

# BRAIN AND BEHAVIOR



*Amy Nusbaum*  
Heritage University

# Brain and Behavior

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## CHAPTER OVERVIEW

### 1: Neuronal Structure

[1.1: The Neuron](#)

[1.2: Action Potentials](#)

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## 1.1: The Neuron

Neurons are the basic units of the brain. Their main function is to send electrical signals over short and long distances in the body, and they are electrically and chemically excitable. The function of the neuron is dependent on the structure of the neuron. The typical neuron consists of the dendrites, cell body, axon (including the axon hillock), and presynaptic terminal.

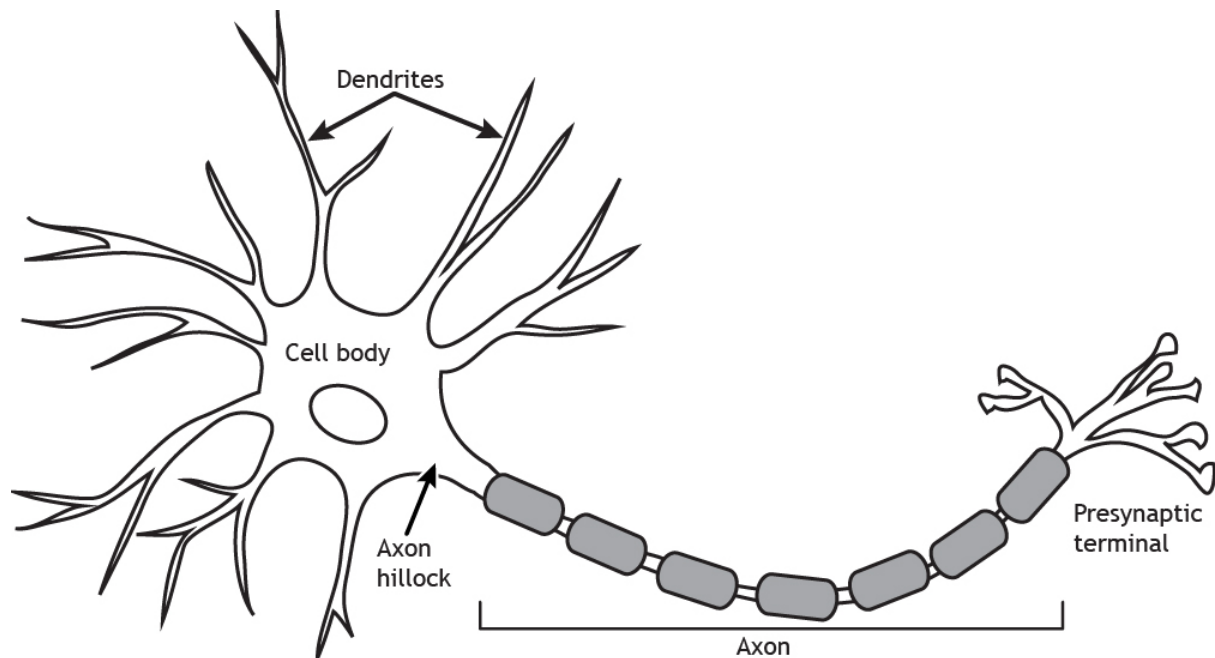


Figure 1.1. A typical neuron. Dendrites branch out from the cell body, where the nucleus is located. The axon hillock is located where the cell body transitions into the axon. The axon begins at the axon hillock and ends at the presynaptic terminal, which can branch into multiple terminals. 'Neuron' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

### Dendrites

Dendrites, shown here in green, are processes that branch out in a tree-like fashion from the cell body. They are the main target for incoming signals received from other cells. The number of inputs a neuron receives depends on the complexity of the dendritic branching. Dendrites may also have small protrusions along the branches known as spines. Spines, illustrated in the inset box, are the sites of some synaptic contacts. Spines increase the surface area of the dendritic arbor, which may be an important factor in receiving communication.

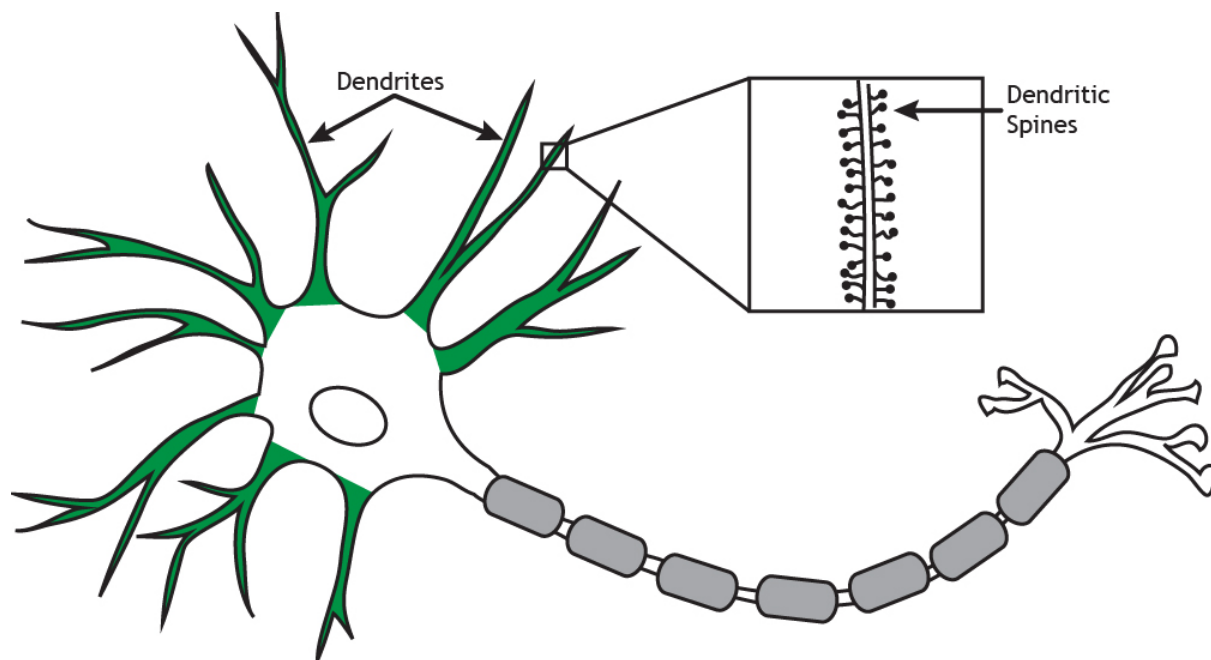


Figure 1.2. Dendrites branch out from the soma. Their function is to receive information from other neurons. Some dendrites have small protrusions called spines that are important for communicating with other neurons. 'Dendrites' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](#).

## Cell Body

The cell body, shown here in green and also known as the soma, contains the nucleus and cellular organelles, including endoplasmic reticulum, Golgi apparatus, mitochondria, ribosomes, and secretory vesicles. The nucleus houses the DNA of the cell, which is the template for all proteins synthesized in the cell. The organelles, illustrated in the inset box, in the soma are responsible for cellular mechanisms like protein synthesis, packaging of molecules, and cellular respiration.

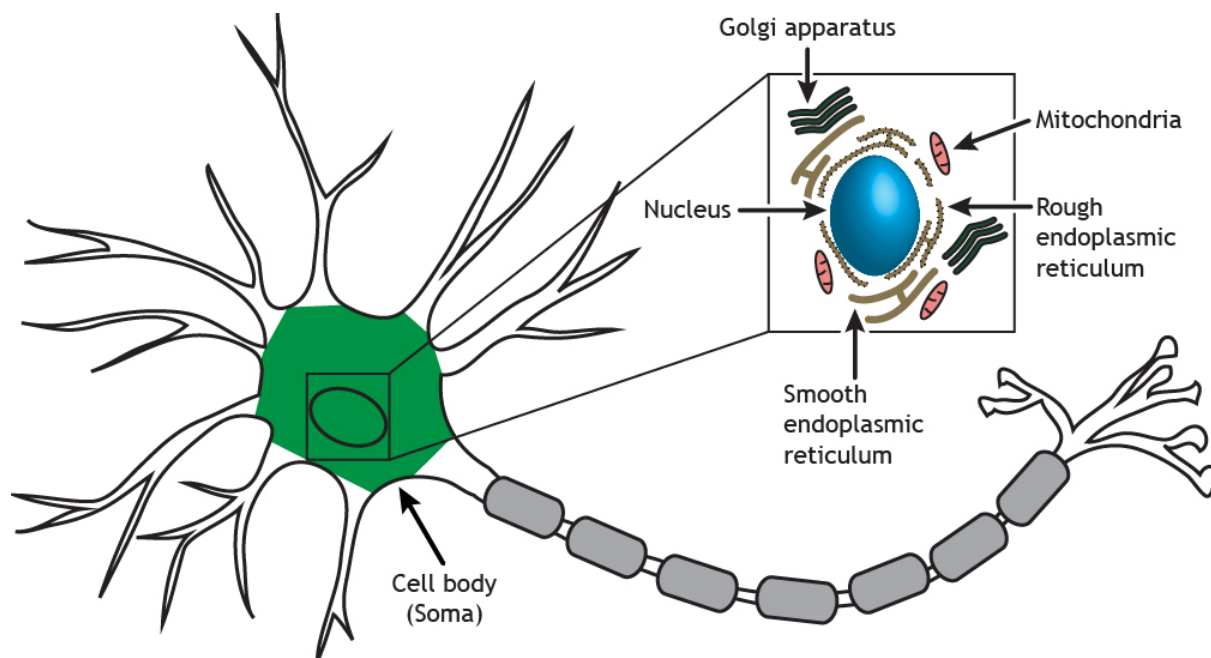


Figure 1.3. The cell body, or soma, of the neuron contains the nucleus and organelles that are commonly found in other cell types and are important for basic cellular functions. These organelles include mitochondria, endoplasmic reticulum, and Golgi apparatus. 'Soma' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](#).

## Axon

The axon, highlighted in green, is usually a long, single process that begins at the axon hillock and extends out from the cell body. The axon hillock is located where the cell body transitions into the axon. Axons can branch in order to communicate with more than one target cell.

