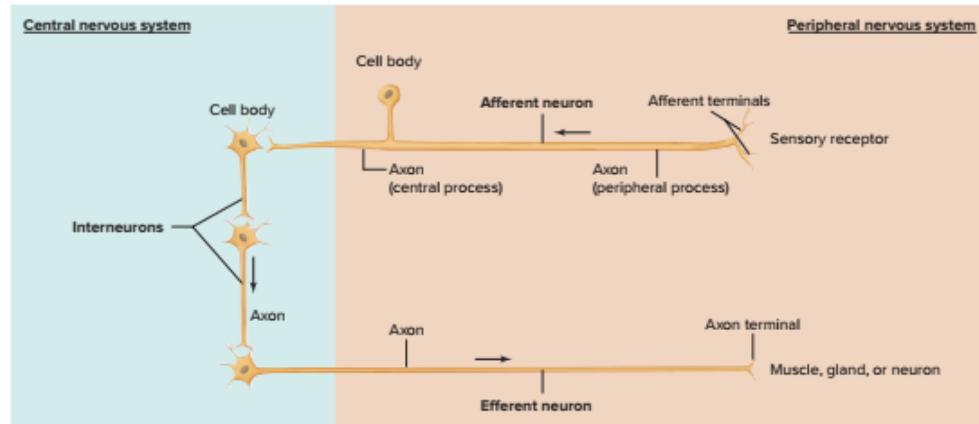


Figure 4: The three main classes of neurons

- **Efferent Neurons:** Carry information *from* the CNS to effector cells. Generally, efferent neuron cell bodies and dendrites are within the CNS while the rest is in the PNS, but
- **Interneurons:** Connect neurons *within* the CNS. All interneurons are entirely in the CNS, and are responsible for the processing of information.

For each afferent neuron entering the CNS, there are about 200k interneurons and 10 efferent neurons, making the majority of neurons are interneurons.

Neurons can also be divided into four classes based on structure:

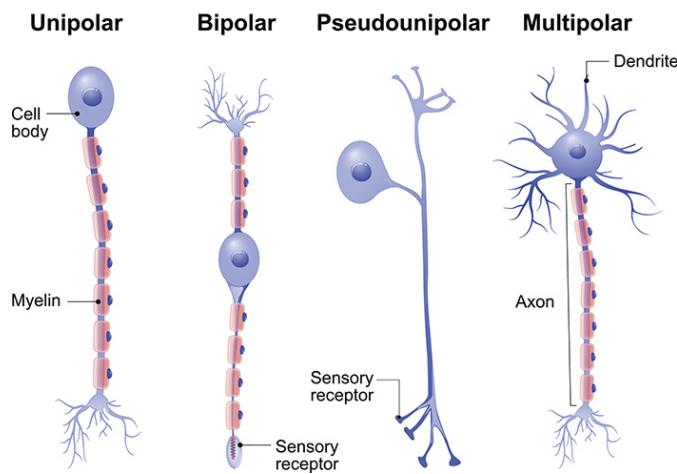


Figure 5: Structural Classification of Neurons, Source: Queensland Brain Institute

- **Unipolar Neurons:** Single process extending from the soma called the **neurite** whose branches form both dendritic and axonal processes; not found in vertebrates.
- **Bipolar Neurons:** Contain 1 axon and 1 dendrite; typically found in special sense organs such as the olfactory epithelium and retina.

- **Pseudounipolar Neurons:** Initially forms as a bipolar neuron but the processes fuse and become one neurite. Sensory neurons involved in transferring information to the CNS; concentrated in sensory ganglia.
- **Multipolar Neurons:** The most common type of neuron; concentrated in the brain and spinal cord functioning in information processing as interneurons and motor function.

The junction between two neurons is called a **synapse** where signals are transmitted through neurotransmitters. Most synapses are axodendritic (axon terminal to dendrite), but there are exceptions such as axoaxonic (axon to axon). These are outlined in this article. The neuron that conducts a signal towards the synapse is called the **presynaptic neuron** and the neuron that receives the signal is called the **postsynaptic neuron**.

2.2 Glial cells

As mentioned in the previous section, glial cells are supportive cells and they play a major role in the formation of the **myelin sheath** which decreases the capacitance of neurons and allows fast transmission of electrical signals. Major components of the myelin sheath include cholesterol, glycosphingolipids, and plasmalogens.

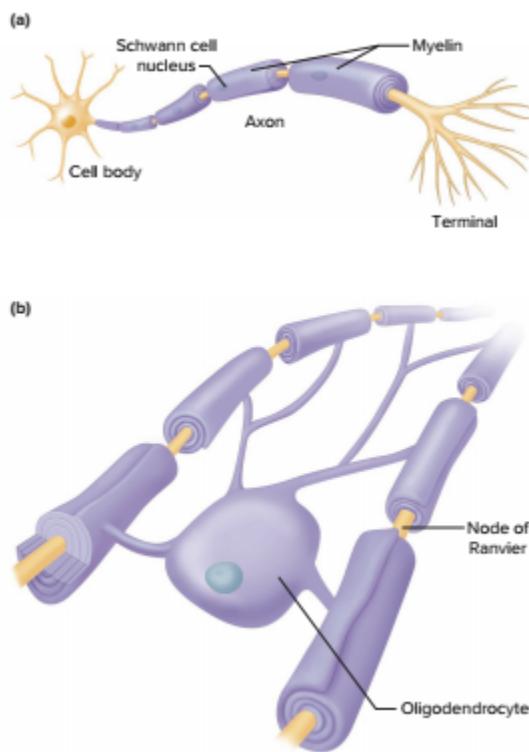


Figure 6: (a) Schwann cells (b) Oligodendrocytes

- **Oligodendrocytes:** Make up the myelin sheath in the CNS. One of these cells can form myelin on 40 different axons.

- **Schwann Cells:** Make up the myelin sheath in the PNS. Each cell forms an individual sheath of myelin.

The areas where the plasma membrane of the axon is exposed inbetween the sheaths of myelin are called **Nodes of Ranvier**. Conduction occurs inbetween these areas called **saltatory conduction**. More on this later.

Most types of neurons are unable to divide throughout life, making them unlikely to produce tumors, etc. Unlike these, glial cells can divide throughout life so most CNS tumors actually arise from glial cells rather than neurons.

There are several types of glial cells found in the CNS (including oligodendrocytes):

- **Astrocytes:** Helps regulate the composition of the fluid in the CNS, removes the potassium ions + neurotransmitters around the synapses. Forms the **blood-brain barrier** (provides a filter for exchanged substances) through the formation of **tight junctions** between the cells that make up the capillary walls in the CNS. Astrocytes also have similar functions to neurons on a much smaller scale as well as guiding CNS neuron migration and the growth of them by secreting growth factors **more in 2.3**.
- **Microglia:** macrophage-like cells that provide immune function in the CNS as well as functioning in plasticity
- **Ependymal cells:** Line the fluid cavities in the brain + spinal cord and produce **cerebrospinal fluid** (more on this later)

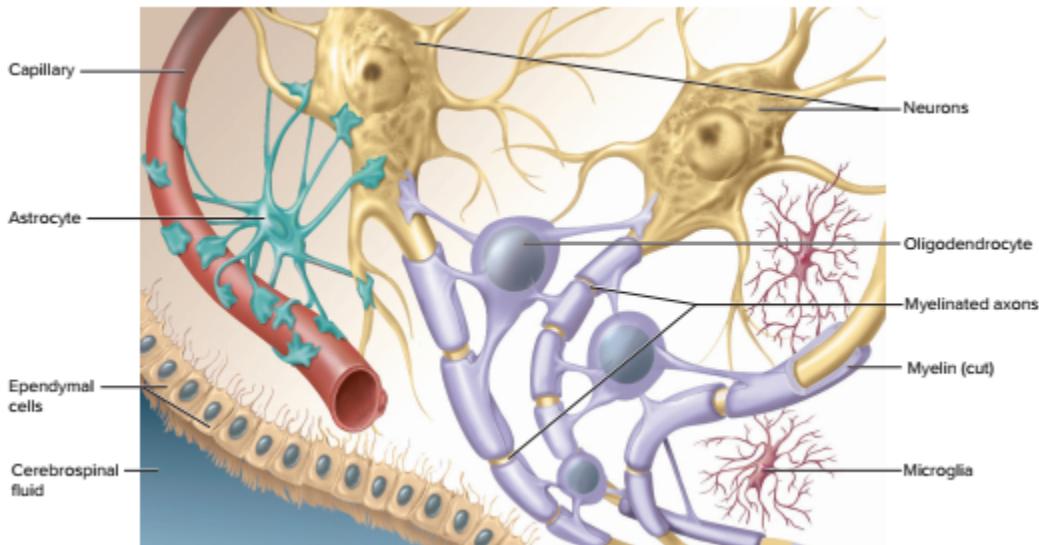


Figure 7: Source: Vander's Human Physiology

2.3 Neuronal Growth and Regeneration

The nervous system development in an embryo starts with the division of **stem cells** which develop into neurons or glia. After the final division in this stage, each neuronal cell migrates to its final location and sends out **process that become axons and dendrites**.

The **growth cone**, a specialized enlargement, forms the tip of each axon and navigates the axon to its target.

- As an axon grows, certain molecules like **cell adhesion molecules**, which reside on the membranes of glia, and **neurotrophic factors**, which surround the growth cone and its target, guide the growth cone to its destination. Some important axon-guidance molecules and their influence modes:
 - Semaphorins (Chemorepulsion)
 - Netrins (Chemoattractant)
 - Cadherins (Contact Attraction)
 - Ephrins (Contact Repulsion)
- After the target of the growth cone is located, **synapses** form. In the early stages of this process, certain harmful agents, such as viruses, can cause permanent damage to the developing nervous system. **Zika virus**, for example, causes infants to be born with underdeveloped brains—a condition called **microcephaly**.

After many of the neurons are settled and find their axonal targets, 50-70 percent of these neurons undergo **apoptosis**. There is no real known reason for this, but neuroscientists speculate that this fine-tunes connectivity in the brain and that it is a major reason for why people don't remember events prior to 4 years of age.

Throughout the lifespan later, the brain has the ability to modify and learn itself, a feature called **plasticity**. Age heavily effects these and other kinds of neuron production and growth, being slowed down with age.

Researchers have been working heavily on axonal and neuron regeneration in the CNS in many different ways and this research can prove monumental in treatment for many kinds of nervous system disorders.

One of these major research efforts focuses around undifferentiated **stem cells** that develop into new neurons, which secrete **neurotransmitters** as well as **neurotrophic factors**. Techniques involve using both embryonic stem cells as well as adult stem cells or regular somatic cells that were reverted to a stem-cell state.

2.4 Resting Membrane Potential

The **resting potential of neurons** refers to the electrical charge difference across the cell membrane of a neuron when it is at rest, (meaning that it is **not actively transmitting signals** or involved in any synaptic activity). This resting potential is crucial for the proper functioning of neurons in the nervous system. The resting potential is typically around **-70 millivolts (mV)** in most neurons, but this value can vary among different types of neurons and depending on the organism.

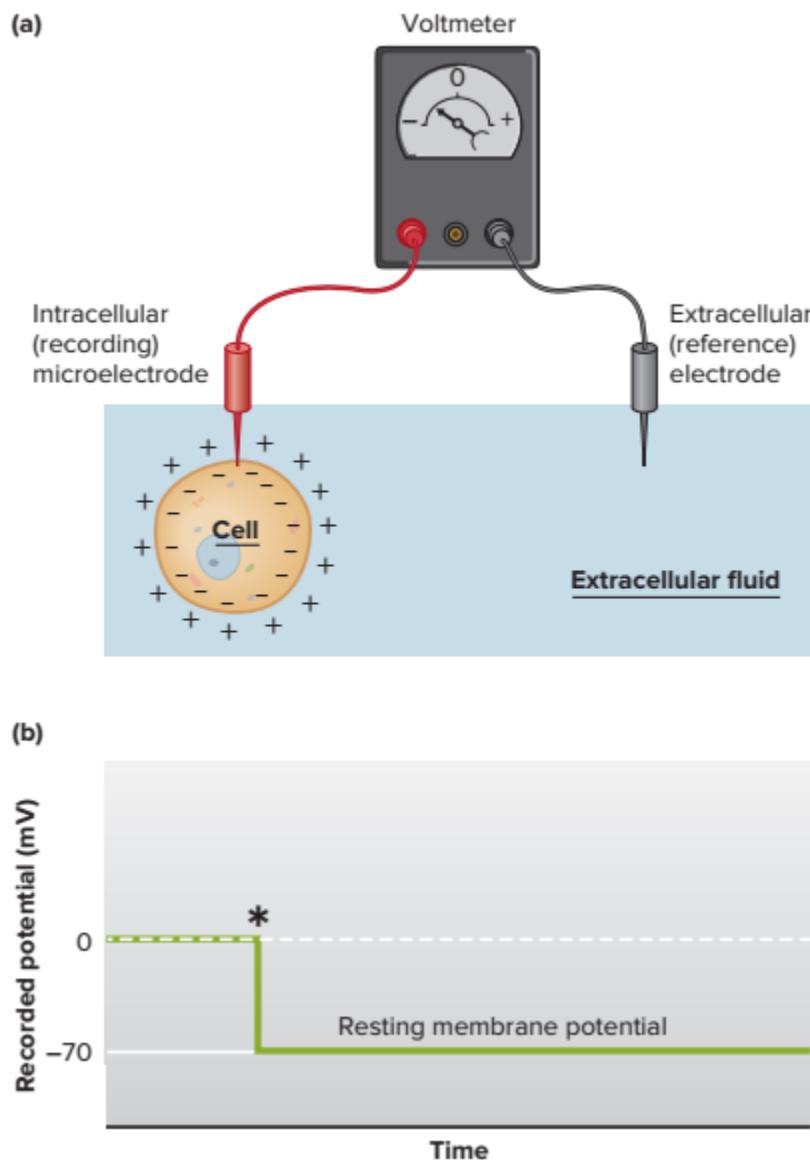


Figure 8: (a) Voltmeter measuring potential (b) Maintenance of negative membrane potential

The resting potential is maintained by the combined action of **ion channels** and **ion pumps** in the cell membrane. Neurons have a higher concentration of sodium ions (Na^+) outside the cell and a higher concentration of potassium ions (K^+) inside the cell. This uneven distribution of ions is maintained by the **sodium-potassium pump**, which actively transports three sodium ions out of the cell and two potassium ions into the cell **against** their respective concentration gradients.

Additionally, the cell membrane of neurons contains ion channels that are **selectively permeable** to specific ions. In particular, there are **leak channels** for potassium that allow some potassium ions to slowly leak out of the cell, contributing to the **negative charge** inside the neuron.

The resting potential allows neurons to be in **ready state**, capable of receiving and processing

Ion	Concentration (mmol/L)	
	Extracellular	Intracellular
Na ⁺	145	15
Cl ⁻	100	7*
K ⁺	5	150

Figure 9: Concentration of major ions across neuronal membrane

incoming signals. When a neuron receives a **stimulus** or signal, it may undergo a change in membrane potential, leading to the generation of an **action potential**, which is a rapid and transient electrical signal that travels down the neuron's axon to communicate with other neurons or effector cells.

A major contributor to the resting potential of neurons are the **equilibrium potentials** (no net movement) of each ion.

There is a way to calculate this called the **Nernst equation**. The Nernst equation describes the electrical potential that is necessary to balance the ionic concentration gradient so that equilibrium potential is met:

$$E_{ion} = \frac{61}{Z} \log \left(\frac{C_{out}}{C_{in}} \right)$$

E_{ion} = equilibrium potential for a particular ion, in mV

C_{in} = intracellular concentration of the ion

C_{out} = extracellular concentration of the ion

Z = the valence (charge) of the ion

61 = a constant value that takes into account the universal gas constant, the temperature (37°C in all our examples), and the Faraday electrical constant

By using the values in the table, Na⁺ flux will tend to bring the **membrane potential** towards +60 mV, while K⁺ flux will bring it toward -90 mV.

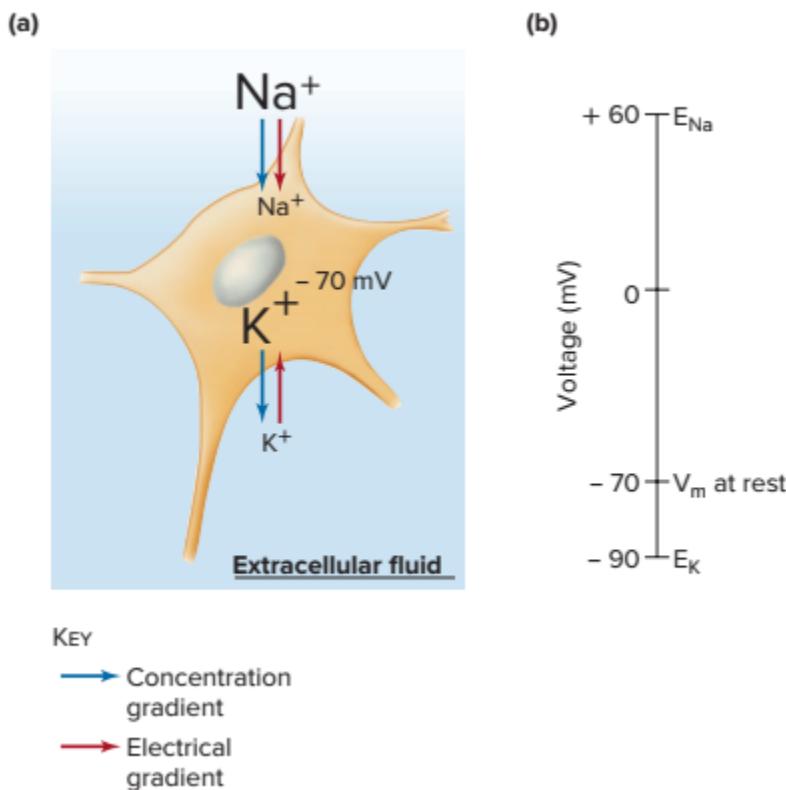


Figure 10: Concentration of major ions across neuronal membrane

To summarize, the resting potential is generated across the plasma membrane mostly because of the movement of potassium ions outside the cell down its concentration gradient through un gated **leak channels**. The inside of the neuron is then negative compared to the outside.

However, the resting potential is not equal to the K^+ equilibrium potential because of the small number of Na^+ ions that bring it more positive. In addition, the concentrations of sodium and potassium ions don't change because of the the **sodium-potassium pump** which keeps the concentrations in balance.

The plasma membrane of many neurons also have chloride (Cl^-) channels but not chloride pumps. This means that the chloride ion concentrations shift until their **equilibrium potential** is equal to the **resting membrane potential**. The negative potential moves chloride ions out of the cell and the chloride ion concentration inside becomes lower than the outside.

Therefore, this cause the diffusion of chloride ions back into the cell (negative so make more negative) that opposes the movement down the **electrical gradient** (will make more negative because negative ions leaving are counteracted).

However, some cells have an **active transport** system that *isn't electrogenic*, moving chloride ions out of the cell, creating a concentration gradient. Therefore, the diffusion of chloride ions back into the cell contributes to the negative charge more than the sodium and potassium ions.

2.5 Action and Graded potentials

In addition to leak channels, neurons (and other cells) have another type of ion channel called **gated ion channels** that are opened or controlled under certain conditions. This property allows neurons the ability to produce signals that can transmit information, a property called **excitability**. The membranes with these property are called **excitable membranes**. The main types of excitable cells are neurons and muscle cells.

Depolarize, repolarize, and hyperpolarize are terms that describe the direction of the change in membrane potential:

- **Depolarize:** Less negative or greater than the resting potential.
- **Overshoot:** Reversal in the membrane potential, the inside becomes positive relative to the negative outside.
- **Repolarize:** The return to the resting potential from depolarization.
- **Hyperpolarize:** More negative, lesser and further away from 0 than the resting potential.

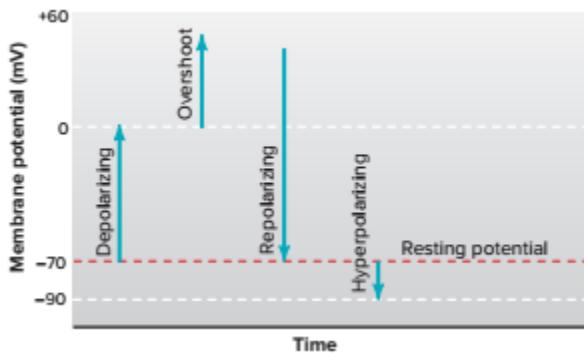


Figure 11: Diagram of action potentials. (Source: Vander's Human Physiology)

Action and graded potentials are two types of electrical signals that occur in neurons, playing essential roles in transmitting and processing information in the nervous system.

- **Action Potentials:** Action potentials are rapid and **all-or-nothing electrical impulses** that allow neurons to transmit signals over long distances. They are triggered when a neuron's membrane potential reaches a certain threshold, typically around -55 millivolts. Once the threshold is crossed, **voltage-gated sodium channels** open, allowing an influx of sodium ions into the neuron, causing a **rapid depolarization**. This creates a **positive feedback loop**, as depolarization further opens more sodium channels, leading to the rising phase of the action potential.