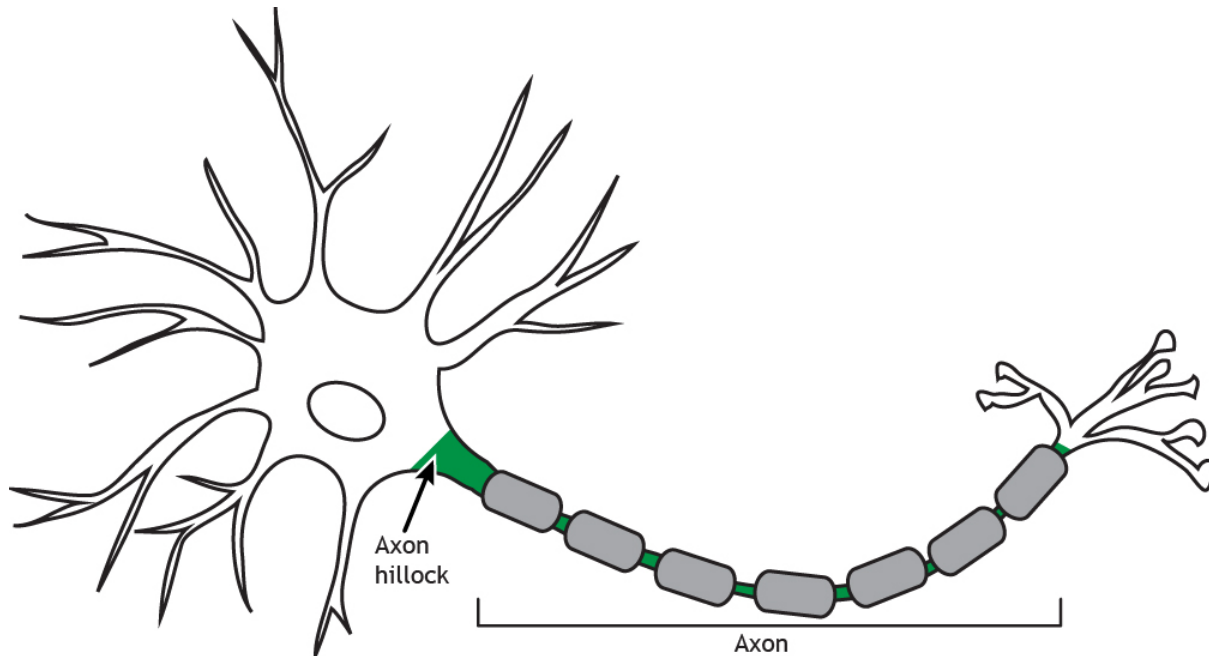
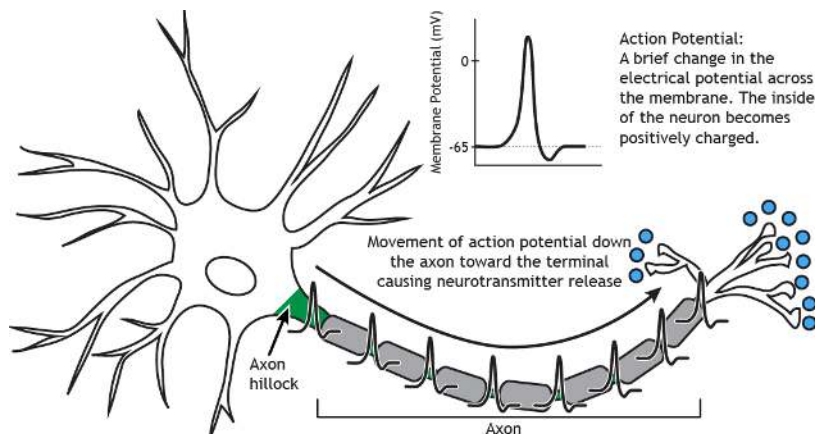


Figure 1.4. The axon is a long single projection that begins at the axon hillock, the region between the cell body and the axon. The axon terminates at the presynaptic terminal. 'Axon' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](#) (CC-BY-NC-SA) 4.0 International License.

## Action Potential

The axon transmits an electrical signal, called an action potential, from the axon hillock to the presynaptic terminal where the electrical signal will result in a release of chemical neurotransmitters to communicate with the next cell. The action potential is a very brief change in the electrical potential, which is the difference in charge between the inside and outside of the cell. During the action potential, the electrical potential across the membrane moves from a negative value to a positive value and back.



Animation 1.1. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will move from a negative, resting membrane potential, shown here as -65 mV, and will rapidly become positive and then rapidly return to rest during an action potential. The action potential moves down the axon beginning at the axon hillock. When it reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](#) (CC-BY-NC-SA) 4.0 International License. View static image of animation.

## Myelin

Many axons are also covered by a myelin sheath, a fatty substance that wraps around portions of the axon and increases action potential speed. There are breaks between the myelin segments called Nodes of Ranvier, and this uncovered region of the membrane regenerates the action potential as it propagates down the axon in a process called saltatory conduction. There is a high concentration of voltage-gated ion channels, which are necessary for the action potential to occur, in the Nodes of Ranvier.

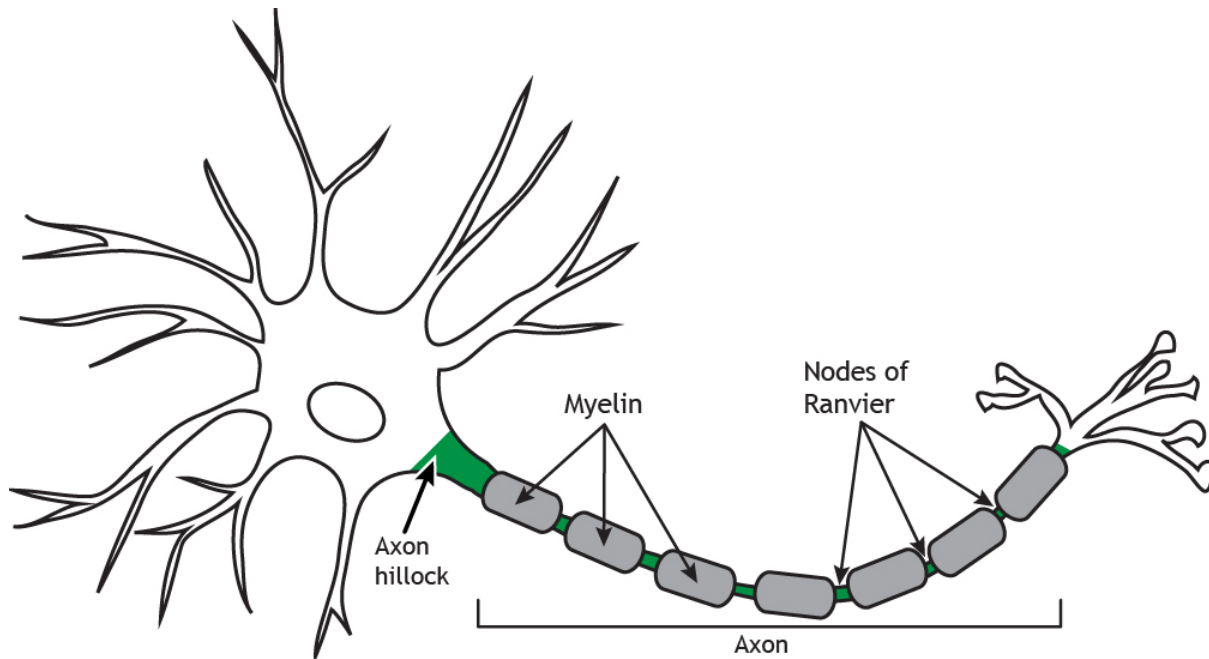


Figure 1.5. Myelin wraps around and insulates the axon. The spaces between the myelin sheath, where the axon is uncovered, are called the Nodes of Ranvier. 'Myelin' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

## Axon Characteristics

### Axon Length

The length of an axon is variable depending on the location of the neuron and its function. The axon of a sensory neuron in your big toe needs to travel from your foot up to your spinal cord, whereas an interneuron in your spinal cord may only be a few hundred micrometers in length.

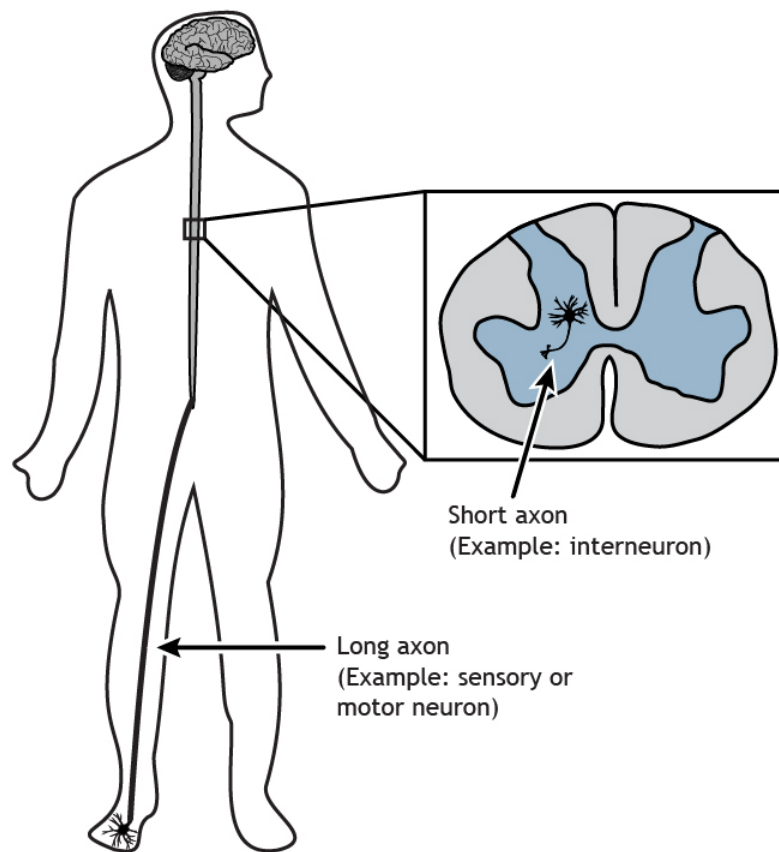


Figure 1.6. Axons vary in length. Spinal interneurons, neurons that fully exist within the spinal cord, can have short axons, whereas sensory or motor neurons, which need to reach from the spinal cord to the appropriate body region, for example the toe, have long axons. 'Axon Length' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\)](https://creativecommons.org/licenses/by-nc-sa/4.0/) 4.0 International License.

### Axon Diameter

Axon diameter is also variable and can be used to differentiate different types of neurons. The diameter affects the speed at which the action potential will propagate. The larger the diameter, the faster the signal can travel. Additionally, larger diameter axons tend to have thicker myelin.