After the action potential peaks, voltage gated potassium channels open, and potassium ions flow out of the neuron, **repolarizing** the membrane and restoring the negative resting potential. This is followed by a brief **hyperpolarization** due to an overshoot of potassium ions, which helps to reset the neuron for the next action potential. The entire process of an action potential is rapid, lasting only a few milliseconds, and allows neurons to efficiently transmit signals over long distances along their axons.

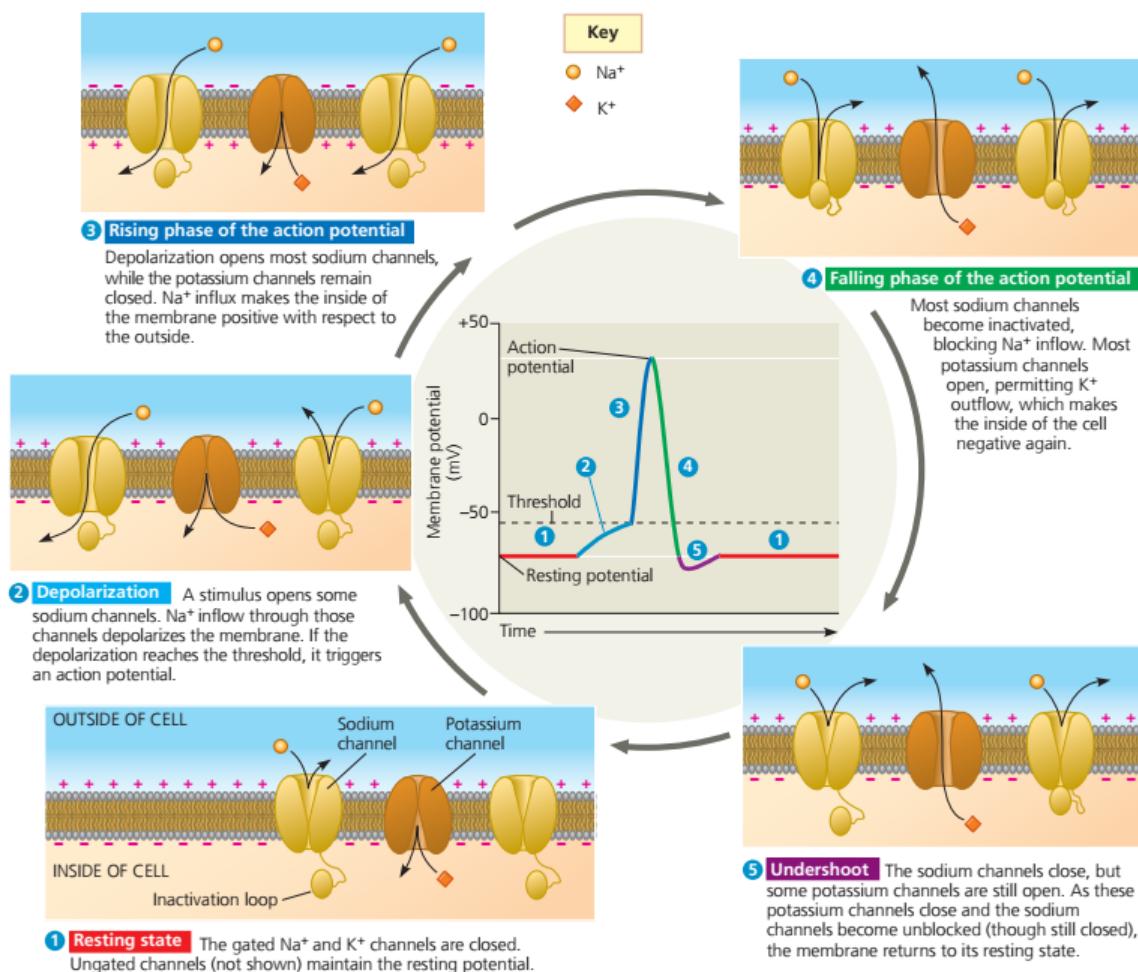


Figure 12: The role of Voltage-Gated Ion Channels in action potentials

Voltage Gated Ion Channels: There are different types of gated ion channels, **ligand-gated ion channels** which open in response to the binding of signaling molecules, **mechanically gated ion channels** which open in response to stretching of the plasma membrane, and voltage-gated ion channels which are specific to certain ions and open in response to a voltage change in the membrane.

The way these Na^+ and K^+ ion channels work is that they have sequences of charged amino acids in their structure that make the channels reversibly change shape in response to membrane potential. Two key differences between the Na^+ and K^+ ion channels allow them to produce action potentials

- Voltage-gated Na^+ channels respond faster to changes in membrane voltage, so they open before the K^+ ion channels do and when the membrane is repolarized, the K^+ ion channels are slower to close.
- Na^+ voltage gated ion channels contain an **inactivation gate** which is shown as the ball and chain pictures in the diagram above. This gate limits the transmission of Na^+ ions by blocking the channel after depolarization opens it. The inactivation gate is then forced out once the membrane repolarizes.

During the falling phase and the early part of the undershoot, there is a certain period called the **absolute refractory period** which is the time when a stimuli cannot initiate second action potential. This is due to the inactivation of the sodium channels afterward. Following this is the **relative refractory period** where the second action potential can be initiated but the stimulus has to be way higher than normal. This is due to the fewer Na^+ ion channels open and the few K^+ ion channels that are still open, needing a larger stimuli to reach the threshold.

The generation of action potential are prevented by certain anesthetics like **procaine** and **lidocaine** because they block voltage gated sodium ion channels so they can't play a role in depolarization. Another example is **tetrodotoxin** which is produced by pufferfish and works the same way as these anesthetics.

Action potentials are usually initiated in the **axon hillock**. From there, Na^+ inflow during the rising phase created a strong enough current that depolarizes the neighboring region of the axon which causes an axon potential and this process is repeated all along the axon. The magnitude of each action potential is obviously the same and this causes the movement of impulses from the cell body to the synaptic terminals.

Action potentials can only travel one direction - **from the axon hillock to the synaptic terminals**. This is because behind the zone of depolarization the sodium channels stay inactivated for a short period of time, called the **absolute refractory period**, which makes the membrane unable to receive further input so the current that depolarizes the axon ahead of the action potential cannot produce another potential behind it. In addition, the period of continued flow of K^+ ions out of the cell, called the **relative refractory period**, lasts longer than the absolute refractory period and makes it difficult (but not impossible) to initiate another action potential.

However, axons insulated by the **myelin** sheath changes this. In axons sheathed with myelin, the voltage-gated sodium channels are restricted to the gaps in between the sheaths of myelin called **Nodes of Ranvier**. Because of this, action potentials are not generated in between the nodes and the current produced in the rising phase of these action potentials travel directly all the way to the next node. It repolarizes the membrane and regenerates the action potential once more. This process is called **saltatory conduction** and like mentioned before, this greatly increases the speed of the conduction of action potentials.

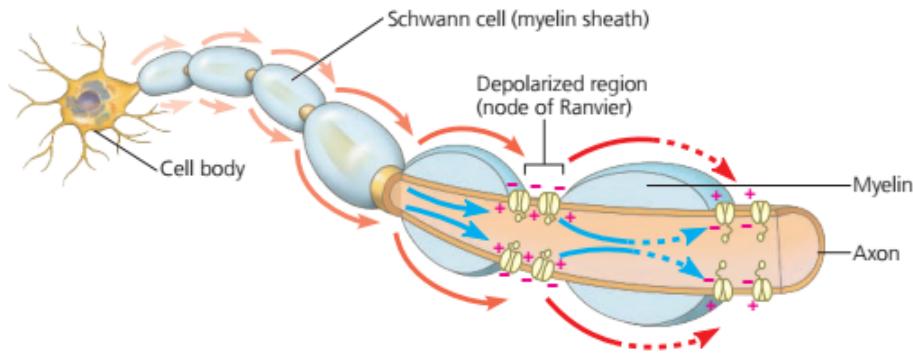


Figure 13: Saltatory conduction

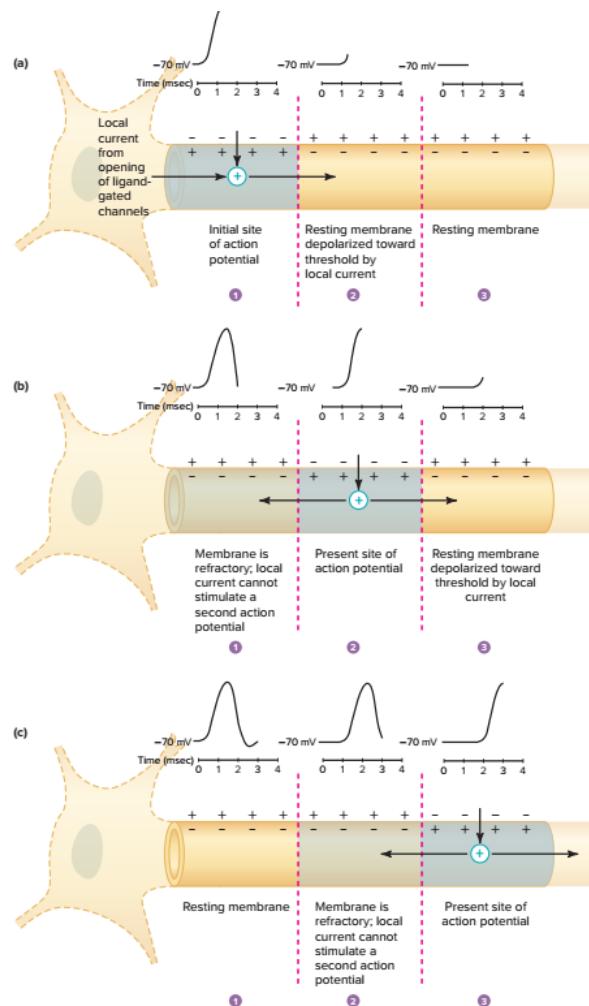


Figure 14: Propagation of action potentials across a regular axon

- **Graded Potentials:** Graded potentials are **slower and localized changes** in the membrane potential that occur in response to incoming signals or stimuli. Unlike action potentials, which are all-or-nothing, graded potentials are **graded in magnitude**, meaning the amplitude of the potential change depends on the strength of the stimulus. Graded potentials

occur primarily in **dendrites** and **cell bodies** of neurons.

Graded potentials can be either depolarizing (**excitatory**) or hyperpolarizing (**inhibitory**) depending on the type of stimulus and the resulting ion movements. For example, if a neuron receives an excitatory signal, it may experience a **depolarizing** graded potential due to an influx of sodium or calcium ions. On the other hand, an inhibitory signal can lead to a **hyperpolarizing** graded potential caused by an efflux of potassium ions or an influx of chloride ions.

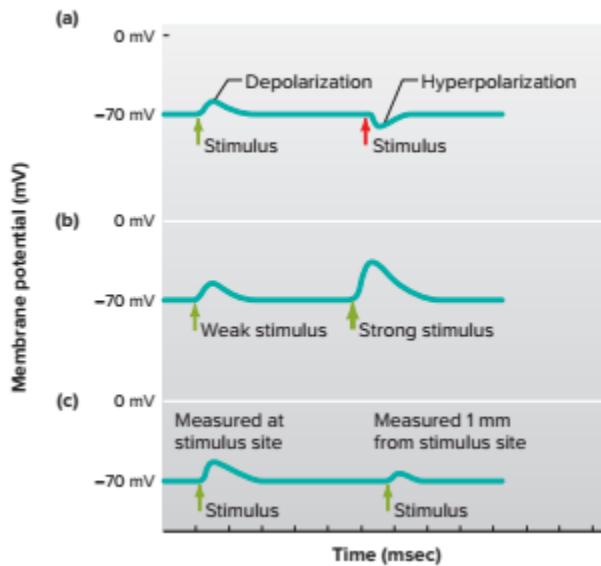


Figure 15: Graded potential activation

In addition to the movement of ions in graded potentials, charge is lost because of the many leak channels. Because of this, the change in membrane potential decreases as it gets farther from the initial site. The local current can be called **decremental**, the flow of the charge decreases and may even die out the farther from the origin site.

Because of this, graded potential can only signal over short distances. However, if another stimuli occurs just before the graded potential dies, the second adds to the first, known as **summation**. Graded potentials are only really used for communication in some neurons.

Graded potentials play a crucial role in integrating incoming signals from multiple sources. If the summation of these graded potentials reaches the threshold, it can trigger an action potential. However, if the summation does not reach the threshold, the neuron will not fire an action potential, and the signal will dissipate.

3 Neuronal Signaling

This section covers the mechanisms of neuronal signaling and how it works.

3.1 Synapses

There are a few different types of synapses. Between those types, there are types discussing the electric potential of them:

- **Excitatory synapse:** The membrane potential of the **postsynaptic** neuron is brought closer to the threshold and depolarized at an **excitatory synapse**.
- **Inhibitory synapse:** The membrane potential of the **postsynaptic** neuron is brought further away from the threshold and hyperpolarized or stabilized at the resting potential at an **inhibitory synapse**.

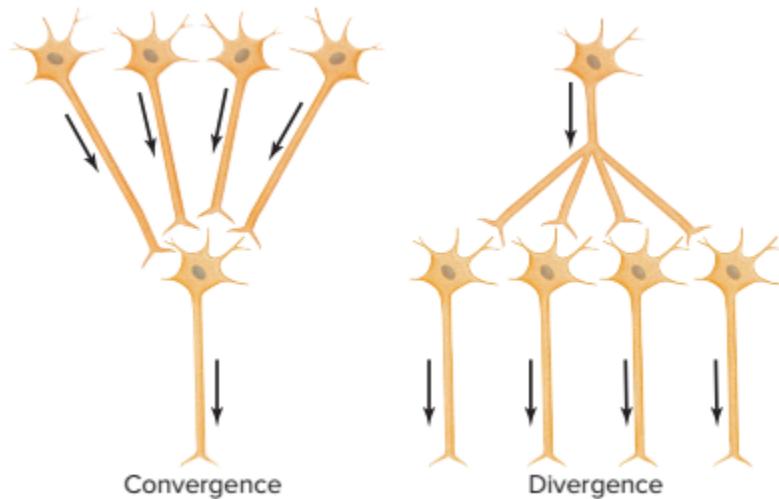


Figure 16: Convergence and Divergence

Many different synapses from many different presynaptic neurons can affect a single postsynaptic cell, called **convergence**, and vice versa a single presynaptic neuron can send processes to affect many other postsynaptic cells, called **divergence**.

Electrical synapses are the connections formed by the two processes involving **gap junctions** (remember from the cell bio handout) which allows the currents from action potentials to pass directly from the presynaptic to the postsynaptic neuron, depolarizing the membrane of the postsynaptic neuron and continuing the propagation of an action potential.

One major advantage of this is that signals are extremely rapid. Because of this, they were found to synchronize activity of neurons in certain groups within the **CNS** as well as playing a major role in the regulation of **cardiac** and **smooth muscle tissues**.

In contrast, **chemical synapses** are just formed via a gap of about 10-20 nm called the **synaptic cleft** between the presynaptic neuron process and the postsynaptic neuron process. The axon of the presynaptic neuron ends in a “bulge” (referred to as the *synaptic knob*) which contains all the **synaptic vesicles** containing the **neurotransmitters** for release. Because of this, the postsynaptic neuron has a high density of membrane proteins that make up an area called the **postsynaptic density**.

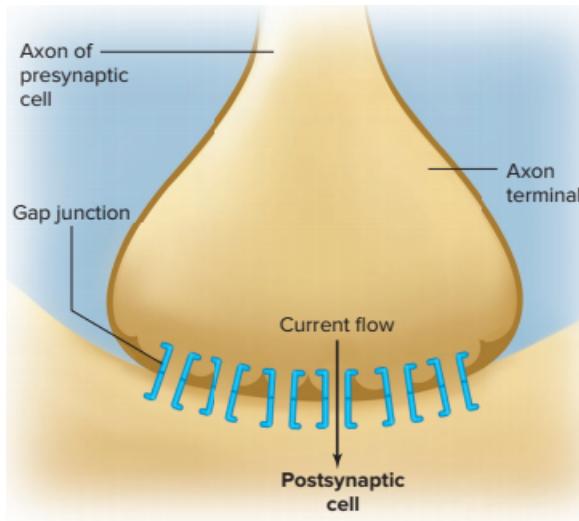


Figure 17: Electrical Synapse

While chemical synapses are slower than electrical synapses, the more complex process gives more opportunity for regulation and control of neurotransmission, which is crucial to the functioning of the nervous system. Thus, chemical synapses are in general more common than electrical synapses, especially in the central nervous system.

The **synaptic cleft** does not allow for the direct propagation of signals like **electrical synapses**, so instead, the signal must be transmitted through **neurotransmitters**, mentioned in the paragraph above. One or more types of neurotransmitters are released by the presynaptic neuron simultaneously (when there is more than one type of neurotransmitter being released *at the same time*, it is called a **cotransmitter**) which bind to the postsynaptic cell and generates another signal. The major advantage of the chemical synapses is that they allow multiple signals to arrive at the certain postsynaptic cell.

3.2 Neurotransmitter Release

Some of the vesicles are docked on certain regions for release called **active zones** while others are dispersed. The release of neurotransmitters is caused when an action potential releases the terminal membrane of the presynaptic neuron. At the neuron terminals, there are voltage-gated Ca^{2+} channels which are opened due to depolarization of the membrane and because the **electrochemical gradient** favors influx, calcium ions flow into the axon terminals.

Before an action potential arrives, vesicles containing neurotransmitters are docked in the active zones through specific proteins called **SNARE proteins**. These proteins are categorized into two main types: **v-SNAREs** (vesicle-SNAREs), which are located on the vesicle membrane, and **t-SNAREs** (target-SNAREs), which are located on the target membrane, such as the presynaptic membrane. The interaction between v-SNAREs and t-SNAREs forms a SNARE complex that facilitates the docking and eventual fusion of vesicles with the membrane. When Ca^{2+} ions bind to proteins called **synaptotagmins**, they trigger a conformational change in the SNARE complex,

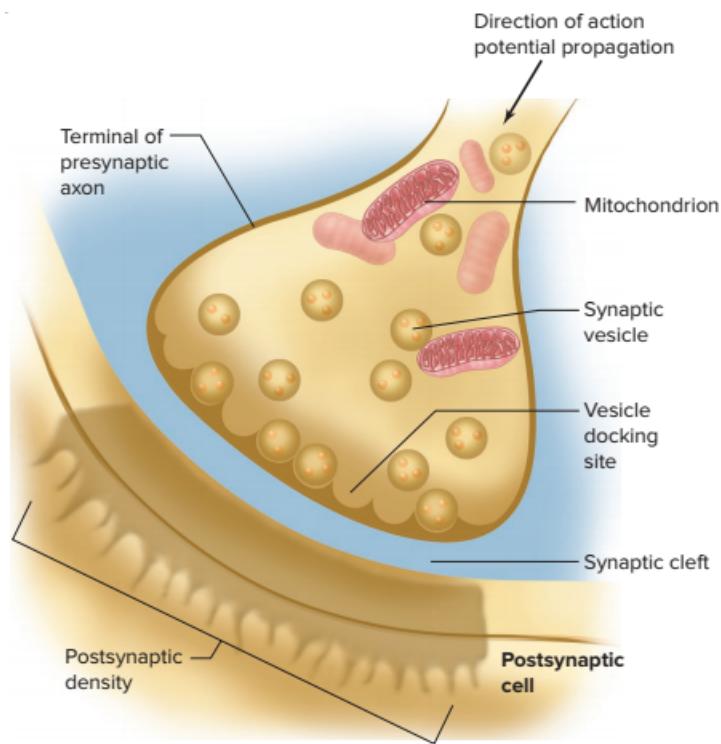


Figure 18: Chemical Synapse

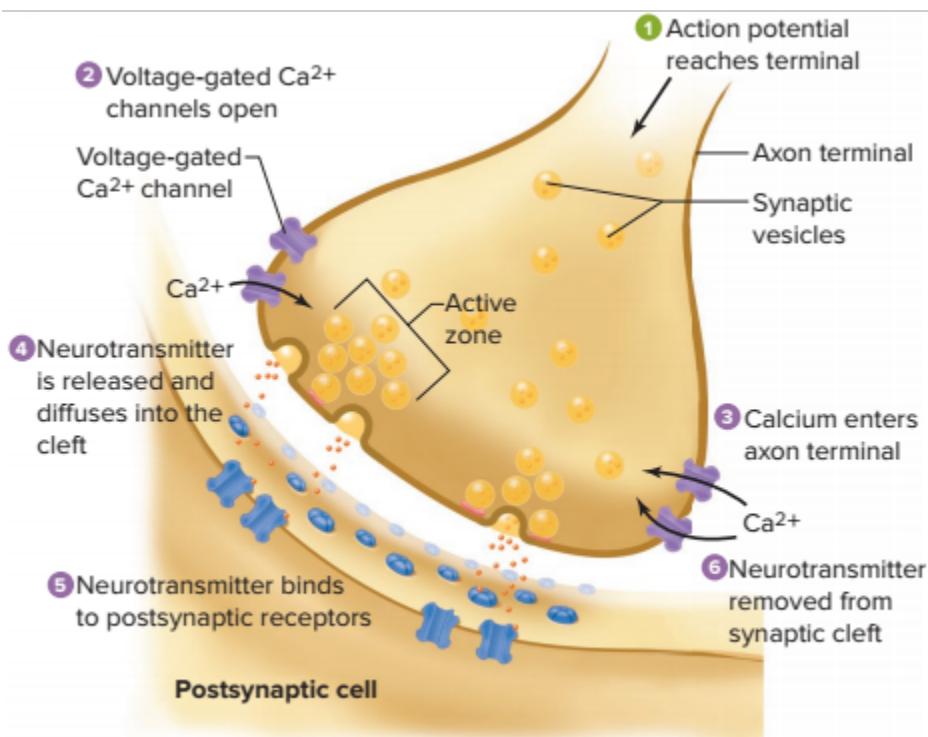


Figure 19: The role of calcium ions in neurotransmitter release

leading to the fusion of vesicles with the membrane and the subsequent release of neurotransmitters into the synaptic cleft. Blockage of these SNARE proteins (such as by the botulinum toxin, also commercially used as Botox) prevents neurotransmitter release, as vesicles cannot fuse with the membrane.