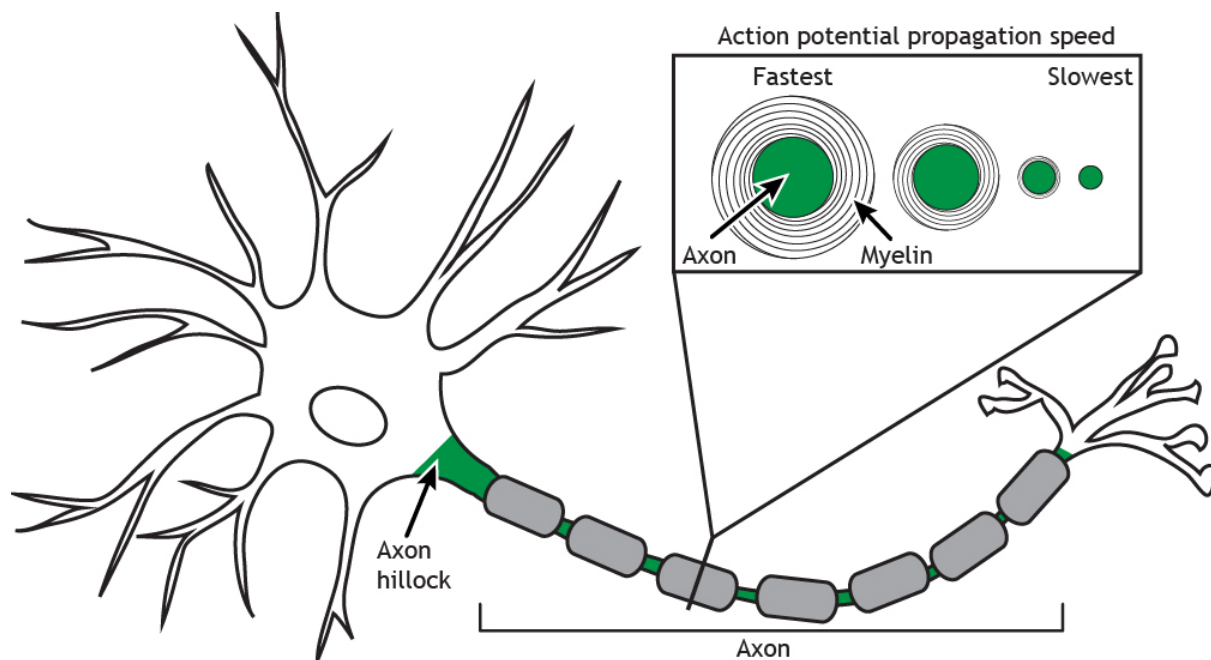


Figure 1.7. The diameter of the axon and the amount of myelination varies. Large diameter axons typically have thicker myelin sheath, which results in fast action potential speed. Small diameter axons may have no myelin present, resulting in slow action potential speed. 'Axon Diameter' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

## Presynaptic Terminal

The axon terminates at the presynaptic terminal or terminal bouton. The terminal of the presynaptic cell forms a synapse with another neuron or cell, known as the postsynaptic cell. When the action potential reaches the presynaptic terminal, the neuron releases neurotransmitters into the synapse. The neurotransmitters act on the postsynaptic cell. Therefore, neuronal communication requires both an electrical signal (the action potential) and a chemical signal (the neurotransmitter). Most commonly, presynaptic terminals contact dendrites, but terminals can also communicate with cell bodies or even axons. Neurons can also synapse on non-neuronal cells such as muscle cells or glands.

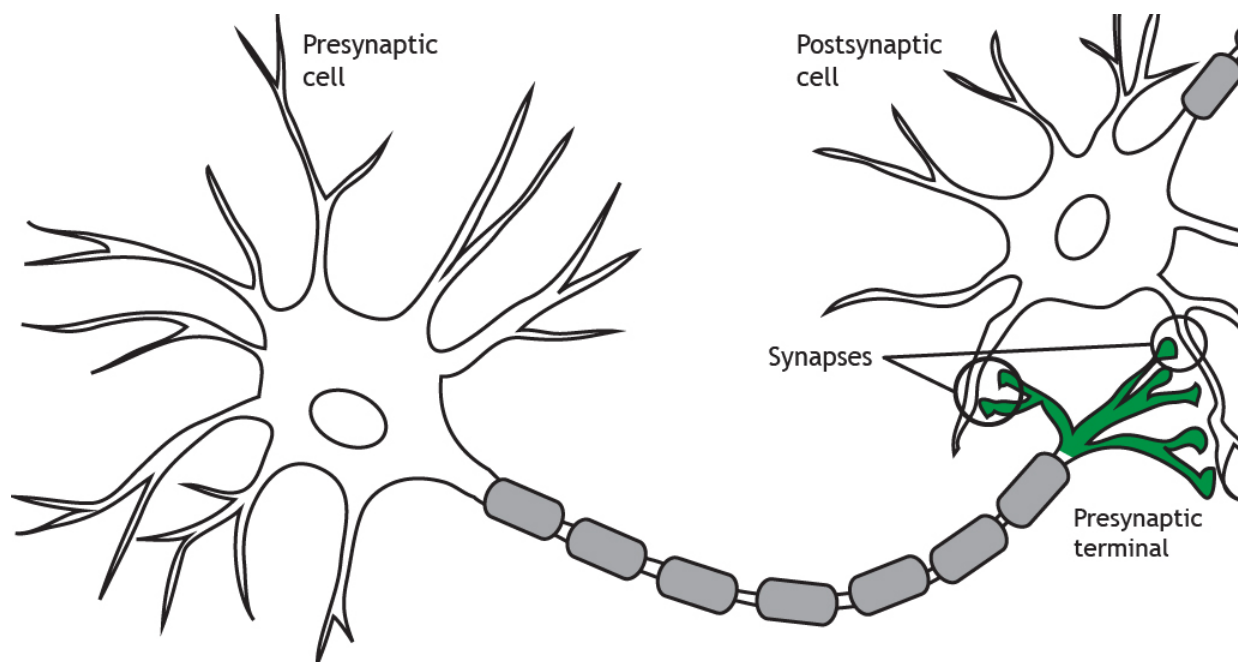


Figure 1.8. The presynaptic terminal forms synaptic contacts with a postsynaptic cell. 'Presynaptic Terminal' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

The terms presynaptic and postsynaptic are in reference to which neuron is releasing neurotransmitters and which is receiving them. Presynaptic cells release neurotransmitters into the synapse and those neurotransmitters act on the postsynaptic cell.

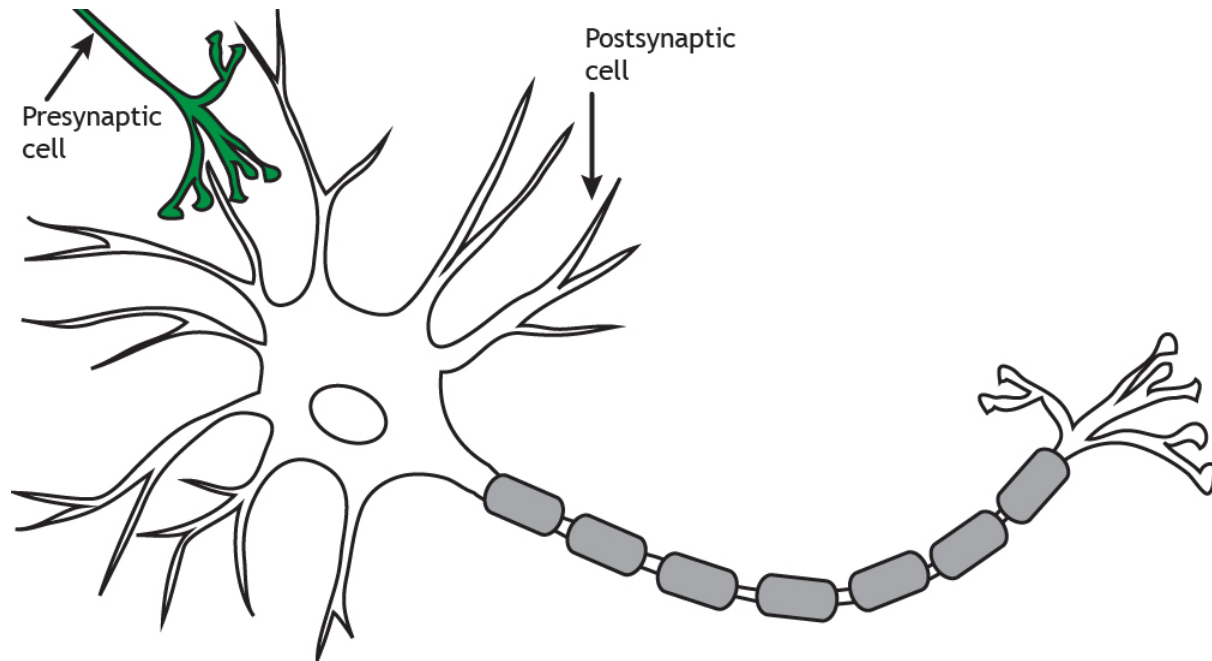


Figure 1.9. The presynaptic cell is the neuron that releases neurotransmitters into the synapse to act upon the postsynaptic cell. 'Postsynaptic Cell' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](#).

## Variations in Structure

Although these typical structural components can be seen in all neurons, the overall structure can vary drastically depending on the location and function of the neuron. Some neurons, called unipolar, have only one branch from the cell body, and the dendrites and axon terminals project from it. Others, called bipolar, have one axonal branch and one dendritic branch. Multipolar neurons can have many processes branching from the cell body. Additionally, each of the projections can take many forms, with different branching characteristics. The common features of cell body, dendrites, and axon, though, are common among all neurons.

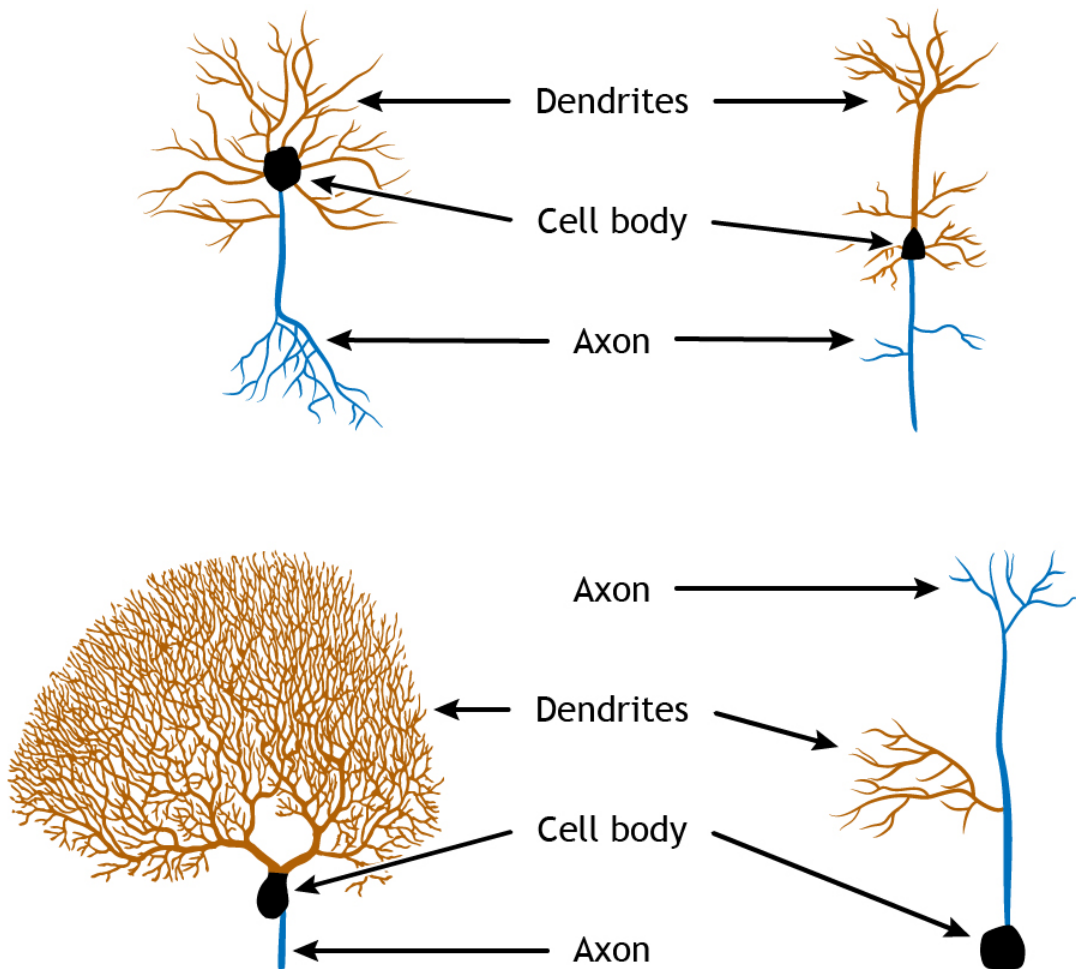
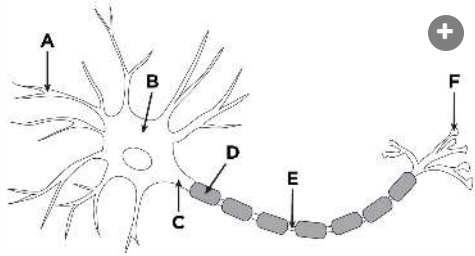