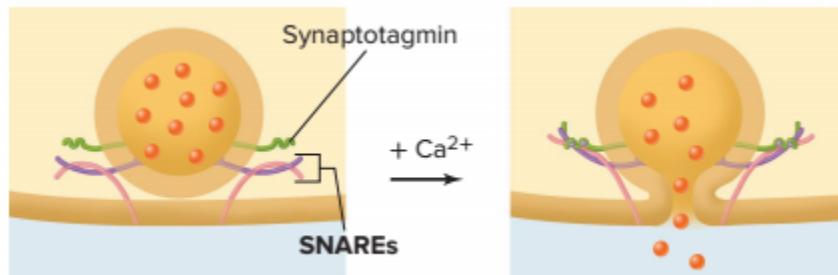


Figure 20: SNARE protein complex in docking of neurotransmitter-containing synaptic vesicles

In some synapses, vesicles are recycled through **endocytosis** (after docking back to the presynaptic terminal membrane) while others fuse only briefly to the terminal membrane before resealing and withdrawing back within the cell called **kiss-and-run fusion** which usually occurs when action potential firing frequencies are high.

In the postsynaptic cells, neurotransmitters bind to receptors that are either ion channels, called **ionotropic receptors** or may indirectly affect ion channels through **GPCRs** (remember from cell bio) and/or a second messenger like **cAMP**, called **metabotropic receptors**. These both involve the opening of **ligand-gated ion channels** through the binding of neurotransmitters.

The bound ligand is always in equilibrium with the unbound form. However, the ion channels return to their resting state when the neurotransmitters aren't bonded anymore.

After the signal is passed, neurotransmitters must be removed from the synaptic cleft in order to not start another signal etc. They are either taken back into the presynaptic cell (**reuptake**) transported to nearby glial cells where they are degraded, diffuse away from the receptor site, or are transformed into inactive substances via enzymes.

The two types of chemical synapses are **excitatory** and **inhibitory synapses**. The response to excitatory is depolarization and it is hyperpolarization for inhibitory.

Excitatory change opens non selective channels to Na^+ and K^+ ions. Both the electrical and concentration gradients drive Na^+ ions into the cell, while the **electrical gradient** promotes the influx of K^+ ions while the **concentration gradient** promotes the efflux so these oppose each other. This results in the large influx of Na^+ ions into the cell and a small number of K^+ out of the cell. This generates a slight depolarization causing a membrane potential change called an **excitatory postsynaptic potential (EPSP)**. An EPSP is a graded potential (**depolarization**) that decreases in size and magnitude the farther away it gets from the synapse. Its main function is it *bring the membrane potential of the postsynaptic neuron closer to the threshold*.

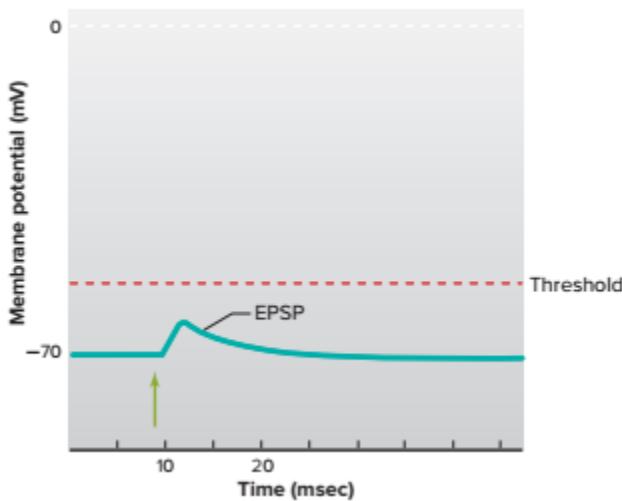


Figure 21: EPSP

Inhibitory change opens non selective channels to Cl^- and K^+ . You may remember from earlier that Cl^- equilibrium potential is more negative than the resting potential so Cl^- ions enter the cell which produces a hyperpolarization, a **inhibitory postsynaptic potential (IPSP)**. The main effect of this is to *bring the membrane potential of the postsynaptic neuron farther from the threshold (hyperpolarization)*.

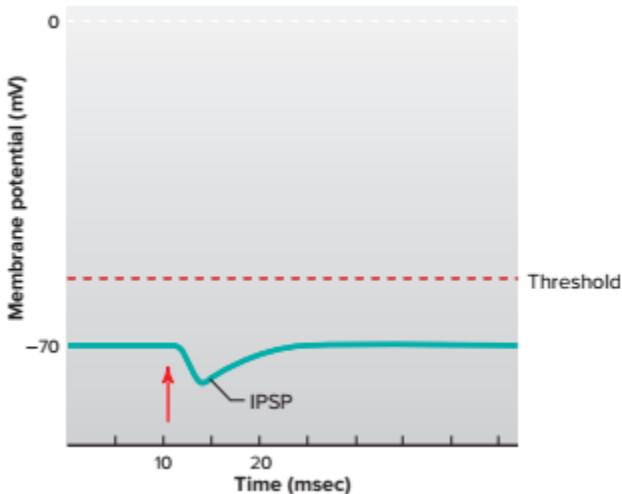


Figure 22: IPSP

3.3 EPSP-IPSP Interactions

There are certain interactions between EPSPs and IPSPs that work together to cause the depolarization of the postsynaptic membrane.

Summation: The addition of EPSPs and/or IPSPs at chemical synapses to cause change.

- **Temporal Summation:** A single EPSP or IPSP is not enough to generate a meaningful signal, so temporal summation is when the input signals arrive from the same presynaptic cell at different *times* at the same location.
- **Spatial summation:** When the input signals arrive at the same time (**multiple neurons**) but at different *locations* on the postsynaptic cells.
- **Cancelling:** EPSPs and IPSPs cause the opposite change in the postsynaptic cell so they end up canceling each other out due to no net change like in number 5 in the diagram below.

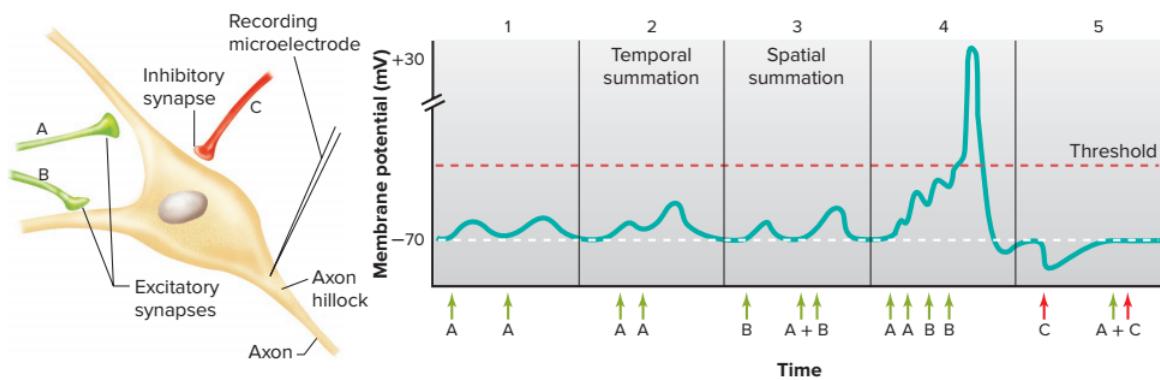


Figure 23: Summation at **Chemical synapses**. A and B - excitatory synapses, C - inhibitory synapse

3.4 Main Neurotransmitters

3.4.1 Acetylcholine

Acetylcholine (ACh) is a compound of acetic acid and *choline* (synthesized by *choline acetyltransferase*) that functions as a neurotransmitter which is vital in many functions such as **muscle stimulation, learning, and memory formation**.

Two main receptors for acetylcholine:

- **Nicotinic:** The nicotinic receptor for acetylcholine is a **ligand-gated ion channel** that produces an **EPSP**, which is then terminated by the enzyme **acetylcholinesterase** which hydrolyzes the neurotransmitter. This receptor functions at the **neuromuscular junctions** in vertebrates, the site where a neuron forms a synapse with a muscle cell.
- **Muscarinic** The muscarinic receptor for acetylcholine in vertebrates is a **GPCR** closely linked to the parasympathetic nervous system and is found at locations like the CNS and the heart. The G proteins inhibits the activation of **adenylyl cyclase**, which controls the formation of **cAMP** as well as opening potassium channels in the cell membrane of the muscle. This reduces the rate at which the heart pumps, making the affect of acetylcholine in cardiac muscle **inhibitory**.

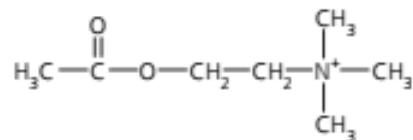
Acetylcholine

Figure 24: Acetylcholine

There are chemicals that have a huge effect on the nervous system which mimic or alter the effects of acetylcholine. Nicotine acts as a stimulant by binding to the nicotinic receptor for acetylcholine. The nerve gas called *sarin* blocks the cleavage of acetylcholine and inhibits **acetylcholinesterase (AChE)**, which causes continuous stimulation, and therefore contraction, of muscles.

3.4.2 Amino Acids

There are certain amino acids that act as neurotransmitters like **glutamate**. Glutamate (excitatory) serves as the main neurotransmitter for the neuromuscular junction rather than acetylcholine in invertebrates and has association with the formation of long-term memories as the most common neurotransmitter in the vertebrate CNS. They primarily act on various ionotropic receptors including **AMPA**, **NMDA**, and **kainate**. In addition, metabotropic glutamate receptors are inhibitory and are found in places like the eye. If present in excessive concentrations, glutamate (or any other excitatory amino acid like aspartate) can cause **neuronal excitotoxicity**, in which high levels of cellular Ca^{2+} cause cell death.

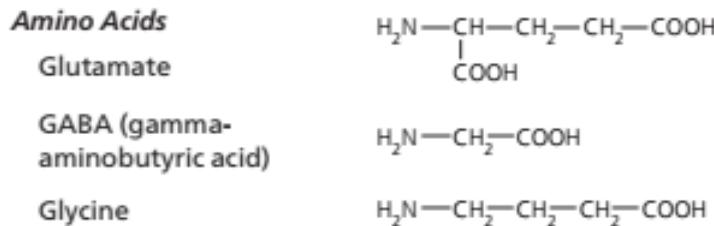


Figure 25: Amino Acids

- **Glycine:** Acts at inhibitory synapses at parts outside of the brain in the CNS like the spinal cord.
- **gamma-aminobutyric acid (GABA):**

- Acts as an inhibitory neurotransmitter within the brain by permeating Cl^- ions.
- Due to GABA's crucial role in inhibition, a loss of GABA can cause over-excitation and seizures.
- GABA is synthesized from glutamate by **glutamic acid decarboxylase (GAD)**.
- GABA is removed from the synapse by glial cells that have Na-dependent co-transporters for GABA called **GATs** (GABA Transporters)

3.4.3 Biogenic Amines

Biogenic amines form another class of neurotransmitters because these neurotransmitters are synthesized from amino acids.

- **Norepinephrine:** Norepinephrine is made from **tyrosine** (neurotransmitters made from tyrosine are known as **catecholamines**) and is an excitatory neurotransmitter that functions in a certain branch of the PNS called the autonomic nervous system (explained later). Catecholamines are degraded by **monoamine oxidase (MAO)** in the mitochondria and **catechol O-methyltransferase (COMT)** in the cytosol.
- **Epinephrine:** Functions in similar sympathetic roles to norepinephrine within the nervous system and also functions as a hormone outside of the nervous system (role in glycogenolysis pathway).
- **Dopamine:** Dopamine (also: 3-hydroxytyramine, 3-HT) is made from **tyrosine** as well and functions in the CNS. Its primary function is in the reward pathway, motor control, and prolactin inhibitory pathways (explained later) and functions in mood.
- **Serotonin:** Serotonin (also: 5-hydroxytryptamine, 5-HT) is made from **tryptophan** and also functions in the CNS. It has complex functions, including mood, digestion, and sleep, although the hormone **Melatonin**, a derivative of Serotonin (produced by acetylation and methylation), mainly regulates circadian rhythm. Serotonin is produced mainly in the intestinal mucosa, but also in the raphe nuclei in the brain stem where it functions as neurotransmitter, and in platelets

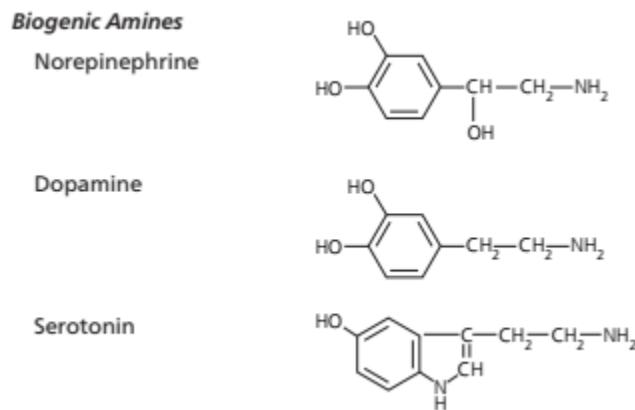


Figure 26: Biogenic Amines

3.4.4 Neuropeptides

Neuropeptides are short chains of amino acids that act as neurotransmitters which operate primarily through GPCRs. They are primarily produced by the cleavage of larger proteins and polypeptides.

- **Substance P:** An excitatory neurotransmitter that controls the perception of pain.

- **Endogenous Opioids:** Function as natural analgesics (painkillers) which decrease the perception of pain. Include **enkephalins**, **dynorphins**, and **endorphins**.

Endorphins are released in times of stress to mediate the pain as well as reducing the urine output and decreasing respiration. Opiates mimic endorphins and bind to the same receptors so they mimic most of the same functions of endorphins.

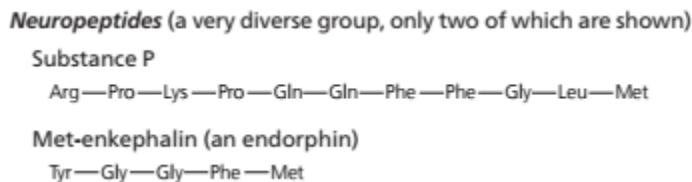


Figure 27: Neuropeptides

3.4.5 Gases

Dissolved gases are also used as neurotransmitters.

- **Nitric Oxide (NO):** NO is used primarily to relax blood vessels and muscles. One of its roles is in erectile function and dysfunction. NO isn't stored in vesicles but instead diffuses directly from the presynaptic to the postsynaptic neuron after made on demand. NO works like most hormones and stimulates an enzyme to activate a secondary messenger that directly affects the cell. Activates guanylyl cyclase to produce cGMP. Produced by nitric oxide synthase which produces NO as a byproduct of converting arginine to citrulline.
- **Carbon Monoxide (CO):** CO is produced in small amounts because it functions as a poison when inhaled. Its main function is to regulate the release of hormones from the hypothalamus in the brain.

3.4.6 Purines

Some modified nucleotides can also be used as neurotransmitters.

- **Adenosine:** Inhibits wakefulness, effects inhibited by caffeine
- **ATP**

4 Structure of the Nervous System

Yaya structure time fun!!!! This section will be going over the main structural aspects and divisions of the nervous system. All these divisions work together to perform the function of controlling us and the emergent properties of the nervous system as a whole.

4.1 Central Nervous System

The CNS is composed of the interneurons within the brain and the spinal cord. This section covers the structure of the CNS.

4.1.1 Brain

The brain can be divided into four main portions: the **forebrain**, **midbrain**, **hindbrain**, and **brainstem**.

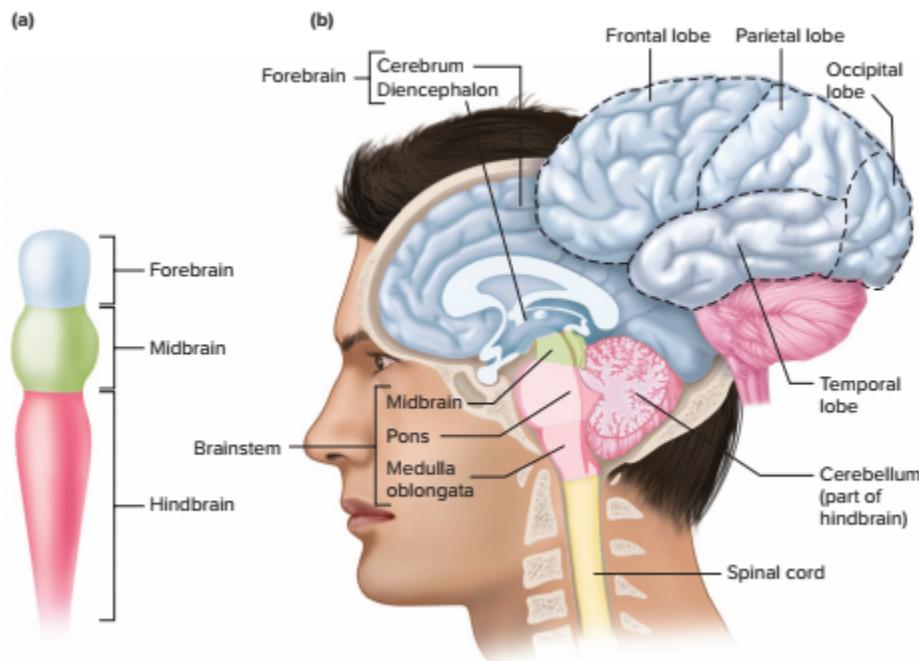


Figure 28: (a) Embryonic developmental structure of the brain (b) The divisions of the adult brain

Forebrain: Cerebrum

The **cerebrum** is made of two hemispheres, the left and the right called the **cerebral hemispheres**. The cerebral hemispheres each include the **cerebral cortex** which is an inner layer of **white matter** (myelinated axons) surrounded by an outer shell of **gray matter** (cell bodies). There are also cell clusters within the cortex with function to transport information called **subcortical nuclei**, and the hemispheres are connected as a whole by a bundle of axons called the **corpus callosum**.

The cerebral cortex is one of the most complex parts in the nervous system and regulates a lot of different signaling processes. It is divided into four main lobes:

Two main parts of the cerebral cortex are the **primary somatosensory** and **primary motor** cortices (plural for cortex). These regulate and transform sensory input into motor functions and therefore play a **HUGE** role in the brain.

In addition, **Broca's area** and **Wernicke's Area** are two commonly confused areas of the brain. Broca's area functions in speech production. Thus, someone with Broca's aphasia would be able to comprehend and form logical sentences but would not be able to speak them. However, those with Wernicke's aphasia would be able to speak but not comprehend words, forming a *word salad*, a series of words with no particular meaning like "chloroplast flagella boba homologous"

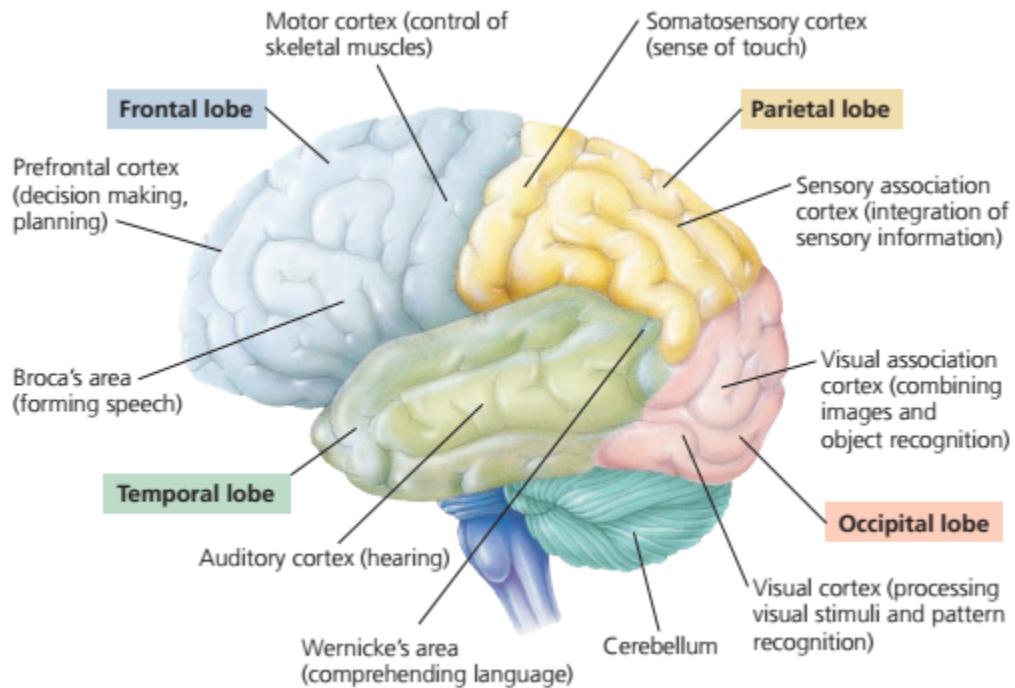


Figure 29: The four lobes of the cerebral cortex (Source: Campbells)

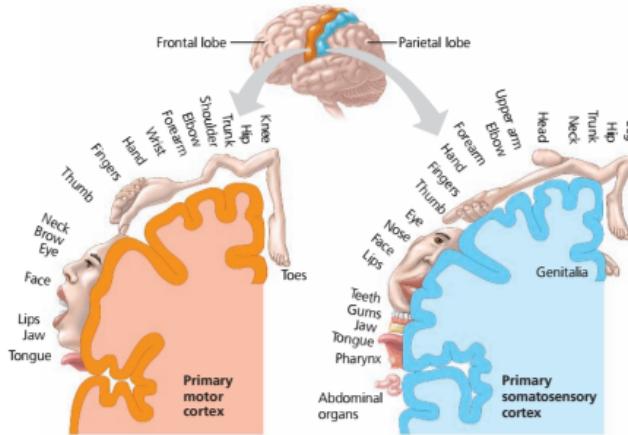


Figure 30: The parts of the brain that represent body parts in the somatosensory and motor cortices (Source: Campbells)

Limbic System

The limbic system is heavily associated with emotional regulation and behavior as well as learning and certain endocrine functions. It consists of many areas in the **forebrain** such as the thalamus, hypothalamus (explained later), portions of the frontal lobe, and portions of the temporal lobe. These sections regulate each other and other parts within the CNS.

Subcortical structures:

- The **basal nuclei** (also known as **basal ganglia**) are subcortical nuclei beneath the cerebral cortex which are groups of gray matter that lie deep within the brain. They have a

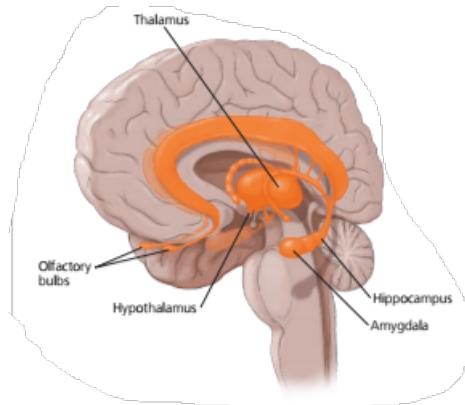


Figure 31: Limbic System

huge effect on functional movement, posture, and other aspects of behavior such as vision. The basal nuclei contain the **substantia nigra** which famously uses dopamine to signal. A nonfunctional substantia nigra and low levels of dopamine are often implicated in Parkinson's disease, characterized by tremors (from one of dopamine's other functions, which is to regulate movement).

- The **circadian cycle** is your body's internal **biological clock** which directs your biological cycles and cues. Its full cycle is about **24.2 hours**. Circadian rhythms in mammals are coordinated by a certain structure within the hypothalamus called the **suprachiasmatic nucleus (SCN)**. In response to the sensory information involving things like light from the eyes, the SCN synchronizes the biological clock to the natural cycles and day length of the world. There will be much more about sleep and consciousness later.
- The **amygdala** is a component of the limbic system which functions mainly in the storage and recall of **emotional memories**. What are emotional memories? They are memories that have an emotional significance added to them that affects future experience and associates something called **autonomic arousal** with these. Autonomic arousal is something that occurs in response to something beyond your control, like sweating when seeing something that ignites a hidden fear.
- The diencephalon is a name for a certain division in the embryo (can read about later, not too relevant right now) which contains the **thalamus**, **hypothalamus**, **epithalamus**, and **hippocampus**.
 - **Thalamus:** The thalamus has a key function in general arousal (more later) and focusing/extending/filtering out excessive extraneous sensory information. Functionally, the thalamus serves as synaptic relay station and is an "integrating center" for inputs to the cortex. Olfaction is the only sense that bypasses the thalamus.
 - **Hypothalamus:** The hypothalamus lies below the thalamus that functions as the "command center" for coordination for neural and **endocrine** systems. The hypothalamus is like the master center for homeostatic regulation and has to do with many behaviors like eating, drinking, and reproduction. The hypothalamus is connected (and

controls) to the **pituitary gland** which has major functions in hormone release and the endocrine system.

- **Epithalamus:** The epithalamus is a small mass of tissues present in the brain which produces cerebrospinal fluid and regulates the **pineal gland** which has important functions in **melatonin release** and circadian rhythms with the SCN (more on this later).

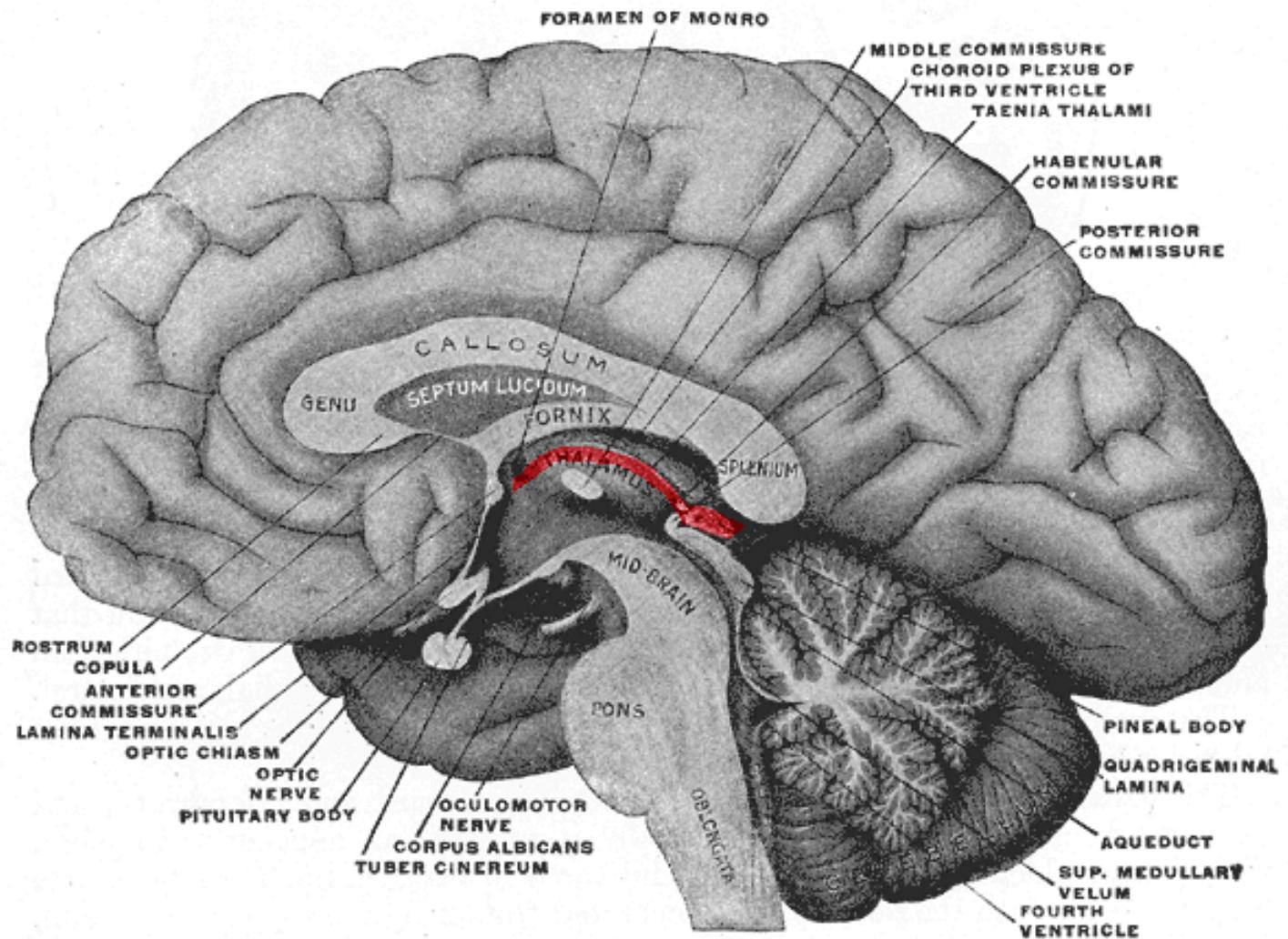


Figure 32: Diencephalon stuff (contains stuff you don't need to know, just there for visual)
WIKIPEDIA

Hindbrain: Cerebellum

The **cerebellum** consists of deeper cell clusters surrounded by an outer layer called the **cerebellar cortex**. The cerebellum plays a huge role in movement, and although it doesn't control voluntary movement, it maintains things like posture and balance and coordinates movements. The cerebellum does this by receiving **sensory input** from multiple different locations. It is also used almost exclusively for motor control, though it has recently been found to have some role in learning.

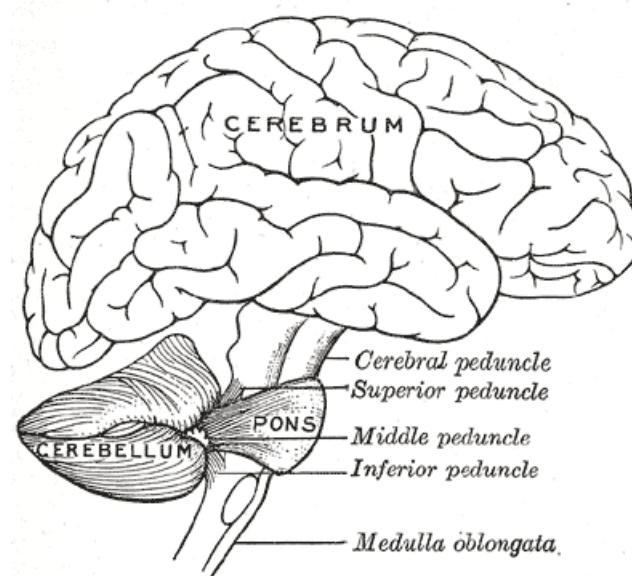


Figure 33: The Cerebellum, latin for little brain

Reticular Formation

The **reticular formation** is one of the most essential parts of the brain that functions mostly in filtering sensory input and sending the filtered input throughout the brain. This is one of the most essential formations and humans **need** this to survive. In addition, the reticular formation includes the **RAS**, or reticular activating system, which regulates arousal and consciousness. Thus, a nonfunctional RAS can lead to narcolepsy, or the tendency to fall asleep suddenly during the day.

4.1.2 Spinal Cord

In this section, we will cover the structural aspects of the spinal cord, the other component of the CNS. The spinal cord is within the vertebral column (bones) so it is protected. It is basically a cylinder of soft tissue.

The **spine** is made up of many bones called **vertebrae** stacked on top of each other. Throughout a human's development, the number of vertebrae in the spine vary from 33 to 24-26. As a human develops into an adult, some of the bottom vertebrae in the initial 33 fuse together to end up having 24-26 vertebrae in total.

- The central gray area in the picture of the cross section is composed of the **gray matter** composed of all three types of neurons as well as glial cells. The parts of the gray matter

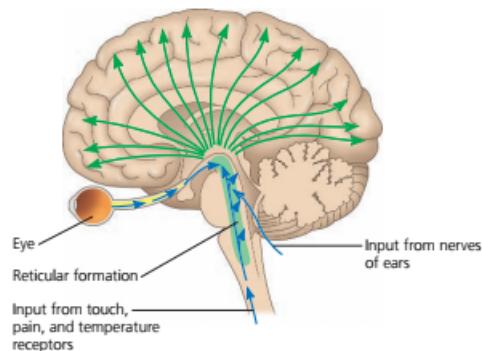


Figure 34: The Reticular Formation

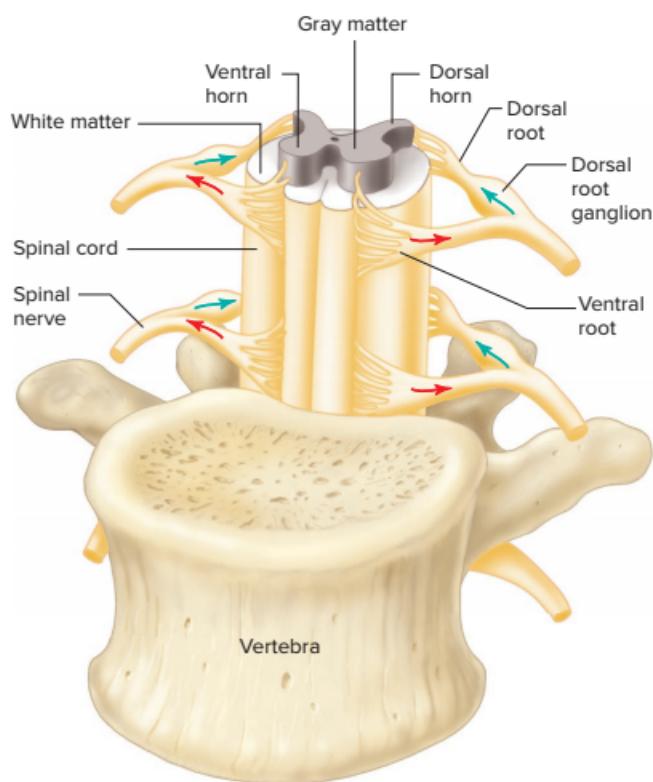


Figure 35: A vertebra (plural: vertebrae)

that stick out toward the back are called **dorsal horns** and the parts that stick out to the front are called **ventral horns**.

- The white matter surrounding the gray matter and the projections that stick out consist of myelinated axons that serve to receive or transmit information to the brain.
- The **afferent neurons** that enter the spinal cord enter on the dorsal side through places called the **dorsal roots**. The bumps on the dorsal roots consist of the cell bodies of these neurons, called **dorsal root ganglia**.

- the **efferent neurons** that enter the spinal cord enter on the ventral side through different places called the **ventral roots**. The ventral roots *do not* have ganglion because they are efferent neurons whose cell bodies are all located in the ventral horn.
- Farther away from the spinal cord, the ventral and dorsal roots combine to form the **sensory nerve** on either side of the spinal cord, transmitting and receiving information.

The spinal cord serves as a huge point for receiving and transmitting information in the CNS and it is heavily protected from damage or anything through the bones of the spine which also provide essential structural support.

4.2 Peripheral Nervous System

The **peripheral nervous system** is the second major division of the nervous system. The neurons in the PNS serve as a gateway for reception and effectors in all the parts of the body and mode of transmission. The PNS consists of 43 pairs (afferent + efferent) of nerves (axons in a bundle) which are 12 pairs of cranial nerves and 31 pairs of spinal nerves.

Spinal Nerves:

- **Cervical:** 8 pairs, connect the neck, shoulders, arms and hands.
- **Thoracic:** 12 pairs, chest and upper abdomen
- **Lumbar:** 5 pairs, lower abdomen, hips, and legs
- **Sacral:** 5 pairs, genitals and lower digestive tract
- **Coccygeal:** 1 pair, skin over the region of the tailbone

Cranial Nerves: (most in PNS some in CNS)

1. **Olfactory:** *Afferent*: gets input from olfactory sensors (nose). More about sensory physio is explained later
2. **Optic:** *Afferent*: gets input from ocular sensors (eyes).
3. **Oculomotor:** *Afferent*: gets information from muscle receptors (eyes, etc.). *Efferent*: Controls main functions in the eye; movement (*vertically*), pupil dilation, eyelid, etc.
4. **Trochlear:** *Afferent*: gets information from muscle receptors (eyes, etc.). *Efferent*: controls horizontal (lateral) and downward movement in the eye.
5. **Trigeminal:** *Afferent*: gets information specifically from receptors in the skin, face muscles, mouth, nose, etc. *Efferent*: controls the muscles used in chewing.
6. **Abducens:** *Afferent*: gets information involving hearing and balance from muscles. *Efferent*: also controls lateral movement in the eye
7. **Facial:** *Afferent*: gets information from taste buds (sensors) in the front of the tongue and the mouth *Efferent*: controls muscles involved in facial expression and swallowing

8. **Vestibulocochlear:** *Afferent:* gets information involving hearing and balance from the inner ear
9. **Glossopharyngeal:** *Afferent:* gets information from taste buds at the back of the tongue and transmits information from baroreceptors (blood pressure) in the carotid arteries. *Efferent:* controls muscles involved in swallowing and the parotid salivary glands
10. **Vagus:** *Afferent:* gets info from receptors in the abdomen and thorax *Efferent:* connects to the muscles of the pharynx, larynx, thorax, and abdomen
11. **Accessory:** *Efferent:* connects to the muscles in the neck (trapezius)
12. **Hypoglossal:** *Efferent:* connects to the muscles of the tongue

The structure of a nerve is organized in a hierarchical manner, with multiple layers of protective tissue surrounding its functional units. At the most basic level, each individual axon is myelinated by Schwann cells (*Recall:* Schwann cells myelinate the PNS while Oligodendrocytes Myelinate the CNS) and enveloped by a layer called the **endoneurium**. Several of these units are contained within another layer known as the **perineurium** which groups them into “**fascicles**”. These fascicles, along with connective tissue and **vasa nervosum** (nerve blood vessels) are covered by the **epineurium**, and this makes the whole nerve.

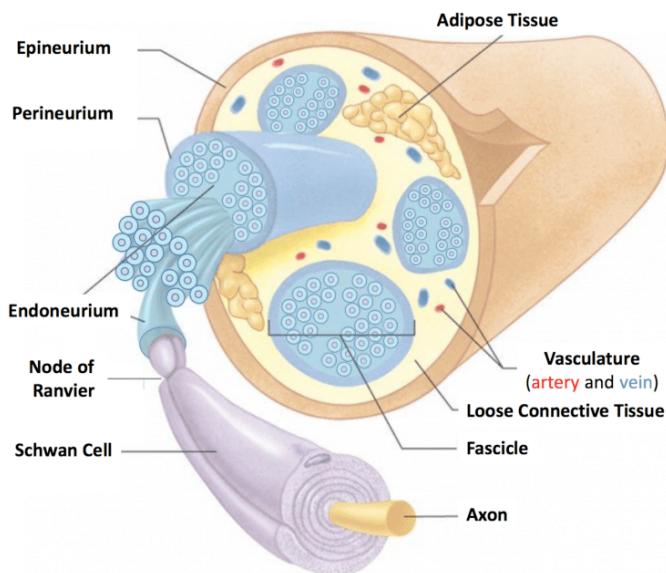


Figure 36: Nerve Structure (Source: C. Kuliasha)

The different peripheral nerves contain axons belonging to the **afferent** and **efferent** divisions of the nervous system. The spinal nerves contain both types while some of the cranial nerves contain only afferent or efferent fibers (ex: optic nerve only has afferent fibers).

Afferent neurons bring information into the CNS so their endings are located within the CNS while the long part (majority) of their axon is in the PNS. On the flip side, efferent neurons bring information out of the CNS to muscles, also having their ending in the CNS but being more

complicated than the afferent division. This is further divided into the **somatic** and **autonomic nervous systems**.

4.2.1 Somatic Nervous System

Unlike the autonomic nervous system, the somatic nervous system connects skeletal muscle. The efferent neurons of the somatic nervous system use and release acetylcholine as the main neurotransmitter. The activity of the neurons therefore leads to the *contraction* of muscle cells so the neurons are called **motor neurons**. The inhibition of the motor neurons in the spinal cord causes muscle relaxation while the stimulation causes muscles to contract.

You can think of the somatic nervous system to be “controllable” by your own thoughts and stimulation.

4.2.2 Autonomic Nervous System

The autonomic nervous system connects smooth, cardiac, and other types of muscle other than skeletal muscle. The autonomic nervous system is made up of two main neurons connection to the **effector cells** and the **CNS**. The first neuron has the cell body in the CNS and the synapse between the two is outside the CNS in a cluster named the **autonomic ganglion**. The neurons connected to the CNS are called the **preganglionic neurons** while the ones that connect to the effector cells are called the **postganglionic neurons**. (Notice the use of the prefixes pre- and post-)

The autonomic nervous system has another “sub-division” called the **enteric nervous system**. The enteric nervous system **innervates** (runs nerves through and controls) the walls of the **gastrointestinal tract**. It also includes sensory and interneurons.