Figure 1.10. Neuron structure is variable, but the main components of cell body (shown in black), dendrites (shown in brown), and axon (shown in blue) are common among all neurons. 'Neuron Types' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

#### Key Takeaways

- Each structural component of the neuron has an important function
- Overall structure of the cell can vary depending on location and function of the neuron

#### Test Yourself!



Which structure is specialized to send electrical signals over varying distances?

☐ F

☐ B

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☐ A

✓ Check

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### Additional Review

1. Draw a neuron and identify the following structures: dendrites, soma, axon hillock, axon, myelin, nodes of Ranvier, presynaptic terminal
2. Describe functions of each neuronal structure depicted in your model.
3. Predict what would happen to neuron function if myelin was destroyed.

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## 1.2: Action Potentials

As covered in Chapter 1, the action potential is a very brief change in the electrical potential, which is the difference in charge between the inside and outside of the cell. During the action potential, the electrical potential across the membrane moves from a negative resting value to a positive value and back.

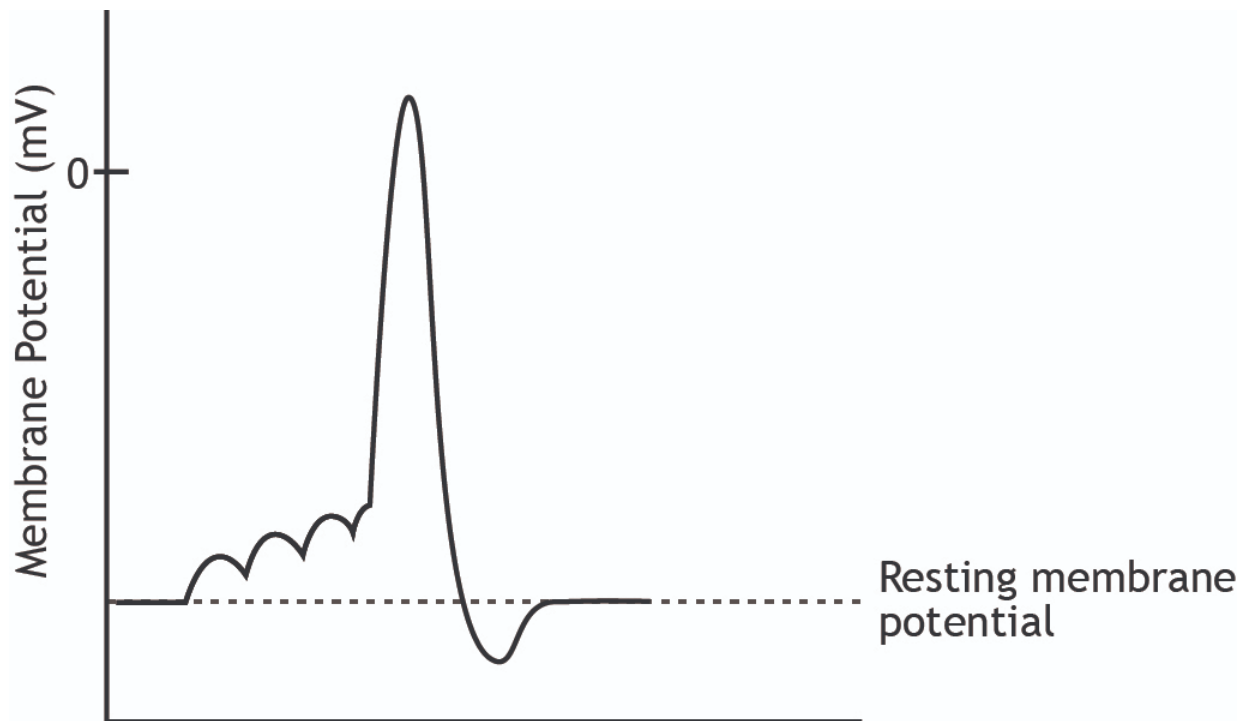
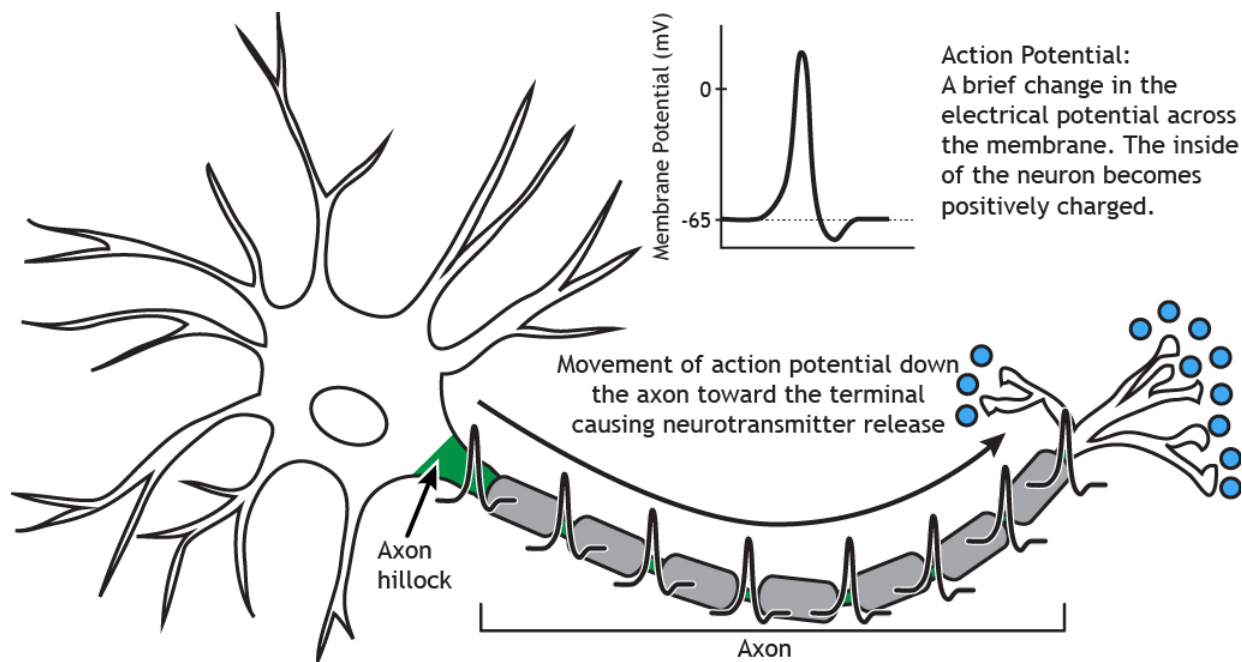


Figure 6.1. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will begin at a negative resting membrane potential, will rapidly become positive, and then rapidly return to rest during an action potential. 'Action Potential' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](#) (CC-BY-NC-SA) 4.0 International License.

### Propagation

The propagation of the action potential from the axon hillock down the axon and to the presynaptic terminal results in release of chemical neurotransmitters that communicate with a postsynaptic neuron.



Animation 6.1. The action potential moves down the axon beginning at the axon hillock. The action potential moving down a myelinated axon will jump from one Node of Ranvier to the next. This saltatory conduction leads to faster propagation speeds than when no myelin is present. When the action potential reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License. View static image of animation.

## Voltage-Gated Ion Channels

The change in membrane potential during the action potential is a function of ion channels in the membrane. In the previous lessons, we have learned about the principles of ion movement and have discussed non-gated (leak) channels at rest, as well as ion channels involved in the generation of postsynaptic potentials. In this chapter, we will examine a different type of ion channel: voltage-gated ion channels. For our purposes, these channels are located primarily at the axon hillock, along the axon and at the terminal. They are necessary for the propagation of the action potential.

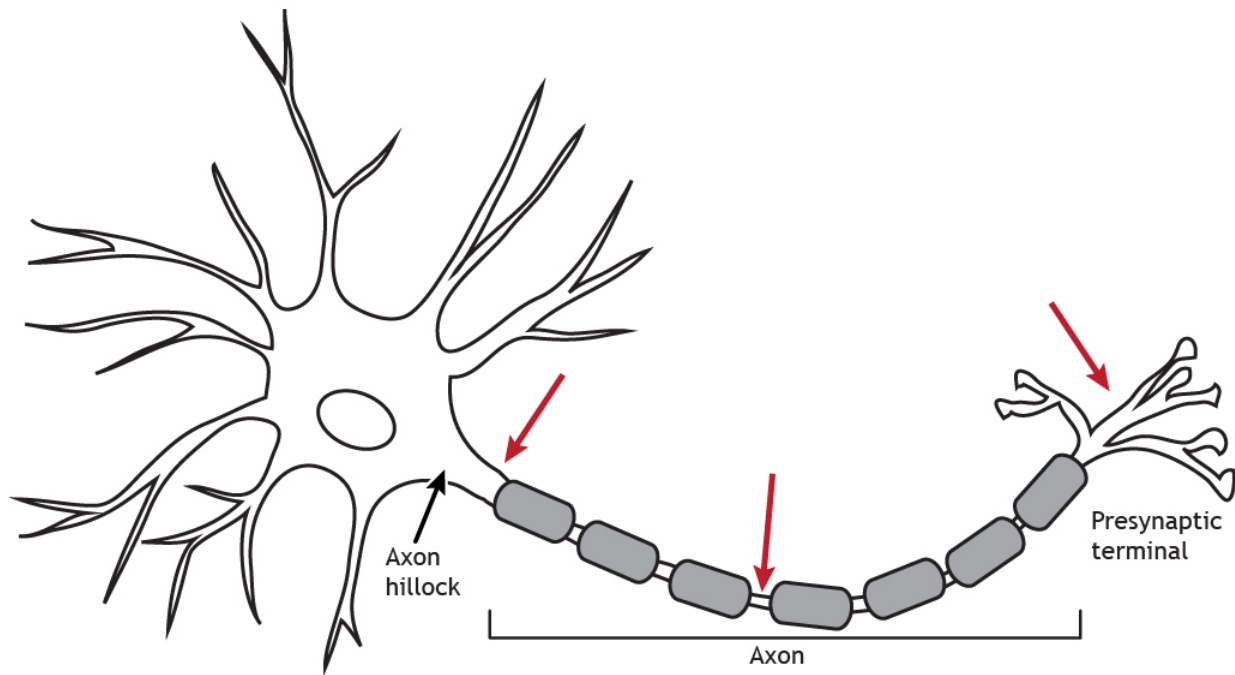
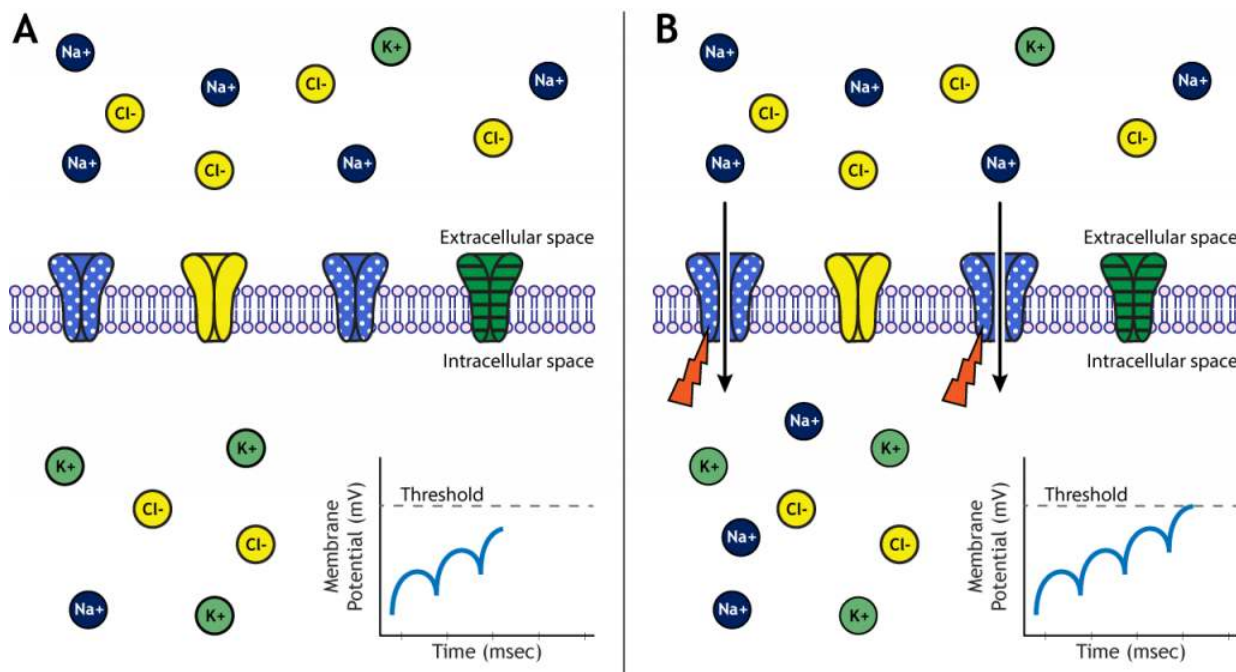


Figure 6.2. Voltage-gated channels critical for the propagation of the action potential are located at the axon hillock, down the axon at the Nodes of Ranvier, and in the presynaptic terminal. 'Voltage-Gated Channel Location' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

Voltage-gated channels allow ions to cross the membrane using the same ion movement principles covered in previous lessons. The main difference between voltage-gated channels and leak channels are how they are opened or “gated”. Voltage-gated channels open when the cell’s membrane potential reaches a specific value, called threshold. The neuron reaches threshold after enough EPSPs summate together.



Animation 6.2. As EPSPs summate, a result of ion movement not shown in the animation, the cell’s membrane potential will depolarize. Reaching threshold causes voltage-gated ion channels to open. Once the channels are open, ions will move toward equilibrium. In the animation, sodium ions flow inward. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels.

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## The Action Potential

The action potential begins when the cell's membrane potential reaches threshold. Once initiated in a healthy, unmanipulated neuron, the action potential has a consistent structure and is an all-or-nothing event. It will run through all the phases to completion.

The rising phase is a rapid depolarization followed by the overshoot, when the membrane potential becomes positive. The falling phase is a rapid repolarization followed by the undershoot, when the membrane potential hyperpolarizes past rest. Finally, the membrane potential will return to the resting membrane potential.

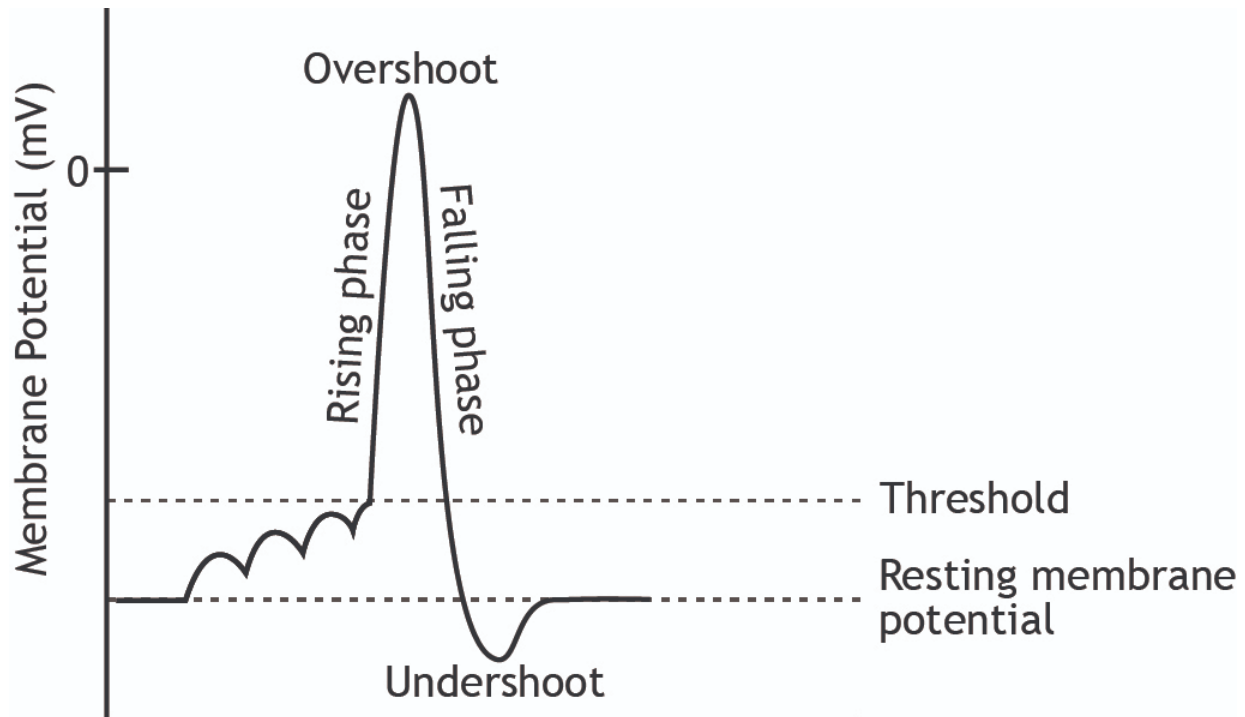
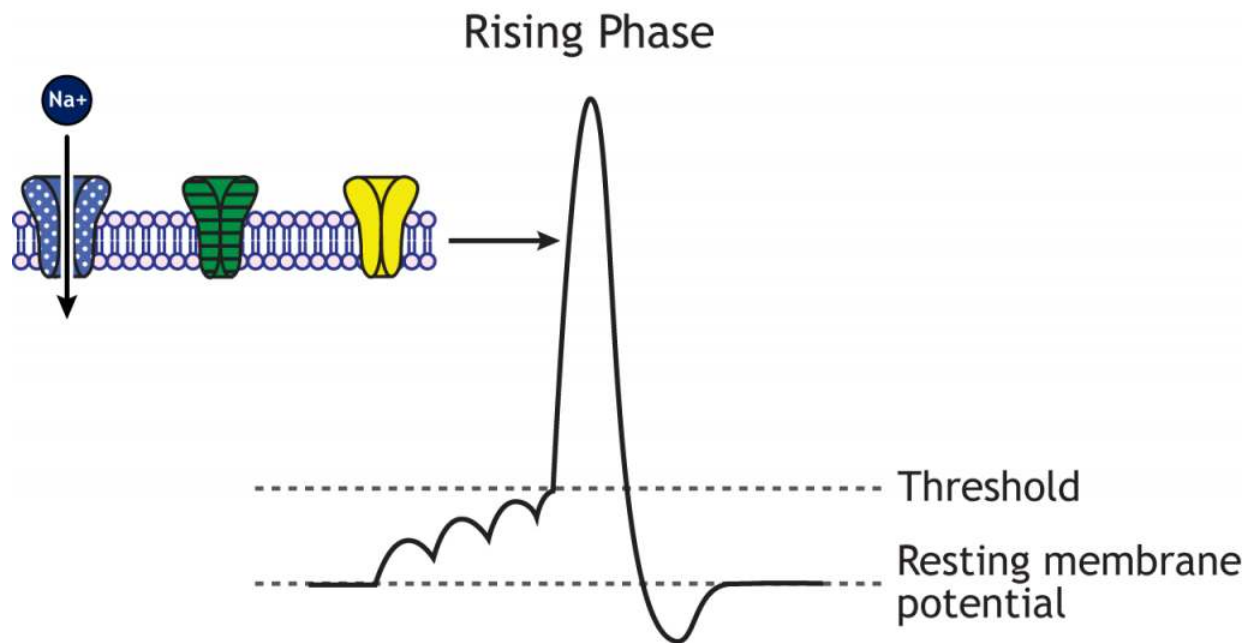


Figure 6.3. EPSPs that summate to reach threshold initiate the action potential. The depolarizing rising phase moves the membrane potential from threshold to above 0 mV. The overshoot is the peak of the action potential where the membrane potential is positive. The falling phase repolarizes the membrane potential, and the undershoot takes the membrane potential more negative than the resting membrane potential. After the undershoot, the membrane potential returns to rest. 'Action Potential Phases' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](#).

### Rising Phase

The rising phase is caused by the opening of voltage-gated sodium channels. These ion channels are activated once the cell's membrane potential reaches threshold and open immediately. The electrochemical gradients drive sodium into the cell causing the depolarization.