The major divisions of the autonomic nervous system are:

- The **sympathetic** division can be remembered as the “fight or flight” division. It acts through adrenergic receptors binding to epinephrine and norepinephrine. For example, inhibition of intestinal smooth muscle, increase in heart contractility, and dilation of pupils are all reactions mediated by the sympathetic nervous system. Some USABO questions will ask about whether something is mediated by the sympathetic versus the parasympathetic. You can go by vibes here—if it’s something that would happen while you’re running from a bear or talking to a crush, it is sympathetic. This division differs mainly from its counterpart on the location of its ganglia. Two main areas of the location of the sympathetic nervous system lie close to the spinal cord and form the **sympathetic trunks**, two long chains of ganglia (also known as the paravertebral ganglia).
- The **parasympathetic** division can be remembered as the “rest or digest” division. It’s mediated by muscarinic acetylcholine receptors and generally does the opposite of the sympathetic nervous system (with some exceptions, of course). It promotes gut motility, constricts the pupils, and stimulates urination. The neurons of the parasympathetic nervous system leave mostly from the brain cell, different from the sympathetic division.

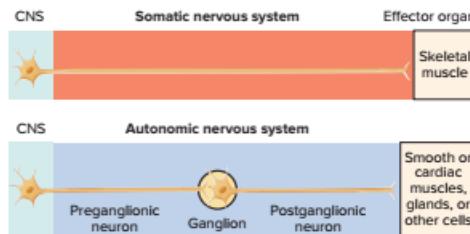


Figure 37: Neurons in the somatic and autonomic nervous systems

4.3 Protective Stuff with the Brain

It is *bad* if your brain is damaged (especially because neurons in the CNS take a long time to regenerate, if they regenerate at all (only in the dentate gyrus of the hippocampus and the olfactory bulb)). Therefore, your brain needs strong protection.

The skull is made of bone and consists of multiple fused plates that form a suture joint and function for mechanical protection. Notably, the occipital, frontal, sphenoid (base of the cranium, behind the eye sockets, and extends laterally), ethmoid (roof of nasal cavity), parietal, and temporal bones.

The **meninges** are protective tissue layers surrounding the CNS. There are three layers of meninges, from innermost to outermost: the pia mater, arachnoid mater, and dura mater. The pia mater (“tender mother” in Latin) is a delicate inner meninge. The middle layer is the arachnoid mater (“spider mother”), characterized by an appearance likened to a spiderweb, and also contained cerebrospinal fluid (which absorbs shock). The outermost layer, dura mater (“hard mother”), is a thick layer of dense connective tissue that protects the brain.

In addition to the arachnoid layer, cerebrospinal fluid (CSF) is primarily circulated in the **ventricular system**. Ventricles are chambers in the brain that produce and circulate the CSF. CSF is produced by ependymal cells located on the **choroid plexus** (found in ventricles) and the central canal of the spinal cord and is reabsorbed by **arachnoid granulations**. Failure to be reabsorbed can cause hydrocephalus. CSF functions to cushion and support the brain as well as acting a diffusion mechanism. Below is a diagram of the ventricles and their locations in the brain:

Another huge part of protection to the brain is the **blood brain barrier (BBB)**. The blood brain barrier is a highly-selective barrier of endothelial cells, astrocytes, and pericytes around the brain that both protect the brain from physical events as well as acting as the brain’s immune regulator. See, the high selectivity of the BBB prevents impurities and dangerous agents from the body to the brain like macrophages (which apoptosis inducing factor due to inflammation is incredibly problematic for the brain’s neurons). There are many more examples of the BBB in act, but it basically provides a massive amount of protection to the brain.

However, the BBB can be quite problematic. Because of its high selectivity, the only drugs that can enter the brain must be in the form of nanoparticles. This prevents the application of traditional anti-inflammatory drugs to the brain at sites of neuroinflammation. A well known example is dopamine for Parkinson’s treatment. Because dopamine is unable to cross the BBB, patients are given L-dopa, a precursor to dopamine that can cross the BBB.

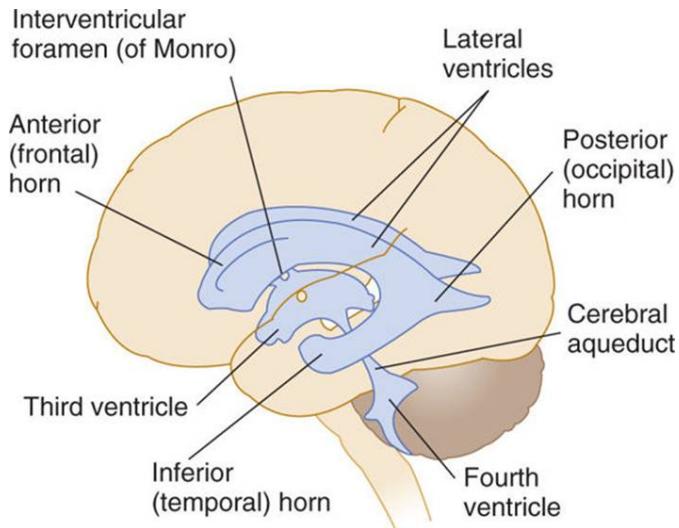


Figure 38: Ventricular System Diagram (Source: doctorlib.info)

4.4 Spinal Tracts

As mentioned previously, the spinal cord acts as a messenger to the brain and transmits signals to and from the PNS. We can subdivide this communication network into smaller components referred to as **spinal tracts**. These tracts are specialized pathways that relay different types of information between the brain and various parts of the body. Each spinal tract is responsible for either sensory input (ascending tracts) or motor output (descending tracts).

Here is an overview for four major spinal tracts:

- The **dorsal column-medial lemniscus (DCML)** pathway is an *ascending* sensory pathway in the central nervous system, responsible for transmitting fine touch, vibrations, and proprioception information from the body to the brain.
- The **corticospinal tract (CST)** is a major *descending* motor pathway in the central nervous system, responsible for voluntary movement control. It consists of several tracts, including the lateral CST (controlling limb movements) and the anterior CST (controlling axial movements). The CST originates in the motor cortex and as it approaches the spinal cord, approximately 90% of fibers cross over to form the lateral CST, while the remaining 10% continue ipsilaterally as the anterior CST. These fibers ultimately synapse in the anterior horn of the spinal cord and exit through spinal motor neurons.
- The **spinothalamic tract** is an *ascending* sensory pathway that transmits non-discriminative touch (crude touch), temperature, and pain sensations.
- The **spinocerebellar tract** is an *ascending* sensory pathway that transmits proprioceptive information to the cerebellum.

4.5 Reflexes

Reflexes are instantaneous, involuntary, unplanned reactions to various stimuli. The pathways that regulate these reflexes are known as **reflex arcs**. Reflex arcs can be classified by complexity based on the number of synapses required. Those that require only 1 synapse are referred to as **monosynaptic**, and those that have several are referred to as **polysynaptic**. Reflex arcs can also be classified based on their effector organ into **somatic reflexes** (muscles) and **autonomic reflexes** (internal organs). While somatic reflexes travel *directly* from the spinal cord to the effector, autonomic reflex arcs synapse at a ganglion *before* reaching the effector.

- Somatic Reflexes

- Spinal Reflex Examples:

- * **Stretch (Myotatic) Reflex:** When a muscle is stretched, muscle spindles send signals causing the muscle to contract
 - * **Tendon Reflex:** To protect against excessive muscle tension, golgi tendon organs causes the inhibition of muscle. This also helps to protect isolated muscle fibers. Basically the opposite of the stretch reflex so it is also commonly referred to as the inverse myotatic reflex. The difference between the two is that the tendon reflex is *intrinsically* induced.
 - * **Withdrawal Reflex:** withdrawal of limbs in response to harmful stimuli
 - * **Crossed Extensor Reflex:** Contraction of the muscle on the contralateral (opposite) side to stabilize the body during a withdrawl response
 - * **Patellar Reflex:** Stretch reflex of the patellar tendon that causes quadricep contraction. Tests L2-4 spinal cord segments.

- Cranial Reflex Examples:

- * **Blink Reflex**
 - * **Gag Reflex**

- Autonomic Reflexes

- **Baroreceptor reflex:** baroreceptors located in the carotid sinus (at branch points of common arteries) and the aortic arch trigger actions to maintain the proper blood pressure. In cases of extreme blood pressure dips, it could induce fainting.
 - **Pupillary Light Reflex:** the size of the pupil changes in response to how much light is present in the environment. When it is extremely bright, the pupil constricts to reduce the amount of light entering. The opposite happens when the environment is dim.

5 Sensory Physiology

Our perceptions of the environment around us is all mediated through various sensory receptors which synapse into our brain to create the images we see, the scents we smell, the sounds we hear and so on.

5.1 Sensory Receptors

Sensory receptors are often dendrite endings of neurons encapsulated within non neuronal structures such as connective tissue, sometimes sensory receptors are even specialized neurons such as photoreceptors found in the retina. Here are a few examples and many more will be covered in detail throughout this handout and in previous handouts.

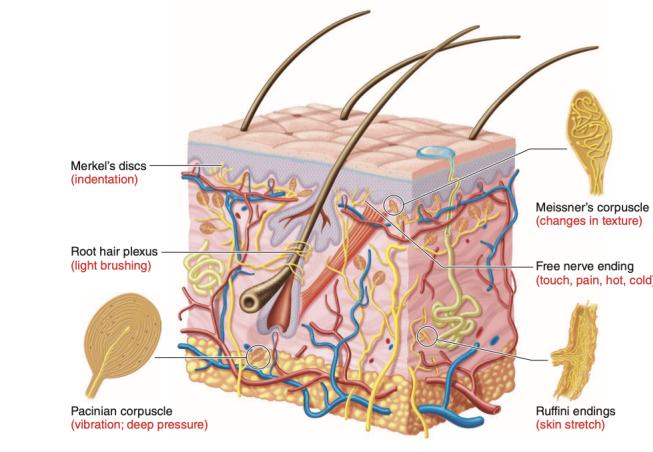
- Baroreceptors - Sense blood pressure
- Chemoreceptors - Sense chemical stimuli, e.g. blood oxygen levels.
- Nociceptors - Sense pain such as high heat, acid and chemicals such as prostaglandins and ATP.
 - Perception of pain can be modulated by an individual's emotions, analgesia, for example, is mediated through endogenous opioids which reduce perception of pain.
 - Split into 2 categories: fast, myelinated A-Delta fibers and slow, unmyelinated C fibers
- Thermoreceptors - Sense heat or cold
- Mechanoreceptors - Respond to mechanical deformation.
- Proprioreceptors - found in the muscles and joints and provide control over skeletal movements and a sense of body position.
- Special Senses - will be discussed in detail in this handout, taste, sight, hearing, equilibrium and smell.
- Cutaneous Receptors - Described in this next section.

5.1.1 Cutaneous Receptors

Cutaneous sensations are sensations that include touch, pain, heat, pressure, etc. There are two types of receptors: tonic and phasic. **Tonic receptors** are slowly adapting—like kids that continuously scream in your ear and taper off as the stimulus disappears. **Phasic receptors** are like door monitors, only letting you know when someone is coming or leaving. Often, phasic receptors are in corpuscles, which "mutes" the "noise" of the stimulus while tonic receptors are more often free nerve endings.

- A type 1 mechanoreceptor (aka **Merkel disc**) detects sustained, gentle touch and is a tonic receptor (as a free nerve ending).
- A type 2 mechanoreceptor (aka **Ruffini corpuscle**) is phasic and detects the stretching of skin, deep tension, and some proprioception (especially at joints).
- A **Pacinian corpuscle** detects fast vibration
- A **Meissner corpuscle** detects slow vibration and fine touch, and is depolarized through mechanical deformation.
- **Krause's corpuscles** sense touch and are particularly involved in sexual stimulation

- A nerve ending senses touch, temperature, and pain



5.1.2 Olfactory receptors

During olfaction, aptly named olfactory receptor neurons surrounded by supporting cells (that detoxify potentially harmful odorants). Stimulation of $\text{Na}^+/\text{Ca}^{2+}$ channels by cAMP (from a G protein) depolarizes the receptors and leads to transmission of the signal.

5.1.3 Photoreceptors

Photoreceptors are specialized, light-sensitive neurons that are responsible for converting light into action potentials through a process known as **phototransduction**. There are 2 primary photoreceptors—**rods** and **cones**—and they differ in their **opsin**. Opsins are G protein-coupled receptors that are bound to **11-cis-retinal** (a vitamin A derivative and light sensitive molecule). Rods contain **rhodopsin** (scotopsin when unbound), while cones have **iodopsin** (photopsin when unbound).

As mentioned previously, phototransduction is signal transduction for visual information. When there is no light present, **cGMP** activates *ligand-gated* ion channels on the membranes of rods and cones are open and allow the influx of Na^+ and Ca^{2+} and the subsequent release of glutamate into the synapse. This is why photoreceptor neurons are the only neurons that are *continuously depolarized*. When light hits the photoreceptor, the following occur:

1. A photon hits **11-cis-retinal** which converts it to **all-trans-retinal**.
2. **Transducin** is activated
3. Transducin activates **cGMP phosphodiesterase (PDE)**
4. PDE converts cGMP into **GMP**
5. Ligand-gated ion channels close due to lack of cGMP
6. Cell becomes hyperpolarized

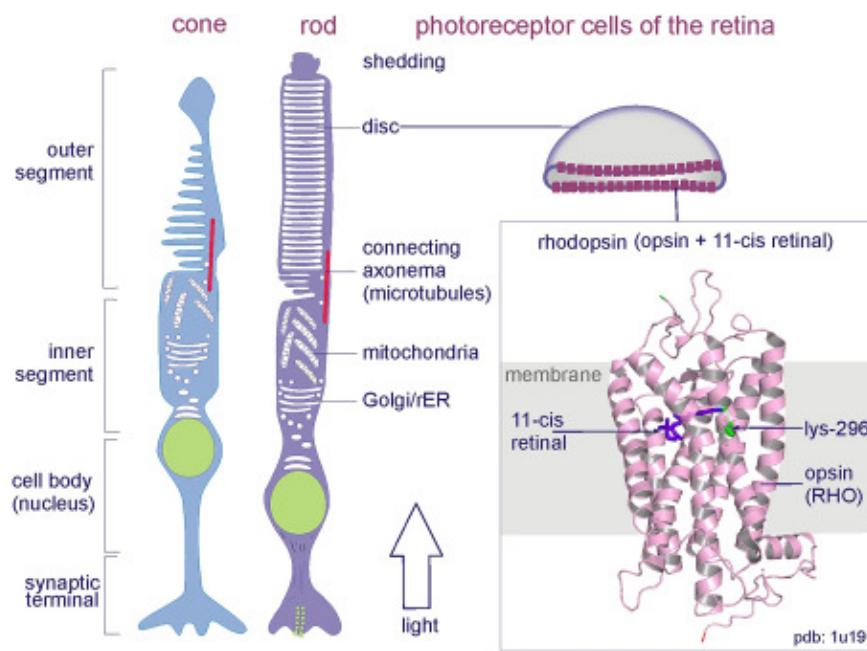


Figure 39: Rod and Cone Structure (Source: *Signal Transduction 3E*)

7. Glutamate release stops

Also: While all-trans-retinal is being converted back into 11-cis-retinal, **arrestin** holds transducin in place so it can't be activated

Details on how this plays into vision will be explained in section 5.4

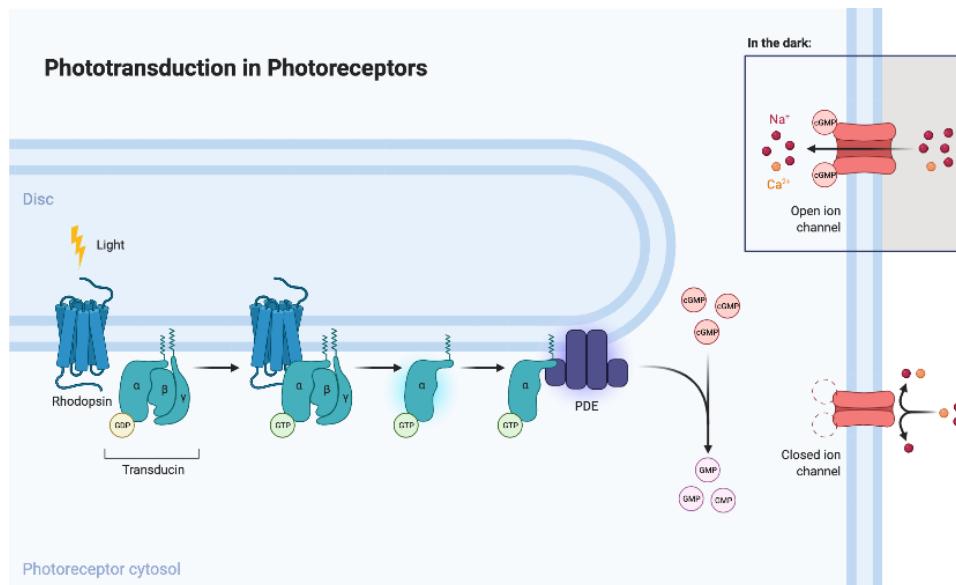


Figure 40: Phototransduction (Source: *Biorender.com*)

5.1.4 Proprioceptors

Proprioception is the sense of body position and movement, and there are 2 main types of proprioceptors: **muscle spindles** and **golgi tendon organs**.

- **Muscle Spindles:** Spiral shaped stretch receptors located within skeletal muscles that sense the length of the muscle. When the muscle is at rest, the muscle spindle is taut so it can feel the muscle getting longer. When the muscle containing the muscle spindle is contracted, the muscle spindle is no longer taut and would not be able to sense stretch very effectively. To correct this, gamma motor neurons (aka fusimotor neurons) are activated to adjust the sensitivity of the muscle spindle to make it taut again. Associated with type Ia sensory nerve fibers.
- **Golgi Tendon Organs:** Proprioceptors located between tendons and muscle fibers that senses the tension in a muscle. The body of a golgi tendon organ is made up of braided strands of collagen. Associated with type Ib sensory nerve fibers.

5.2 Vision

The visual processing pathway starts with our eyes.

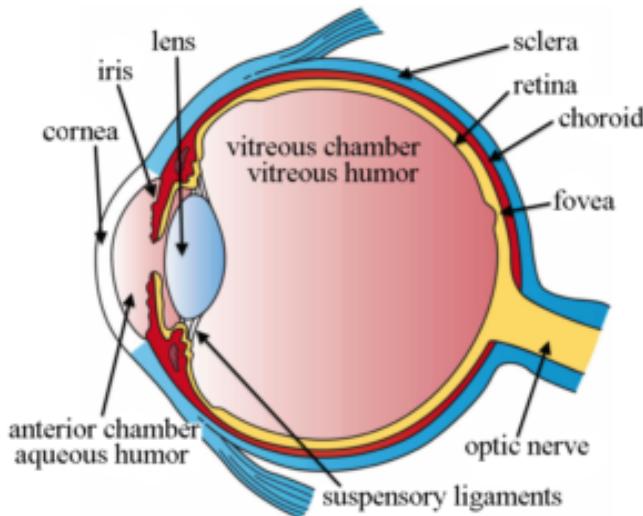


Figure 41: Eye Anatomy (Source: Harvard Eye Associates)

As light enters, it first passes through the **cornea**, a protective covering that also helps focus the light. Next comes the **aqueous humor**, a liquid produced by the **ciliary body** (the muscle that controls the lens) that helps focus the light further as well as supporting the structure of the eye by maintaining intraocular pressure. A build up of humors in the eye increases intraocular pressure which can damage the retina and cause **glaucoma**. After this comes the most important structure in focusing light, the lens. The **lens** is a flexible ellipsoid containing **crystallins** (clear structural protein) that can be shaped by the ciliary body to adjust focal distance. As we age, crystallins can accumulate and break down causing a visual obstruction you might know as a

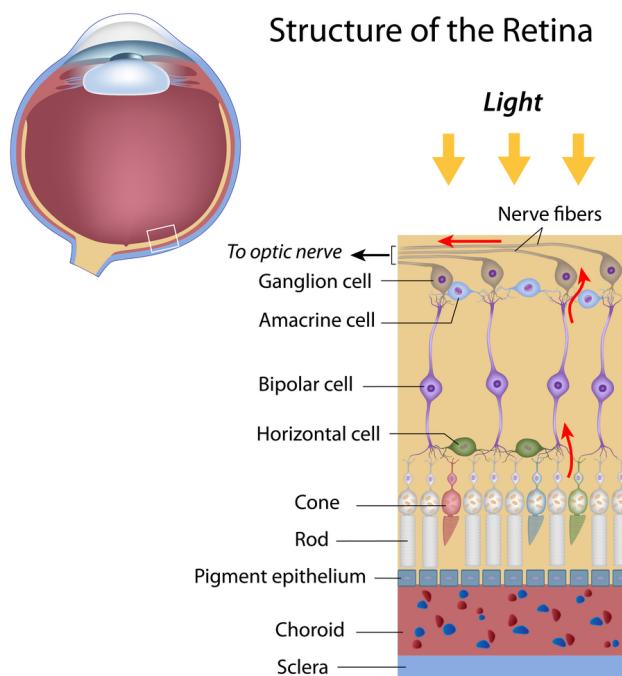


Figure 42: Retinal Cells (Source: discoveryeye.org)

cataract. The last layer light goes through before reaching the retina is the **vitreous humor** which functions similarly to the aqueous humor.

The **retina** is composed of layers of glial cells and photoreceptors that line the back wall of the eye. Since the photoreceptors make up the outer-most layer of the retina, light passes through all of the glial cells before reaching them. To aid this process, the retina contains special glial cells known as **Müller cells** that act as mini fiber optic cables to channel light directly to the photoreceptors. In addition to this, Müller cells also provide metabolic support and mediate neurotransmitter degradation.

The different kinds of photoreceptors aren't spread evenly across the retina. Instead, red and green cones are concentrated in a region called the **fovea** (looks like an indentation of the retina) and no rods or blue cones are present here. This is the part of the eye with the highest visual acuity. The fovea is contained in a slightly larger region known as the macula. The **macula** is the center portion of your retina and provides high visual acuity and is the center of your field of vision. As you radiate out from the fovea, the number of cones decreases and the number of rods increases.

After phototransduction, the signal needs to be transmitted to the occipital lobe for processing. From the photoreceptors, the next stop is the bipolar cells. There are 2 different kinds of bipolar cells, those of the ON Pathway and those of the OFF Pathway. Bipolar cells of the **ON pathway** are depolarized and send signals in the absence of input while **OFF pathway** bipolar cells are hyperpolarized in the absence of input. Recall that photoreceptor cells are inverted in the sense that they are hyperpolarized in the absence of light, make sure to account for this when analyzing ON/OFF Pathway bipolar cells. **Ganglion cells** then take input from one or more bipolar cells. The portion of your field of vision that a single ganglion cell controls is known as the receptive field. If the center of a receptive field is lit, the ganglion cell will be excited. On the other hand,

if the rim of the receptive field is lit, the ganglion cell will be inactive. If the whole receptive field is lit, the ganglion cell will be slightly active. When a rod or cone is illuminated, it inhibits other distant non-illuminated photoreceptors and bipolar cells. This phenomenon is known as **lateral inhibition** and it increases visual contrast to increase detail perception. **Horizontal cells** and **Amacrine cells**, also found in the retina, carry out **convergence** which is where signals from several bipolar cells can be fed in and turned into one signal. Covering the retina, we have 3 layers: the outer fibrous sclera, middle vascular choroid, and pigmented epithelium (dark color absorbs stray light that makes it past the photoreceptors). The axons of all these bipolar cells converge at the **optic disc** (forms a blind spot) and turn into the optic nerve (Cranial Nerve 1).

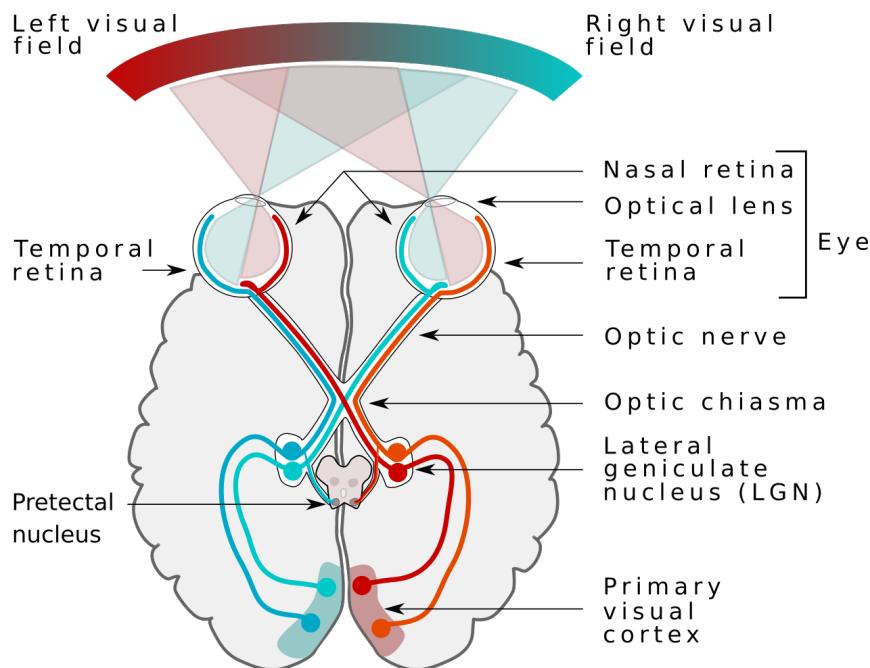
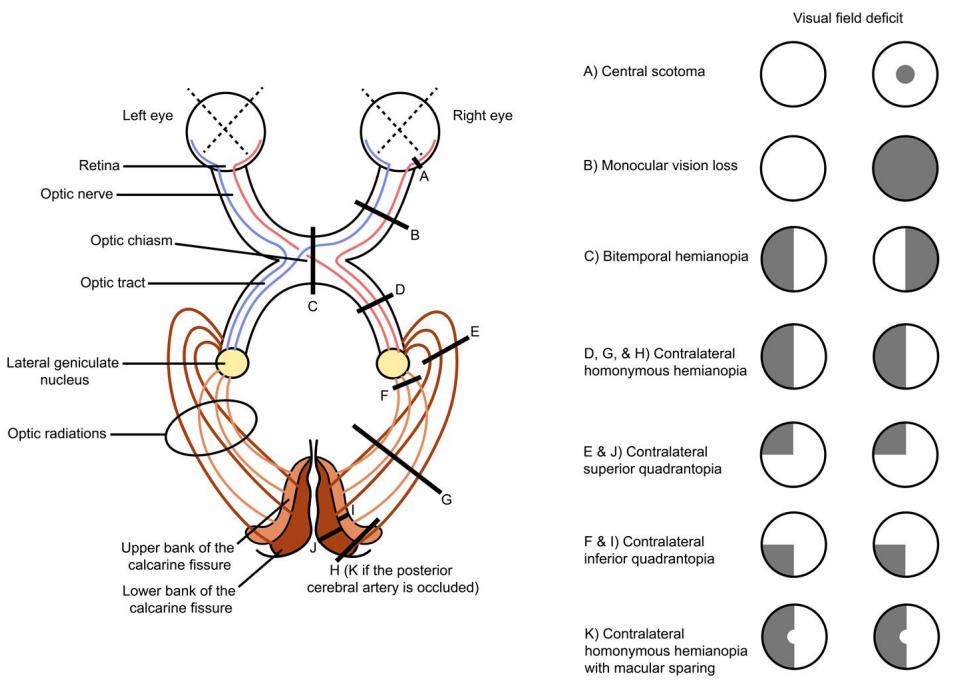


Figure 43: Visual Pathway (Source: Wikipedia)

The nasal retinas of the optic nerve converge and swap sides at the optic chiasm and join the opposite optic nerve and turn into the optic tracts. This flip makes it so that the information past the **optic chiasm** is segmented into left/right visual fields instead of left/right eye. The optic tract then synapses at the **lateral geniculate nucleus (LGN)** where shape, color, and movement are processed. And lastly, the information reaches the **primary visual cortex** of the occipital lobe through the **optic radiations** where edges are extracted and the visual information is integrated with the other senses. In addition, the processed information is further divided into two streams for higher-level processing. The ventral ("What") stream, involving neurons in the temporal lobe, specializes in object recognition and the processing of unconscious visual information. Meanwhile, the dorsal ("Where") stream, located in the parietal lobe, is responsible for detecting spatial locations of objects, combining spatial relationships, motion, and timing to create action plans without requiring conscious thought.

When a part of this intricate network disconnects, you get blindness. The exact form of blindness depends on the specific location of the lesion:

Visual Field Defects



© Lineage

Moises Dominguez

5.3 Audition

Audition, or hearing, is the signal transduction and interpretation of sound waves for language, reflexes, and more. As sound waves approach your ear drum, they first have to pass through the outer ear. Also known as the **auricle** or **pinna**, the **outer ear** is a cartilaginous structure responsible for funneling sound waves inwards. From here, the waves reach the **tympanic membrane**—the barrier between the outer ear and the middle ear. The tympanic membrane is a thin, flexible membrane that transmits the vibrations into the middle ear. In the middle ear, 3 small bones (malleus, incus, stapes *or* hammer, anvil, stirrup) known as the auditory **ossicles** amplify the waves and transfer them to the inner ear by vibrating the oval window—the entrance of the **cochlea**.

The cochlea is a spiral shaped organ that sound waves enter through the oval window, travel through the **vestibular canal** (scala vestibuli), around the apex, through the tympanic canal, and then out the round window. The middle of the cochlea, also known as the **cochlear duct**, houses the centerpiece of audition: the **organ of corti**.

The organ of corti contains **hair cells** that are attached to the **basilar membrane**. Vibrations of the **perilymph** (fluid of the cochlea) vibrate the **tectorial membrane** located above the hair cells causing it come in contact with the hair cell's stereocilia. This contact causes mechanical deformation of receptors that allow for the depolarization of the hair cells and subsequent signal propagation. The axons of these hair cells aggregate into cranial nerve VIII or the **vestibulo-cochlear nerve** which transports the signal to the thalamus which in turn filters and relays it to the **primary auditory cortex** of the temporal lobe.

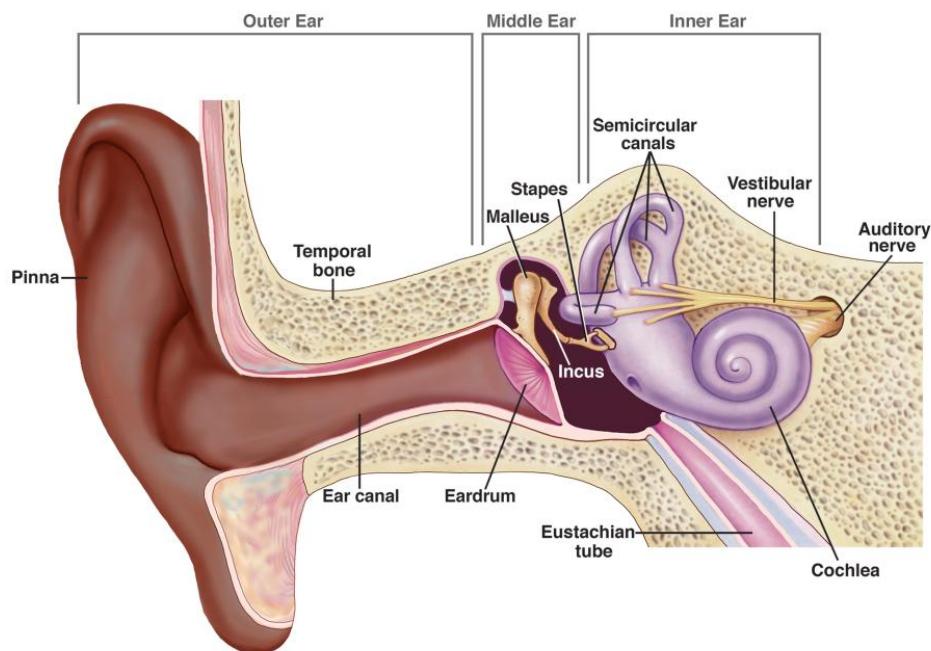


Figure 44: Ear Anatomy (Source: NIH)

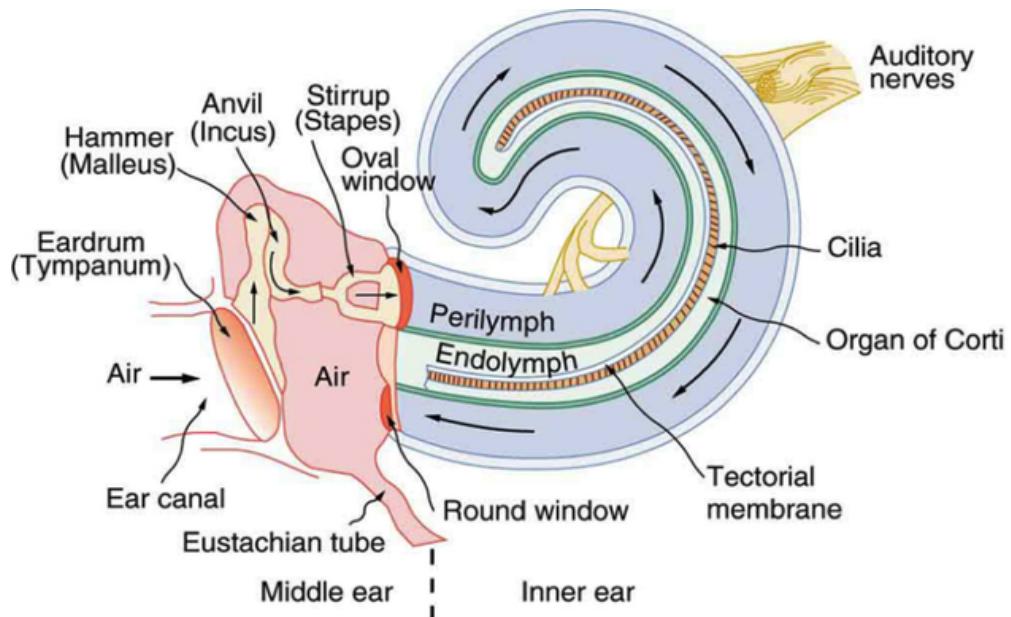


Figure 45: Partially Uncoiled Cochlea (Source: Socratic)

As you probably know, sound has 2 properties that help us interpret it: pitch and volume. As you go further in the cochlea, the membranes become stiffer. This means that as distance from the oval window increases, it requires a higher vibration frequency to resonate with the tectorial membrane. This allows us to map sound frequencies to different locations on the cochlea with low pitch sounds being transduced at the oval window and high pitched sounds at the round window.

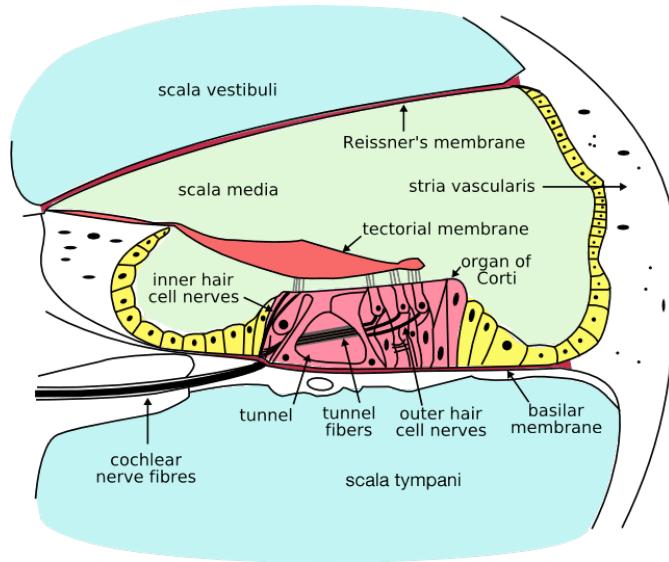


Figure 46: Cross section of Cochlea and Organ of Corti (Source: AskNature)

To indicate a higher volume, the hair cell fires action potentials at a faster rate. This is actually common for the majority of sensory receptors with many indicating the intensity of the stimuli by the frequency of action potentials, not the length or amplitude.

To determine where a sound is coming from, the brain makes use of the unique anatomy of the auditory system. The shape of the auricle alters the sound waves allowing for vertical sound localization (determining the elevation at which the sound was produced). For horizontal sound localization, the brain relies on individual input from both ears. To determine the direction on the horizontal plane, the brain is able to calculate the difference in times when each ear heard the sound. For example, because the ears are on opposite sides of the head, a sound on your left would be heard milliseconds before by your left ear compared to your right ear. Then, to determine distance, the brain can use the volume of the sound to estimate distance to the sound.

5.4 Vestibular System

Imagine being blindfolded and gently spun around in different directions. Despite the absence of visual input, you still have a sense of your movement and orientation. As you are shifted to the left or tilted forward, you can perceive changes in the direction and speed of your movement. This remarkable ability to detect spatial orientation and maintain balance is due to the vestibular system, a complex sensory network located in the inner ear. The vestibular system plays a crucial role in our everyday activities, allowing us to coordinate movements, maintain posture, and stabilize our gaze, even in the absence of visual cues.

5.4.1 Dynamic Equilibrium

Dynamic, or angular, equilibrium is the sense of **rotational acceleration**. Imagine spinning rapidly in a swivel chair: when you stop suddenly, you still feel as though you are moving. This sensation arises from the detection of rotational acceleration in the 3 **semicircular canals** located above the cochlea. Each canal is oriented in a different plane, allowing your brain to detect

movement in any direction. At the end of each semicircular canal is an **ampulla**.

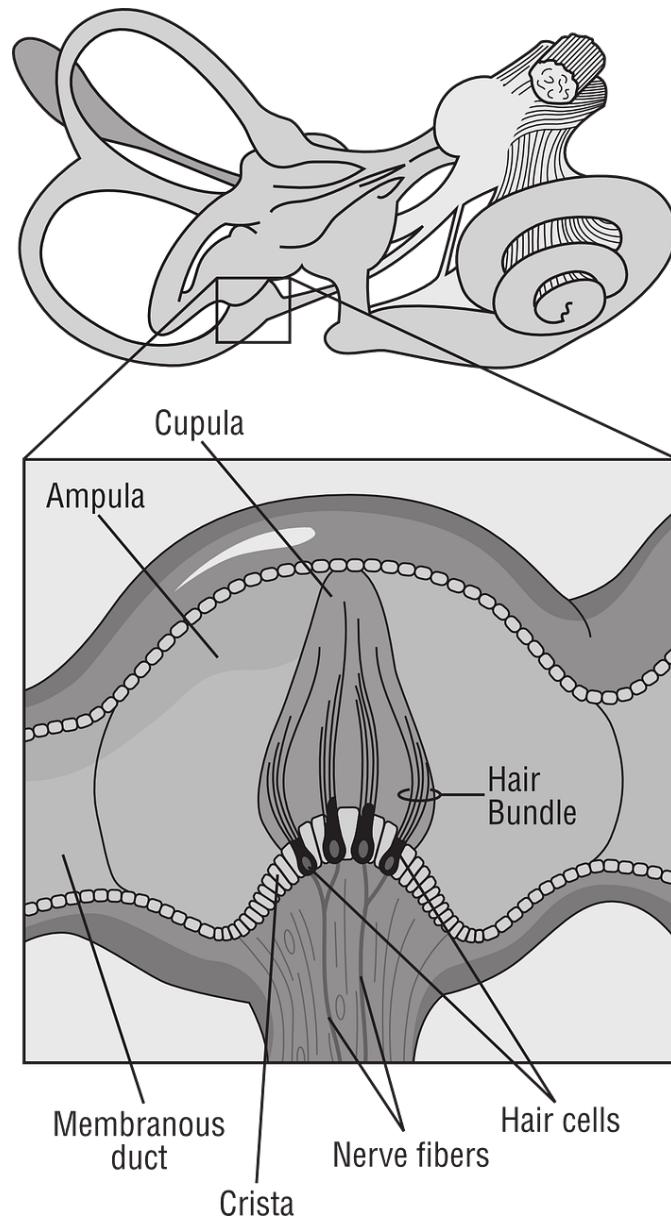


Figure 47: Ampulla

An ampulla is made up of **hair cells** with stereocilia covered in a gelatinous substance that forms the **cupula**. When the cupula bends due to rotational acceleration, the stereocilia are moved and in turn depolarize and send signals through cranial nerve VIII.

5.4.2 Static Equilibrium

Static (linear) equilibrium is detected by the utricle and saccule. The utricle is responsible for horizontal orientation, while the saccule handles vertical orientation. Both the utricle and saccule contain a sensory epithelium called the macula. Within the macula, the stereocilia of hair cells are embedded in the otolithic membrane, which contains otoliths (calcium carbonate crystals). When

there is a change in position, the gelatinous otolithic membrane moves according to the forces of gravity and pulls against the hair cells. This causes the stereocilia on the hair cells to bend, resulting in the stimulation of receptor cells.

5.5 Chemical Senses

Sensing various chemicals allows animals to detect pheromones, identify toxins, and more, which is crucial for survival and interaction with their environment. In humans, this ability is divided into two primary types of chemical sensing: **olfaction** (smell) and **gustation** (taste). Molecules detected by the olfactory system are called **odorants**, while those detected by the gustatory system are referred to as **gustants**. But how exactly are these chemicals perceived by our sensory systems?

5.5.1 Olfaction

Smell, or olfaction, is one of the most primal and powerful senses, allowing organisms to detect and interpret a wide array of chemical signals in their environment. Unlike vision and hearing, which rely on light and sound waves, smell involves the detection of airborne odorants. These molecules trigger specific responses in the olfactory system, giving rise to the perception of different smells.