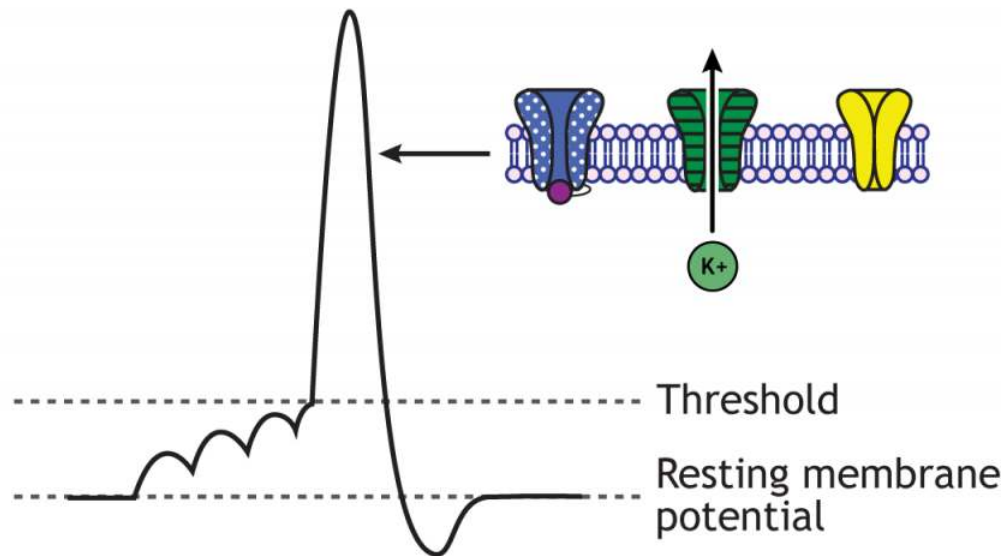
Animation 6.3. Voltage-gated sodium channels open once the cell's membrane potential reaches threshold. The rapid influx of sodium results in a large depolarization called the rising phase. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Rising Phase' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](#). View static image of animation.

### Falling Phase

The falling phase of the action potential is caused by the inactivation of the sodium channels and the opening of the potassium channels. After approximately 1 msec, the sodium channels inactivate. The channel becomes blocked, preventing ion flow. At the same time, the voltage-gated potassium channels open. This allows potassium to rush out of the cell because of the electrochemical gradients, taking its positive charge out of the cell, and repolarizing the membrane potential, returning the cell's membrane potential back near rest.

Like the voltage-gated sodium channels, the voltage trigger for the potassium channel is when the cell's membrane potential reaches threshold. The difference is that the sodium channels open immediately, whereas the potassium channels open after a delay.

## Falling Phase

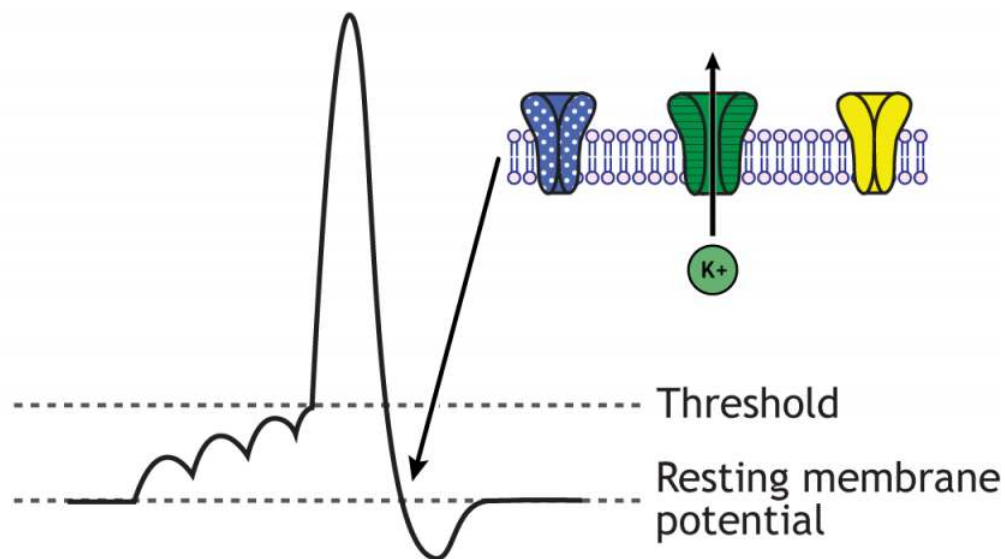


Animation 6.4. After approximately 1 msec, the voltage-gated sodium channels inactivate, which prevents any further ion flow into the cell. Although the voltage-gated potassium channels are activated in response to the cell reaching threshold, their opening is delayed and occurs alone with the sodium channel inactivation. This allows an efflux of potassium ions, which causes the repolarization of the falling phase. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Falling Phase' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](#) (CC-BY-NC-SA) 4.0 International License. View static image of animation.

## Undershoot

As the membrane potential returns to resting level, the sodium channels will de-inactivate, returning to the closed position, ready to be opened by a voltage change again. The potassium channels will also close, but they remain open long enough to cause a hyperpolarizing undershoot as potassium continues to move toward its equilibrium potential of -80 mV.

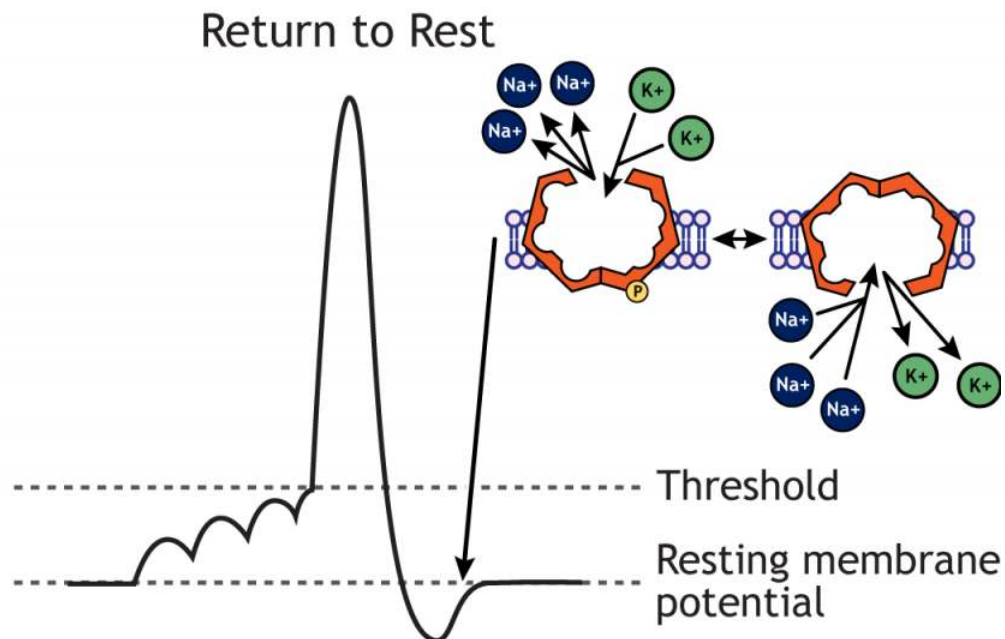
## Undershoot



Animation 6.5. Once the cell's membrane potential repolarizes, the voltage-gated sodium channels de-inactivate and return to their closed state. The voltage-gated potassium channels remain open long enough for the undershoot to occur as potassium continues to flow out of the cell. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Undershoot' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](#) (CC-BY-NC-SA) 4.0 International License. View static image of animation.

## Return to Rest

Once the voltage-gated channels close, the sodium-potassium pumps will reestablish the proper ionic concentrations needed for the electrochemical gradients. This action along with open leak channels will return the cell to its resting membrane potential.



Animation 6.6. Once the voltage-gated potassium channels close, the sodium-potassium pump will work to re-establish the electrochemical gradients and return the cell to its resting membrane potential. 'Return to Rest' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](#) (CC-BY-NC-SA) 4.0 International License. View static image of animation.

## Refractory Periods

### The Absolute Refractory Period

Each neuron does have a maximum firing rate. And even if the stimulus continues to increase in strength, the neuron cannot fire at a higher frequency. The maximum firing rate of a cell is determined by the status of the ion channels in the neuronal membrane during the different phases of the action potential. During the absolute refractory period, a second action potential cannot be fired under any circumstances regardless of the strength of the stimulus. The voltage-gated sodium channels are either open (during the rising phase) or inactivated (during the falling phase).

### The Relative Refractory Period

When the cell repolarizes and the voltage-gated sodium channels de-inactivate and return to a closed state, the cell is again able to fire another action potential. However, during the end of the falling phase and the during the undershoot, voltage-gated potassium channels are still open. During the undershoot, while the neuron is hyperpolarized, a larger-than-normal stimulus is needed to make the cell reach threshold again. This segment of the action potential is called the relative refractory period. Action potentials can be fired, but a stronger stimulus is needed than when the cell is at rest.