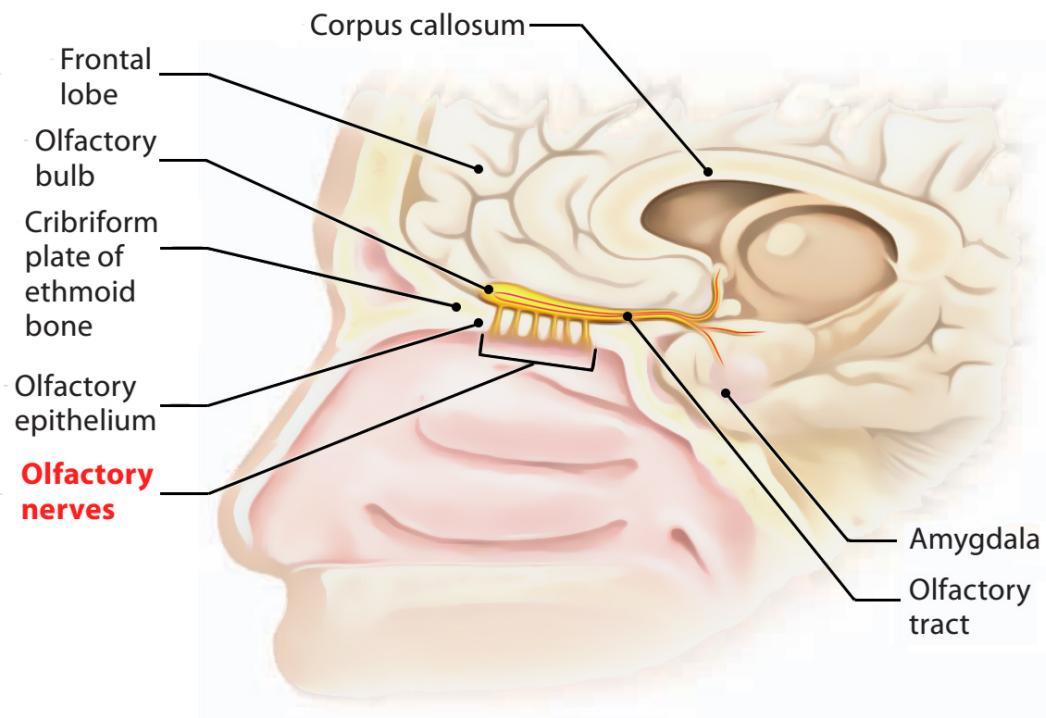


Figure 48: Olfaction (Source: Earth's Lab)

When you inhale, odorants enter your nasal cavity and make their way to the olfactory epithelium. The **olfactory epithelium** is made up of a lamina propria (of areolar connective tissue), simple columnar supporting epithelia, olfactory receptor cells (bipolar neurons), and basal stem cells. Cilia of the olfactory receptor cells extend into the covering mucus layer where they bind to odorants. To convert the presence of an odorant into a signal, the odorant binds to a **GPCR** that

activates **adenylyl cyclase** and consequently stimulates the production of cAMP. This cAMP then activates **ligand gated Na⁺ channels** which causes the depolarization of the neuron and subsequent propagation of an action potential. As mentioned previously, olfaction is the only sense that doesn't relay at the thalamus; instead, the axons of these olfactory neurons form several small nerves (collectively known as **cranial nerve I**) which reaches the **olfactory bulb** and the **olfactory cortex** in the temporal lobe for processing.

5.5.2 Gustation

We humans can taste 5 primary flavors: **sweet, sour, salt, bitter, and umami**. Sweetness is sensed by the presence of simple sugars, sourness by **H⁺ ions** (*Recall:* acidity is defined by proton concentration), saltiness by **Na⁺**, umami by **glutamate** (this is why some cuisines make use of monosodium **glutamate**), and bitterness by a variety of stimuli. Spice, however, is actually sensed by a class of thermoreceptors known as transient receptor potential channels.

The smallest unit of taste is the **taste bud**. With a covering of **epithelial cells** and **supporting cells**, taste buds contain **gustatory cells**, each of which detect a single flavor, and **basal cells** to replace the gustatory cells as they die.

Taste buds are in turn found on **papillae** (the raised bumps on your tongue), and there are several types:

Circumvallate papilla

- Found deep at the back of the tongue, arranged in a V-shape.
- Contain 50% of your taste buds.
- Large, mushroom-shaped with a deep trench surrounding them.

Fungiform papilla

- Scattered across the front two-thirds of the tongue.
- Small, reddish bumps resembling mushrooms.
- Contain about 25% of your taste buds, sensitive to sweet and savory flavors.

Filiform papilla

- Cover most of the tongue's surface, especially the front and sides.
- Tiny, thread-like projections give the tongue its rough texture.
- Provide mechanical friction, helping manipulate food and keep the mouth clean. They do not contain taste buds.

Foliate papilla

- Found on the back sides of the tongue, near the base.
- Appear as ridges or folds arranged in parallel lines.

- Contain about 25% of your taste buds.

After gustatory cells encode the tastant into action potentials, the signal needs to be transported to the brain for further processing. Signals from the anterior two thirds of the tongue are transported by cranial nerve **VII** while **IX** and **X** service the posterior third. The sensory information makes its way to the thalamus which directs the gustatory information to the **primary gustatory cortex** which includes parts of the inferior frontal lobe and anterior insula where it is processed and integrated with other senses (primarily olfaction).

6 Consciousness, Sleep, and the Circadian Rhythm

The regulation of sleep and consciousness is a complex interplay of circadian rhythms, homeostatic mechanisms, and arousal systems in the brain. These systems work together to coordinate our wakefulness and sleep cycles, ensuring proper rest and maintaining physiological functions.

6.1 Factors Influencing Sleep and Wakefulness

Two main systems influence sleep and wakefulness:

- **Circadian System:** Regulated by the body's internal clock, this system aligns physiological processes to the 24-hour day-night cycle.
- **Homeostatic System:** Tracks how long an individual has been awake. Adenosine levels increase during wakefulness and drive the need for sleep. More adenosine correlates with an increase in slow-wave activity during sleep.

6.2 Circadian Rhythm

The circadian rhythm is primarily regulated by the **suprachiasmatic nucleus (SCN)**, located in the hypothalamus.

- SCN neurons express clock proteins with a 24-hour cycle, which govern transitions between active and silent states through cyclic interactions between two protein sets.
- During the day, the SCN emits a steady stream of action potentials and receives light input from the retina to maintain synchronization.
- The SCN contacts:
 - The **ventrolateral preoptic (VLPO) nucleus**, influencing sleep induction.
 - **Orexin-producing neurons** in the hypothalamus, promoting wakefulness.
- The SCN signals the pineal gland via the paraventricular nucleus (PVN) to regulate melatonin secretion, which is inhibited by light.

6.3 Homeostatic Sleep Drive

The homeostatic system regulates sleep need based on the duration of prior wakefulness:

- Adenosine accumulates as ATP is broken down during the day, driving the urge to sleep.
- During slow-wave sleep (SWS), adenosine levels decrease, and ATP is replenished.
- Higher adenosine levels are associated with increased slow-wave activity during SWS.

6.4 Arousal and Sleep Mechanisms

The regulation of arousal and sleep involves various neurotransmitters, hormones, and brain structures:

- **Arousal Systems:** Located in the upper brainstem, these systems use neurotransmitters such as acetylcholine (ACh), norepinephrine, serotonin, and glutamate to maintain wakefulness.
- **Sleep Mechanisms:**
 - The balance of ACh and norepinephrine determines sleep-wake states:
 - High levels of both promote wakefulness.
 - Low levels promote Slow Wave Sleep (SWS).
 - During REM sleep, norepinephrine remains low while ACh levels are high, activating the thalamus and neocortex for dreaming.
 - The VLPO nucleus in the hypothalamus promotes sleep by releasing inhibitory galanin and GABA, suppressing arousal systems.
 - Orexin-producing neurons in the hypothalamus excite arousal systems and release histamine to sustain wakefulness. Orexin production increases metabolic rate and can be stimulated by low blood sugar.

6.5 Sleep Architecture

Sleep consists of two main phases:

- **Slow-Wave Sleep (SWS):** Characterized by high-amplitude, low-frequency brain waves indicating synchronized neuronal activity. During SWS:
 - Individuals may recall fragmented thoughts if awakened, but not dreams.
 - SWS dominates the earlier portion of the night, lasting 75–80 minutes in each cycle.
- **Rapid Eye Movement (REM) Sleep:** EEG patterns are similar to wakefulness, indicating high brain activity. REM sleep features:
 - Dreaming and REM paralysis, which inhibits muscle activity except for breathing and eye movements.
 - REM periods lengthen throughout the night, following SWS in 90-minute cycles.

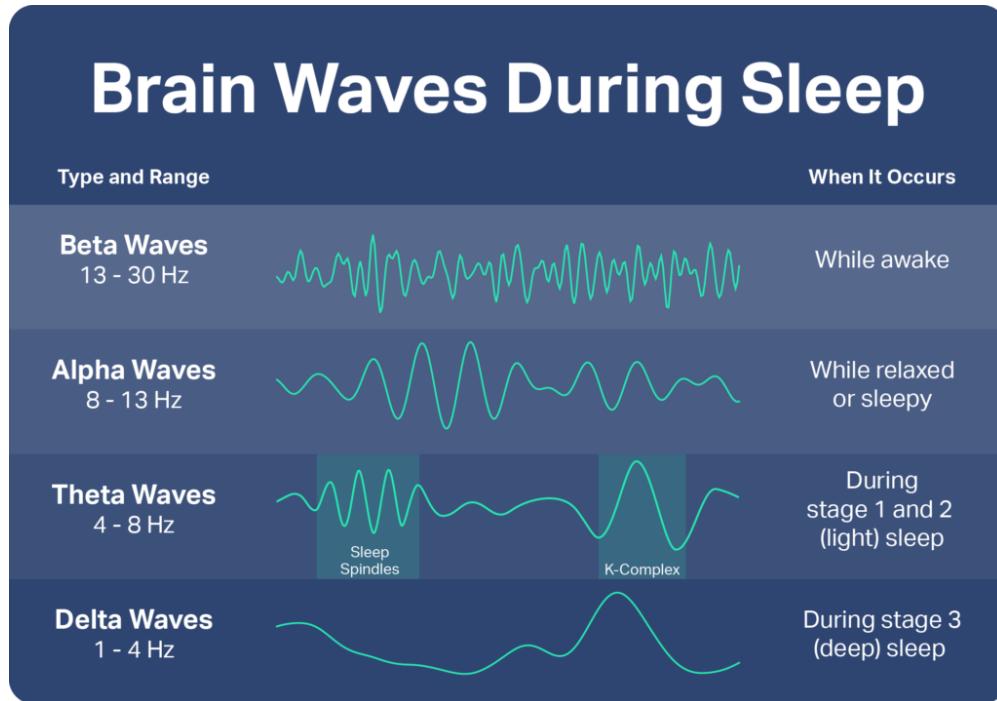


Figure 49: EEG Wave Types (Source: SleepFoundation.org)

6.6 Brain Waves During Sleep

Different stages of sleep are associated with distinct brain wave patterns:

- **Awake:** Beta waves (high frequency, low amplitude) dominate during active thinking and alertness, while alpha waves (lower frequency) appear during relaxed wakefulness.
- **NREM Stage 1:** Theta waves (low frequency, moderate amplitude) signal light sleep.
- **NREM Stage 2:** Sleep spindles and K-complexes appear, representing the transition into deeper sleep.
- **NREM Stage 3 (SWS):** Delta waves (low frequency, high amplitude) dominate, indicating deep, restorative sleep.
- **REM Sleep:** EEG resembles wakefulness with beta-like waves and rapid, low-amplitude fluctuations.

7 Learning, Memory, and Plasticity

At a synaptic level, we learn by strengthening frequently used neural pathways and degrading others. This happens through the processes of long-term potentiation and long-term depression.

7.1 Long-Term Potentiation

Long-term potentiation (LTP) is a fundamental mechanism underlying the brain's ability to learn and form memories. This process plays a crucial role in strengthening neural connections that are frequently activated, thereby facilitating the consolidation of information. This usually occurs either through increasing the number of AMPA receptors or by increasing the efficiency of AMPA receptors. The following steps outline the essential pathway through which synaptic strengthening takes place:

1. At a glutamate synapse, **Glutamate** binds to **AMPA** because **NMDA** is blocked by magnesium
2. **Na⁺** flows in and depolarizes the post-synaptic neuron
3. This causes the removal of **Mg²⁺** from NMDA because the influx of positive Na⁺ ions repel the positively charged Mg²⁺ ions
4. NMDA allows Na⁺ and Ca²⁺ in
5. Ca²⁺ binds to **calmodulin**
6. This activates **calcium–calmodulin-dependent protein kinase II (CaMKII)**
7. CaMKII binds to NMDA-type glutamate receptors and produces potentiation by phosphorylating principal and auxiliary subunits of AMPA
8. Results in a cascade that activates **Adenylyl Cyclase (AC)**, which produces **cAMP**, which activates **PKA (protein kinase A)**, which activates transcriptional coactivator **CREB (cAMP response element binding protein)**, leading to increased transcription of AMPA
9. Vesicles with AMPA embedded in their membrane fuse with the post-synaptic membrane and increase the number of receptors so that any subsequent activation produces a stronger EPSP

7.2 Long-Term Depression

Long-Term Depression (LTD) is the opposite of Long-Term Potentiation (LTP). When a synapse isn't being used often, it can be degraded through LTD. LTD increases calcium levels in the postsynaptic cell, but to a lesser extent than in LTP, leading to the activation of phosphatases. This enzymatic activity can result in the weakening and degradation of the synapse. Learning skills is a common example of LTD use.

8 Neuropathophysiology

Neuropathophysiology encompasses the study of diseases affecting the nervous system. These conditions vary widely in their etiology, pathophysiology, and treatment, yet they all share a profound impact on neural function and patient quality of life. Below is an overview of key neuropathophysiological disorders, highlighting their major features and mechanisms.

Stroke

Transient Ischemic Attack (TIA)

- Transient loss of blood supply to the brain
- Neurons fail to generate action potentials due to lack of ATP
- No permanent damage occurs

Stroke

- Prolonged lack of blood flow in the brain
 - Note: This can either be due to a clot, or because of a hemorrhage (pooling of blood in the brain compresses smaller blood vessels thereby restricting blood flow and creating ischemic conditions), so the type must be determined before administering tPA. As you can probably tell, giving a patient who's bleeding out blood thinners is probably not a good idea.
 - Leading cause of long-term disability in the US
 - Causes increased glutamate levels, leading to neuronal excitotoxicity (overactivation of NMDA receptors, which increases calcium influx and triggers cell death)

Symptoms:

- Sudden numbness or weakness in the face, arm, or leg, particularly on one side of the body
- Confusion, trouble speaking, or difficulty understanding speech
- Vision problems in one or both eyes
- Trouble walking, dizziness, or loss of balance and coordination
- Severe headache with no known cause

Penumbra Region: The area surrounding the infarct in the brain that is at risk of further damage but may be salvageable with prompt treatment.

Treatment:

- Tissue plasminogen activator (tPA): clot-dissolving drug effective within 3 hours
- Reduces risk of clots forming elsewhere in the body

Multiple Sclerosis

- Autoimmune inflammatory demyelination of the central nervous system (CNS)
- Targeted destruction of oligodendrocytes leads to scar tissue formation

Symptoms:

- Double vision, blindness
- Muscle weakness, poor coordination
- Decreased sensation

Treatment:

- Steroids such as glucocorticoids to reduce inflammation
- Shorten acute attacks by inhibiting the immune response

Guillain-Barré Syndrome

- Autoimmune inflammatory demyelination of the peripheral nervous system (PNS)
- Targets Schwann cells

Symptoms:

- Muscle weakness, typically beginning in the feet and hands

Creutzfeldt-Jakob Disease (CJD)

- Prion disease caused by misfolded prion proteins (PrP^{Sc})
- Transmission occurs through contaminated surgical instruments, eating infected tissue (e.g., Kuru), or spontaneous mutations
- Protein misfolding involves a shift in secondary structure from alpha-helices to beta-sheets

Symptoms:

- Rapid neurodegeneration
- Memory loss, personality changes
- Death

Alzheimer's Disease**Causes:**

- Genetics, advanced age
- Head trauma (e.g., chronic traumatic encephalopathy)
- Vulnerability of acetylcholine (ACh) neurons

Pathology:

- Formation of amyloid-beta plaques and tau tangles

- Damage to neuronal transport systems due to tau protein malformations
- Initially appears in the neocortex and exacerbates oxidative stress
- Leads to cortical thinning and ventricular enlargement

Symptoms:

- Memory loss, disorientation
- Cognitive decline, mood changes

Parkinson's Disease

- Loss of dopaminergic neurons in the substantia nigra (part of the basal ganglia)
- Neuronal death likely linked to mitochondrial respiration issues
- Pathological hallmark: Accumulation of Lewy bodies containing alpha-synuclein, neurofilament, ubiquitin, and tau

Symptoms:

- Motor problems: muscle rigidity, poor coordination, resting tremor
- Cognitive decline with varying severity

Treatment:

- Levodopa (L-Dopa): Temporarily relieves motor symptoms but does not halt disease progression. As mentioned previously, dopamine (deficient in Parkinson's patients) cannot cross the blood brain barrier, and as a result, treatment is done by giving a precursor (L-Dopa). The exact pathway is shown here:



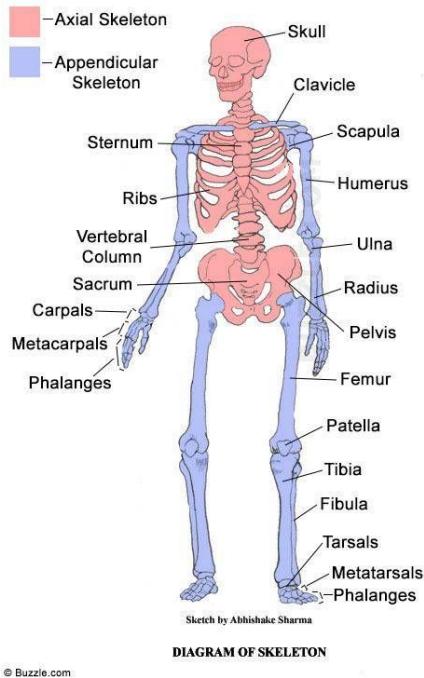
- Long-term use may cause dyskinesia (involuntary movement)

Epilepsy

- Dx: Two or more seizures that cannot be explained by a temporary underlying medical condition
- Causes: Premature birth, brain trauma, or abnormal development
- Some seizures suppress dendrite growth, leading to emotional instability or learning difficulties

Treatment:

- Medication and ketogenic diet (high fat, useful for generalized seizures)



- Surgical options: Destroy instigating brain region or split-brain surgery

Presentation on EEG: Seizures appear as abnormal, excessive, and synchronized brain wave patterns.

Meningitis

- Inflammation of the leptomeninges (pia and arachnoid)
- Typically caused by bacteria (e.g., *Neisseria meningitidis*), viruses, or fungi

Diagnosis:

- Lumbar puncture to analyze cerebrospinal fluid (CSF) for infection markers

9 Skeletal System

The skeletal system serves as the structural foundation of the body, providing support, protection, and mobility. Its components include bones, cartilage, ligaments, tendons, and other connective tissues. These elements collectively protect internal organs, store minerals and lipids, facilitate movement, and produce blood cells.

The skeletal system is divided into two parts:

- **Axial skeleton:** Includes the skull, ribs, and spine, providing central support and protecting vital organs.
- **Appendicular skeleton:** Comprises the peripheral bones including limbs, pelvic, and pectoral girdles, enabling movement and locomotion.

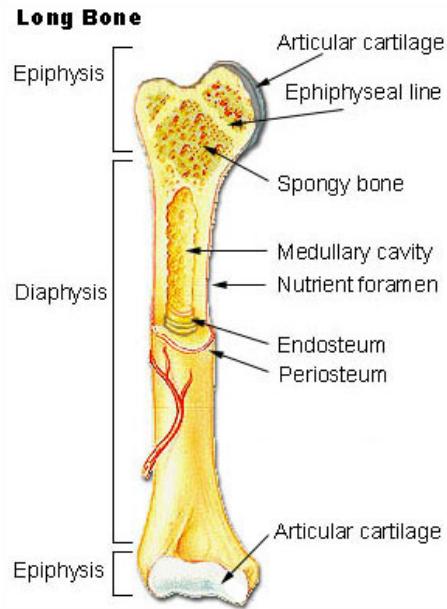


Figure 50: Long Bone Diagram (Source: Lumen)

9.1 Bone Structure

Bone can be categorized into compact and spongy types:

- **Compact bone**: Composed of osteons, which consist of concentric lamellae surrounding a central canal containing blood vessels and nerves.
- **Spongy bone**: Lacks osteons and is composed of trabeculae, containing red bone marrow.

Bones are classified based on their shape and function:

- **Long Bones**: Cylindrical and longer than they are wide. Found in limbs (e.g., femur, humerus), they provide leverage and support for movement.
- **Periosteum**:
 - Outer covering of the bone with two layers:
 - Fibrous outer layer: Provides structural support
 - Cellular inner layer: Contains osteoprogenitor cells for bone growth and repair
 - Nourishes bone tissue through blood vessels and nerves
- **Endosteum**:
 - Thin cellular layer lining the medullary cavity and central canals.
 - Contains osteoprogenitor cells that participate in bone growth and repair.
- **Short Bones**: Cube-shaped and provide stability with limited motion. Found in areas like the wrists (carpals) and ankles (tarsals).
- **Flat Bones**: Thin and often curved. These include the skull, ribs, and scapulae, offering protection and a surface for muscle attachment.