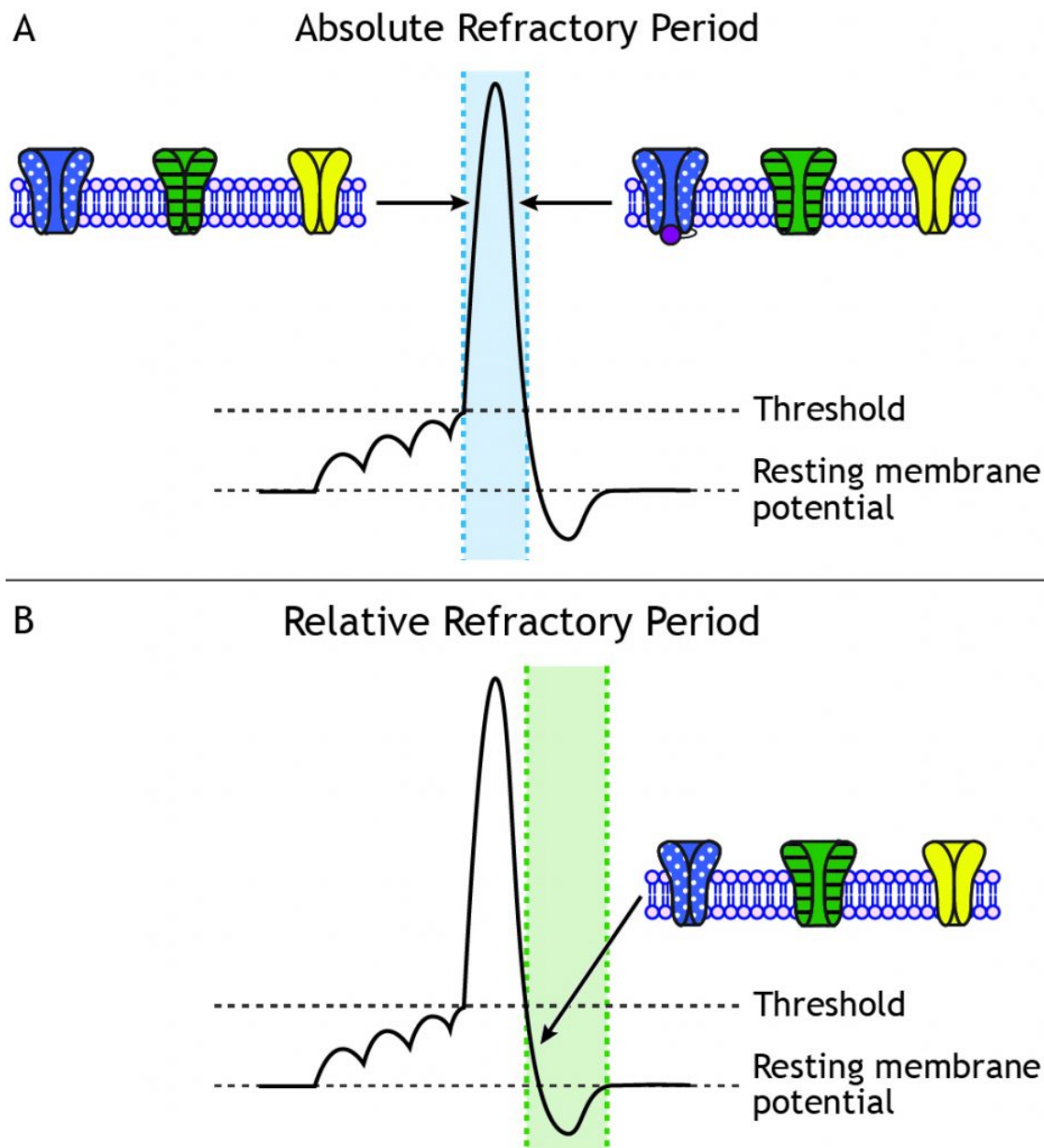


Figure 6.6. The maximum firing rate of a neuron is determined by the refractory periods. A) During the absolute refractory period no additional action potentials can be fired because the voltage-gated sodium channels are either already open (rising phase) or inactivated (falling phase). In these states, they cannot be opened again to begin a second action potential. B) The relative refractory period occurs when the voltage-gated sodium channels are closed, but the voltage-gated potassium channels remain open, causing a hyperpolarization of the membrane. Action potentials can be fired during this time, but a stronger stimulus is required to reach threshold compared to when the cell is at rest. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels; the solid yellow channels represent chloride channels. 'Refractory Periods' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

## Action Potential Characteristics

For a given cell, all action potentials have the same characteristics; they depolarize to the same membrane potential value and take the same amount of time. However, different neurons may exhibit different action potential characteristics. Likewise, if a neuron has a change in its environment, like altered extracellular ion concentrations, the shape of the action potential would change due to a change in the electrochemical gradients. For example, if the external concentration of sodium is decreased, the equilibrium potential of sodium, as well as the strength of the electrochemical gradients will change, which will result in a slower rate of rise and a lower amplitude of the action potential.

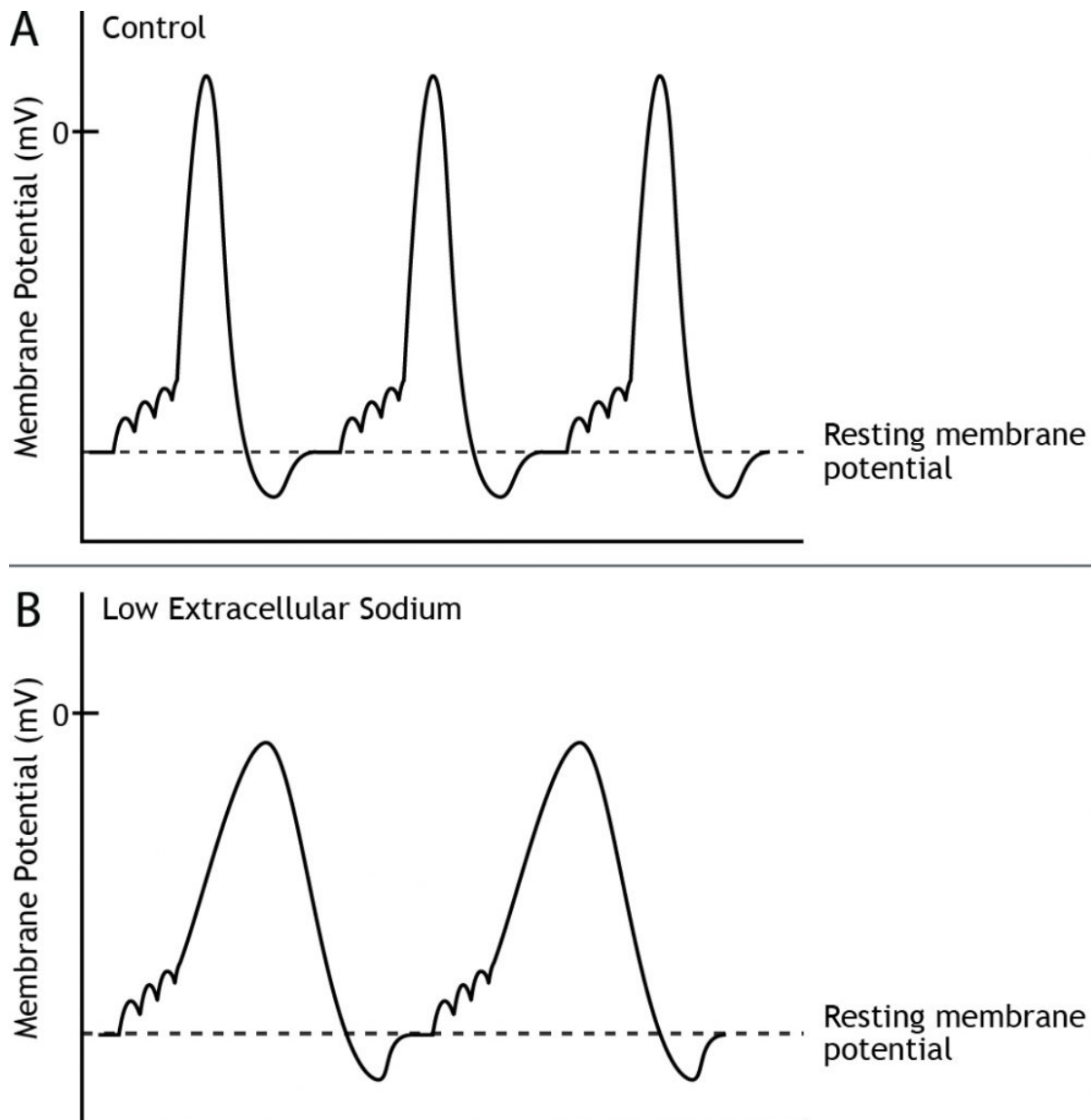


Figure 6.4. A) A neuron kept under the same conditions will display action potentials of similar height and length. B) However, if cellular conditions change, so will the action potential characteristics. If extracellular sodium levels are decreased compared to control levels, the action potential will show a slower rate of rise and a decreased height. 'Low Sodium Action Potential' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](#) (CC-BY-NC-SA) 4.0 International License.

## Stimulus Strength

The strength of a stimulus needs to be encoded by the neurons. We need to be able to perceive the difference, for example, between a dim light and a bright one. The frequency or rate of action potential firing informs the nervous system of stimulus strength.

Since the height of the action potential is always the same for a given neuron, the strength of the stimulus is determined by the frequency of action potential firing. A weak stimulus would cause fewer action potentials to be fired than a strong stimulus.