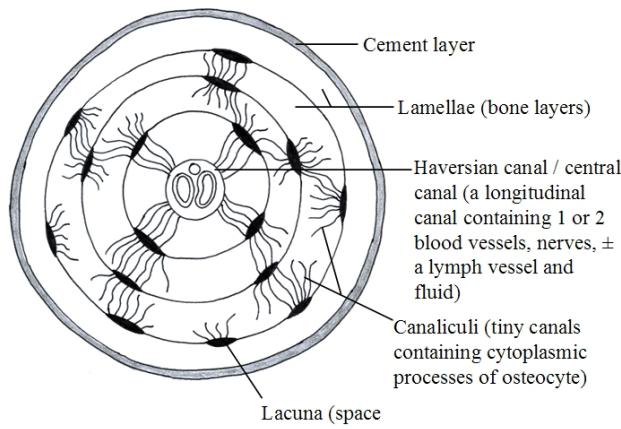
**A single osteon in cross-section**

Figure 51: Compact Bone Cross Section (Source: Socrative)

- **Irregular Bones:** Complex shapes that don't fit into other categories. Examples include the vertebrae and certain facial bones.
- **Sesamoid Bones:** Embedded within tendons (e.g., patella), they reduce friction and modify pressure in tendons.

9.1.1 Haversian System (Osteons)

The Haversian system is the structural unit of compact bone, designed to optimize strength and nutrient delivery:

- **Structure:**
 - Composed of concentric rings called lamellae.
 - Central (Haversian) canal contains blood vessels and nerves.
- **Osteocytes:**
 - Reside in small spaces called lacunae, located between lamellae.
 - Connected to neighboring osteocytes through canaliculi, allowing nutrient and waste exchange.
- **Function:**
 - Provides strength and resistance to compression.
 - Facilitates nutrient and waste exchange via the vascular network.

9.1.2 Composition of Bone

- **Matrix:** Comprises 90% of bone tissue:
 - **30% osteoid:** Organic components such as proteins like collagen and ground substance for flexibility.
 - **60% hydroxyapatite:** Densely packed crystals for hardness
- **Cells:** Constitute 2% of bone and include osteoprogenitor cells, osteoblasts, osteocytes, and osteoclasts.

9.1.3 Cells of The Skeletal System

- **Osteoprogenitor cells:** Stem cells involved in repair and growth, found in the periosteum and endosteum. Develop into osteoblasts.
- **Osteoblasts:** Produce bone matrix and initiate calcification, later differentiating into osteocytes.
- **Osteocytes:** Mature bone cells located in lacunae, linked via canaliculi, and specializing in bone repair.
- **Osteoclasts:** Large, multinuclear cells derived from monocytes that break down bone (called **osteolysis**) via lysosomal enzymes and acids.

9.1.4 Osteogenesis

Bone development occurs via two pathways:

- **Intramembranous ossification:** Mesenchymal cells form flat bones like the skull and clavicle by differentiating into osteoblasts at ossification centers.
- **Endochondral ossification:** Hyaline cartilage is replaced by bone, forming long and short bones.

9.1.5 Bone Remodeling

Bone remodeling is a dynamic process balancing resorption and formation:

- Osteoclasts resorb bone using HCl and lysosomal enzymes.
- Osteoblasts deposit new matrix, including osteoid and alkaline phosphatase.
- **Wolff's Law:** Bone adapts to mechanical stress, becoming stronger with use and weaker with inactivity.

9.2 Joints

9.2.1 Structural Joints

Joints are classified by structure:

- **Fibrous:** Immovable, such as sutures in the skull.
- **Cartilaginous:** Slightly movable, like intervertebral discs.
- **Synovial:** Highly mobile joints. These include six types:
 - **Ball-and-Socket Joints:** Allow movement in all directions, including rotation. Examples include the shoulder and hip joints.
 - **Hinge Joints:** Permit movement in one plane, like the opening and closing of a door. Examples are the elbow and knee joints.
 - **Pivot Joints:** Allow rotational movement around a single axis. An example is the joint between the atlas and axis vertebrae in the neck.
 - **Condyloid (Ellipsoid) Joints:** Enable movement in two planes, such as flexion/extension and abduction/adduction. Examples include the wrist and knuckle joints.
 - **Saddle Joints:** Provide flexibility in two planes and are found in the thumb's carpometacarpal joint, allowing for opposition.
 - **Plane (Gliding) Joints:** Allow sliding or gliding movements between flat surfaces. Examples include intercarpal joints in the wrist and intertarsal joints in the foot.

9.2.2 Physiological Joints

Joints are also classified by function, based on the degree of movement they allow:

- **Synarthrosis:** Immovable joints that provide stability and protection.
 - **Synostosis:** Fused bones, such as the epiphyseal lines in mature long bones.
 - **Suture:** Interlocked bones held together by dense connective tissue, such as the sutures in the skull.
 - **Gomphosis:** Peg-in-socket joints, like teeth anchored in their alveolar sockets by the periodontal ligament.
 - **Syndesmosis:** A bridge of hyaline cartilage between bones, such as the connection between the first rib and the sternum.
- **Amphiarthrosis:** Slightly movable joints that balance stability and mobility.
 - **Syndesmosis:** Bones connected by a ligament
 - **Symphysis:** Bones separated by a pad of fibrocartilage, such as the intervertebral discs.
- **Diarthrosis:** Freely movable joints, most commonly associated with synovial joints, allowing for a wide range of motion.

TYPES OF SYNOVIAL JOINTS

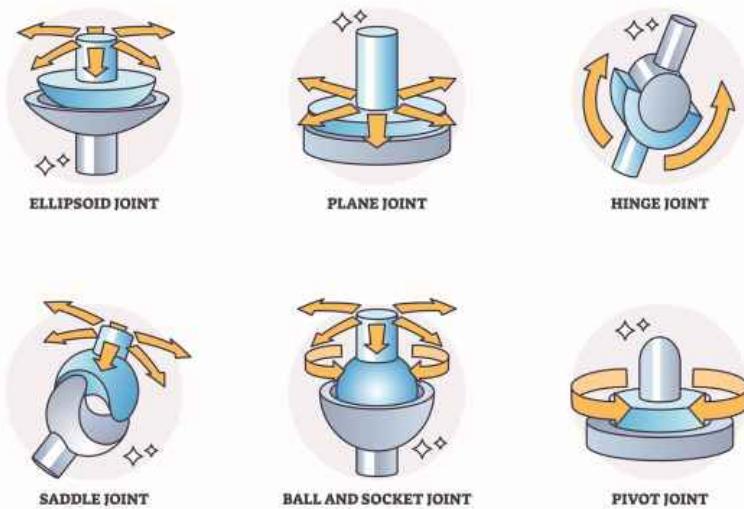


Figure 52: Synovial Joint Types (Source: Brookbush Institute)

10 Muscular System

The muscular system facilitates movement, stabilizes joints, maintains posture, and generates heat. It includes three primary types of muscle: skeletal, smooth, and cardiac, each adapted to specific functions and control mechanisms.

Composition and Function:

- Composed of skeletal muscle fibers, connective tissue, blood vessels, and parts of the GI tract.
- Functions include producing movement, digestion, maintaining posture, stabilizing joints, and generating heat (e.g., shivering).

10.1 Skeletal Muscle

Skeletal muscle, or striated muscle, is the type of muscle most commonly associated with the term "muscle." Unlike smooth and cardiac muscle, skeletal muscle is under voluntary control and is responsible for the movements and physical actions we consciously perform.

10.1.1 Structure and Types

The structure of a muscle begins at the molecular level with **actin** and **myosin** filaments, the primary proteins responsible for contraction. These filaments are organized into repeating units called **sarcomeres**, which are the smallest functional units of muscle and are aligned end-to-end

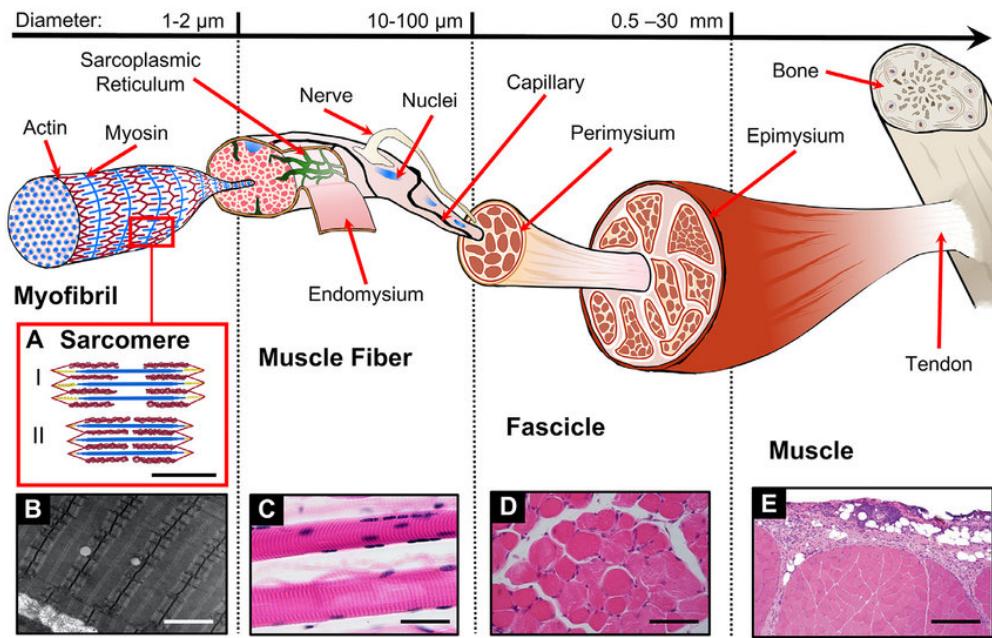


Figure 53: Muscle Structure Hierarchy (Source: Alberto Sensini)

along the length of a **myofibril**. Myofibrils are bundled together within individual **muscle fibers** (muscle cells), which are elongated, multinucleated cells. The naming conventions of the muscle coverings follow a naming scheme similar to nerves. Muscle fibers are encased in a connective tissue layer known as the **endomysium**. Groups of muscle fibers are then bundled together into fascicles, which are surrounded by another connective tissue layer called the **perimysium**. Finally, multiple fascicles are grouped together to form the entire muscle, which is encased in the **epimysium**, a tough outer layer of connective tissue.

Muscle Coverings

- **Endomysium:** Surrounds individual muscle fibers; contains satellite cells (stem cells), capillaries, and nerves.
- **Perimysium:** Groups muscle fibers into fascicles; contains collagen, elastin, blood vessels, and nerves.
- **Epimysium:** Covers the entire muscle, separating it from surrounding tissues.

Roles in Movement: Skeletal muscles work in coordinated pairs or groups to create movement, often classified as follows:

- **Flexors:** Muscles that decrease the angle between two bones at a joint during contraction. Example: the biceps brachii flexes the elbow joint.
- **Extensors:** Muscles that increase the angle between two bones at a joint during contraction. Example: the triceps brachii extends the elbow joint.
- **Agonists:** The primary muscle responsible for a specific movement. Example: the quadriceps femoris is the agonist for knee extension.

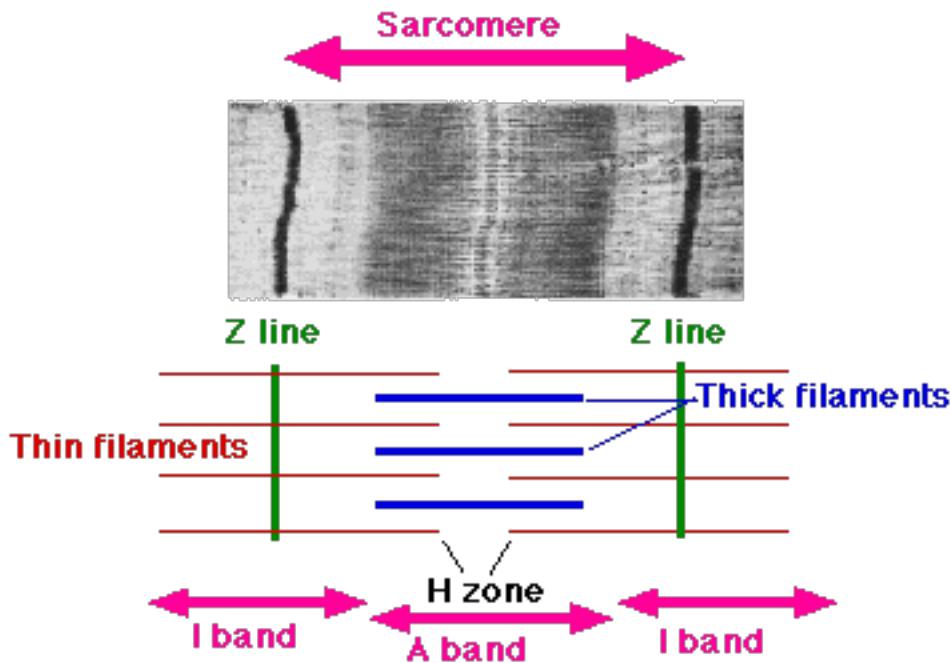


Figure 54: Sarcomere Structure (Source: Physiopedia)

- **Antagonists:** Muscles that oppose the action of the agonist, helping to control and refine the movement. Example: the hamstrings act as antagonists to the quadriceps during knee extension.

10.1.2 Metabolism

Skeletal muscle relies on several pathways for energy production:

- **At Rest:** Aerobic metabolism of glucose and fatty acids; ATP is stored as creatine phosphate (CP) or used to synthesize glycogen.
- **Moderate Activity:** Aerobic metabolism of stored glycogen.
- **High Activity:** Anaerobic glycolysis leads to lactic acid production when oxygen is insufficient.
 - Lactic acid enters the bloodstream, where the liver converts it back to glucose via the Cori cycle.

10.1.3 Fiber Types

- **Fast Glycolytic Fibers:**

- Pale in color, rely on anaerobic metabolism → less mitochondria (no need for electron transport chain) and less vascular (anaerobic → no need for oxygen).
- Fast, powerful contractions but fatigue rapidly.
- Larger diameter

- Abundant in sprinters

- **Slow Oxidative Fibers:**

- Red in color, use aerobic metabolism → lots of mitochondria and myoglobin.
- Contract slowly, resistant to fatigue.
- Abundant in marathon runners

- **Intermediate (Fast Oxidative) Fibers:**

- Combine features of fast and slow fibers.
- Aerobic, fast contraction, moderate fatigue resistance.

10.2 Smooth and Cardiac Muscle

Smooth Muscle: Found in internal organs and skin, smooth muscle facilitates involuntary movements such as peristalsis.

- Spindle-shaped cells with a single nucleus, lacking sarcomeres or T tubules.
- Contraction is triggered by Ca^{2+} binding to calmodulin, which activates myosin light chain kinase (MLCK).

Cardiac Muscle: Found only in the heart, cardiac muscle maintains involuntary rhythmic contractions.

- Branched cells with one or two nuclei, connected by intercalated discs (gap junctions and desmosomes).
- Contains sarcomeres and relies on troponin for Ca^{2+} regulation.
- Specialized to resist fatigue and sustain continuous activity by only using aerobic respiration.

11 Controlling Movement

The control of movement in the human body involves a hierarchical structure that integrates the central and peripheral nervous systems. This section highlights the mechanisms involved in motor control, from higher-order planning to local execution at the level of motor neurons.

11.1 Control Hierarchy

Higher-Order Control:

- The primary motor cortex and associated brain areas (e.g., premotor cortex, supplementary motor area) generate movement plans.
- Signals are sent to the spinal cord via descending tracts, such as the corticospinal tract.
- The cerebellum refines movements by integrating sensory input and motor commands, ensuring precision and balance.
- The basal ganglia regulate the initiation and cessation of movements.

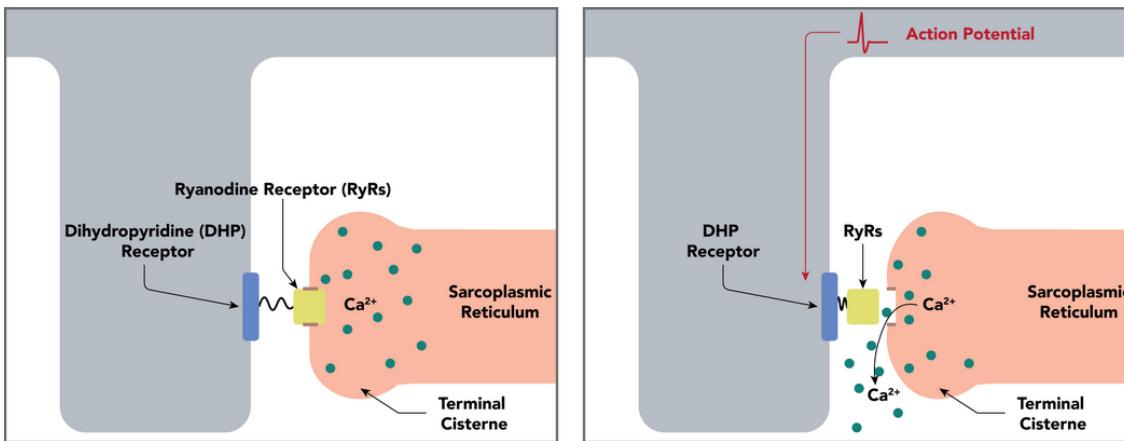


Figure 55: Calcium Release Mechanism (Source: Daniel Walsh and Alan Sved)

11.2 Local Motor Neuron Control

Motor Neurons and Neuromuscular Junction:

- Motor neurons in the spinal cord transmit signals to skeletal muscle fibers via alpha motor neurons (alpha motor unit + the muscle fiber it controls = motor unit).
- At the neuromuscular junction (NMJ), acetylcholine (ACh) is released and binds to nicotinic receptors on the muscle cell membrane.
- ACh binding triggers sodium ion influx, depolarizing the muscle cell and initiating contraction.
- Acetylcholinesterase (AChE) breaks down ACh, terminating the signal.

Mechanism of Contraction:

- Action potentials travel through the transverse tubules (T tubules), activating dihydropyridine (DHP) receptors.
- DHP receptors trigger ryanodine receptors on the sarcoplasmic reticulum, releasing Ca^{2+} .
- Ca^{2+} binds to troponin, allowing myosin cross-bridges to form, leading to muscle contraction.

Tetanus:

- Sustained muscle contraction results from repeated stimulation at high frequencies, preventing relaxation.
- Tetanus maximizes force output by keeping intracellular Ca^{2+} levels elevated.

11.3 Sliding Filament Model

The sliding filament model explains the mechanism of skeletal muscle contraction:

- A nerve impulse triggers the release of calcium ions (Ca^{2+}) from the sarcoplasmic reticulum.

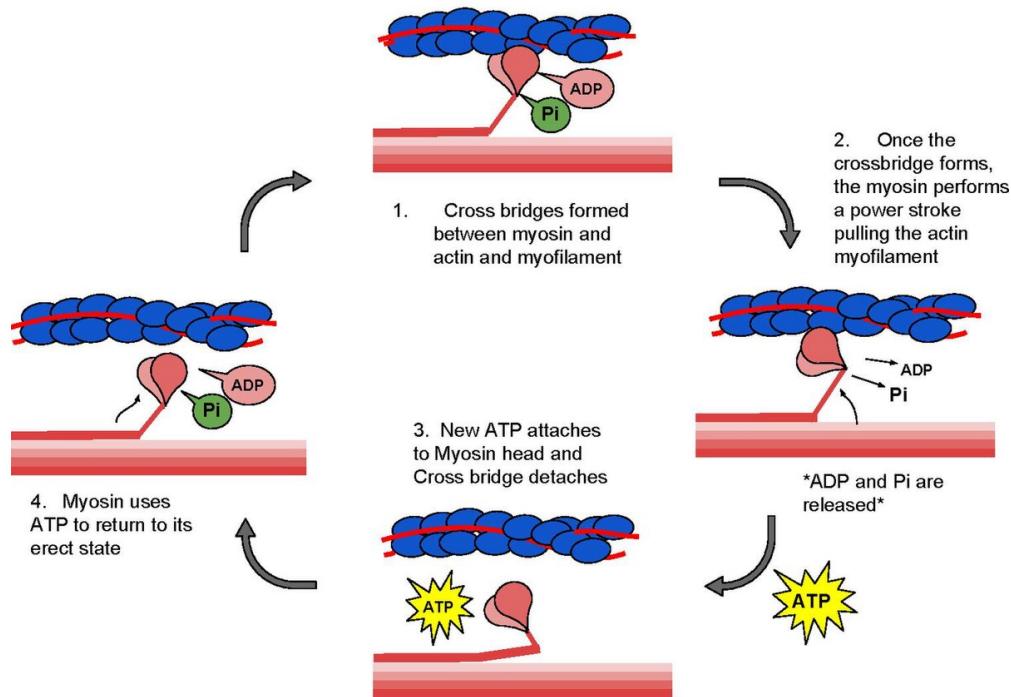


Figure 56: Sliding Filament Model (Source: Wyatt Johnston)

- Ca^{2+} binds to troponin, causing tropomyosin to shift and expose myosin-binding sites on actin filaments.
- Myosin heads bind to actin, forming cross-bridges.
- ATP hydrolysis provides energy for myosin heads to pull actin filaments toward the sarcomere center, shortening the muscle.
- ATP binds to myosin heads to release them from actin, allowing the cycle to repeat.