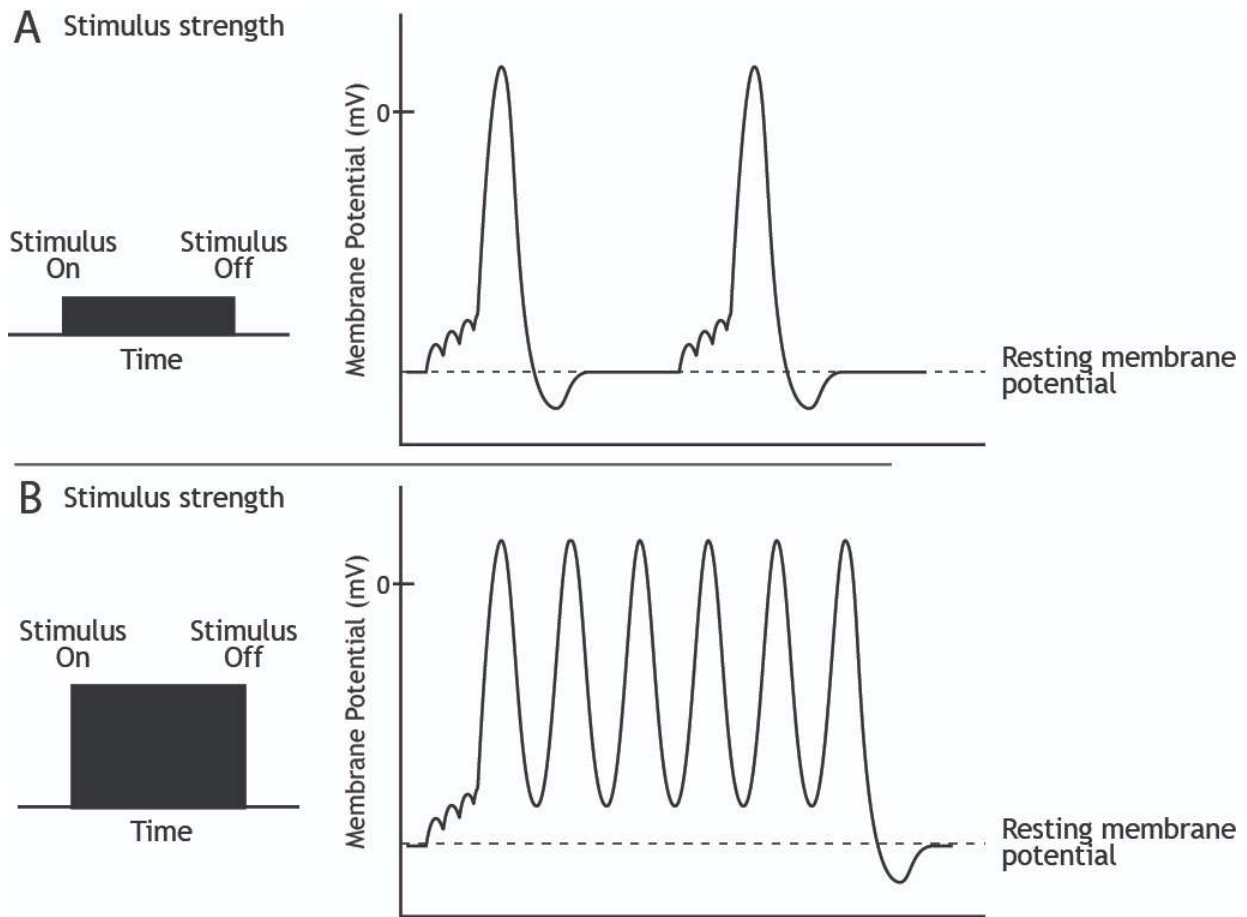
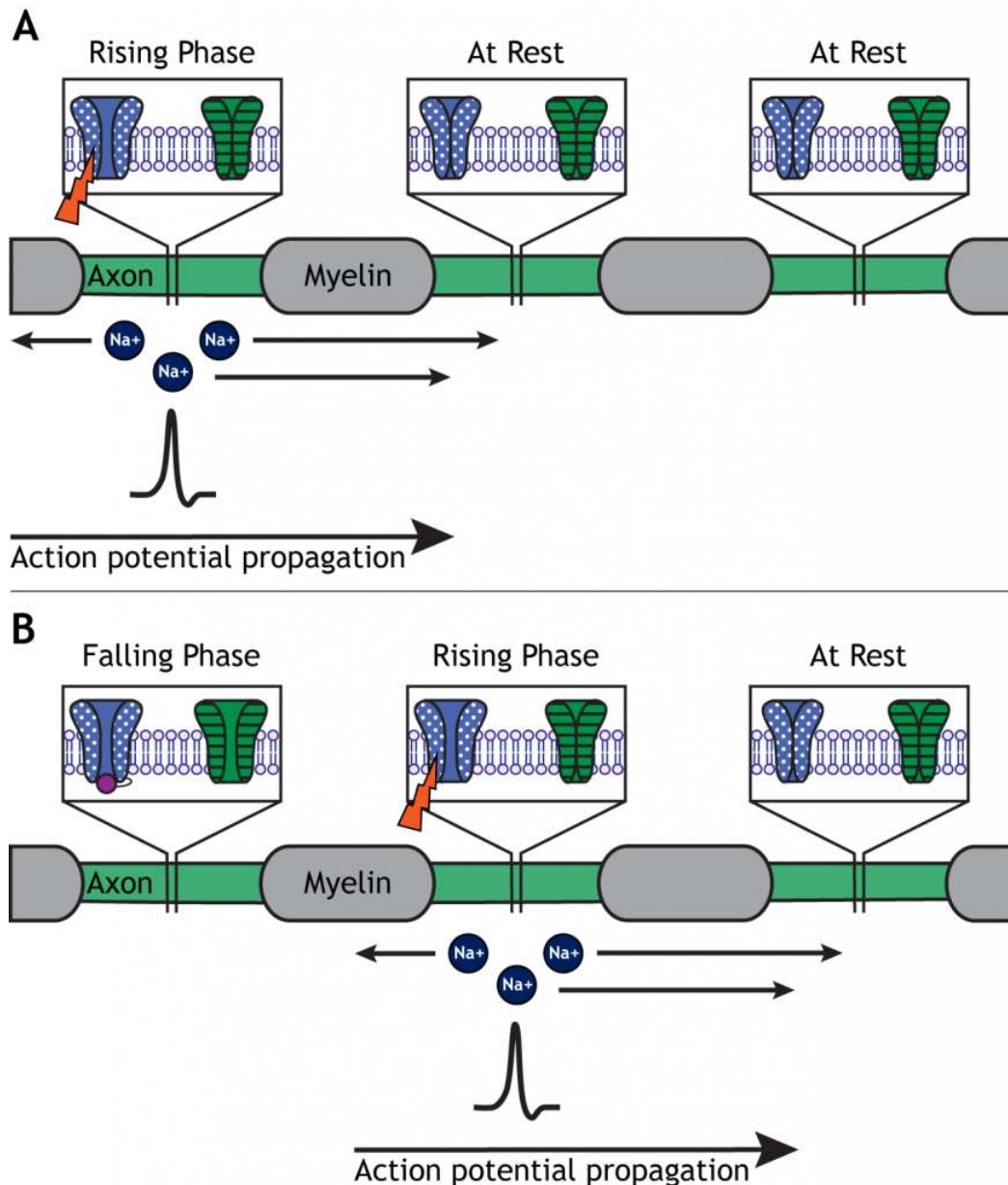


Figure 6.5. Information about the strength of a stimulus is encoded by the rate of action potential firing. A) A weak stimulus results in few action potentials being fired. B) A strong stimulus results in many action potentials firing in a row. 'Stimulus Strength' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

## Direction of Propagation

The action potential moves down the axon due to the influx of sodium depolarizing nearby segments of axon to threshold.



Animation 6.7. A voltage change that reaches threshold will cause voltage-gated sodium channels to open in the axonal membrane. The influx of sodium causes the rising phase of the action potential, but the ion flow also depolarizes nearby axon regions. As the depolarization reaches threshold, the action potential moves down the axon. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. ‘Action Potential Movement’ by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/). View static image of animation.

Action potentials only move in one direction, though, from the cell body to the presynaptic terminal. The refractory period keeps the action potential from moving backward down the axon. As the action potential moves from one Node of Ranvier to the next, the inactivated sodium channels in the previous axon segment prevent the membrane from depolarizing again. Therefore, the action potential can only move forward toward axon segments with closed sodium channels ready for rising phase depolarization.

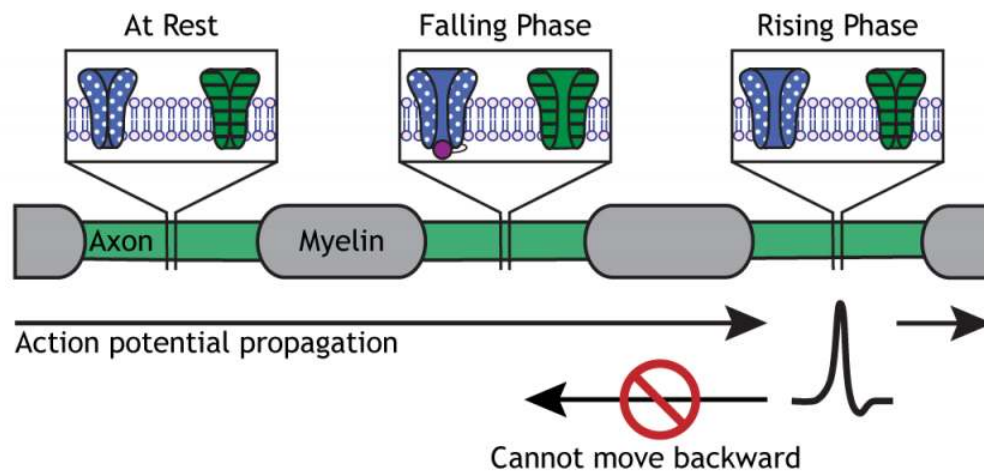


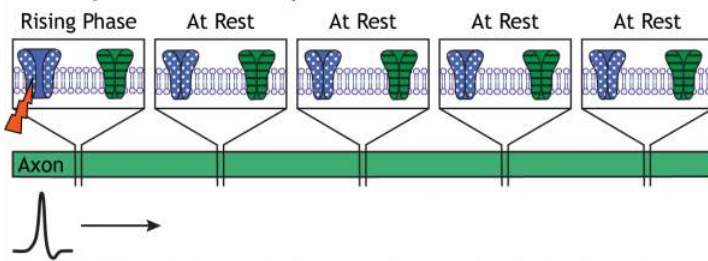
Figure 6.7. Action potentials only travel in one direction. The inactivated sodium channels prevent the action potential from moving backward down the axon. Blue dotted channels: sodium channels; green striped channels: potassium channels. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. 'No Backward Propagation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

## Speed of Propagation

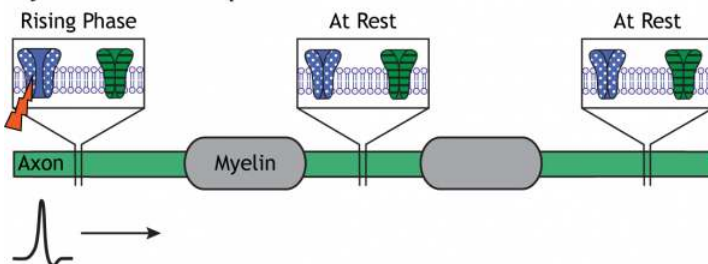
### Presence of Myelin

The presence of myelin leads to a significant increase in action potential conduction speed compared to an unmyelinated axon. For a myelinated axon, the action potential “jumps” between Nodes of Ranvier in a process called saltatory conduction. The nodes have a high density of voltage-gated channels, and the action potential is able to skip the axon segments covered by the myelin. In an unmyelinated axon, the action potential moves in a continuous wave. In addition to the saltatory conduction process, the presence of myelin also insulates the axon, preventing charge loss across the membrane, which also increases speed of the action potential.

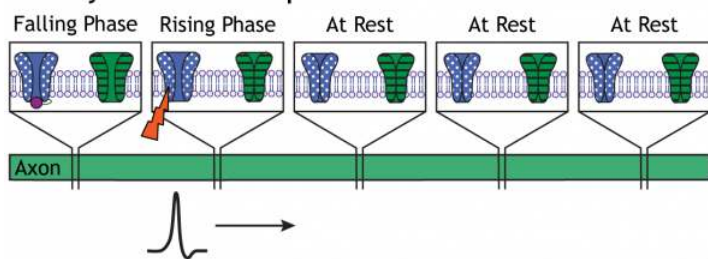
### A Unmyelinated - Time point 1



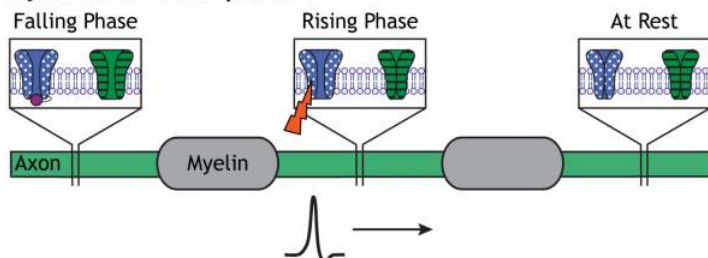
### Myelinated - Time point 1



### B Unmyelinated - Time point 2



### Myelinated - Time point 2



Animation 6.8. The action potential moves down an unmyelinated axon like a wave, opening voltage-gated channels along the length of the axon. In a myelinated axon, though, the action potential is able to skip portions of the axon that are covered by the myelin; the action potential jumps from node to node and travels further down the axon in the same amount of time. The dotted, blue channels represent voltage-gated sodium channels; the striped, green channels represent voltage-gated potassium channels. ‘Action Potential Speed’ by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License. View static image of animation.

### Diameter of Axon

The diameter of the axon also affects speed. The larger the diameter of the axon, the faster the propagation of the action potential down the axon. A larger axon leads to less resistance against the flow of ions, so the sodium ions are able to move more quickly to cause the regeneration of the action potential in the next axon segment.

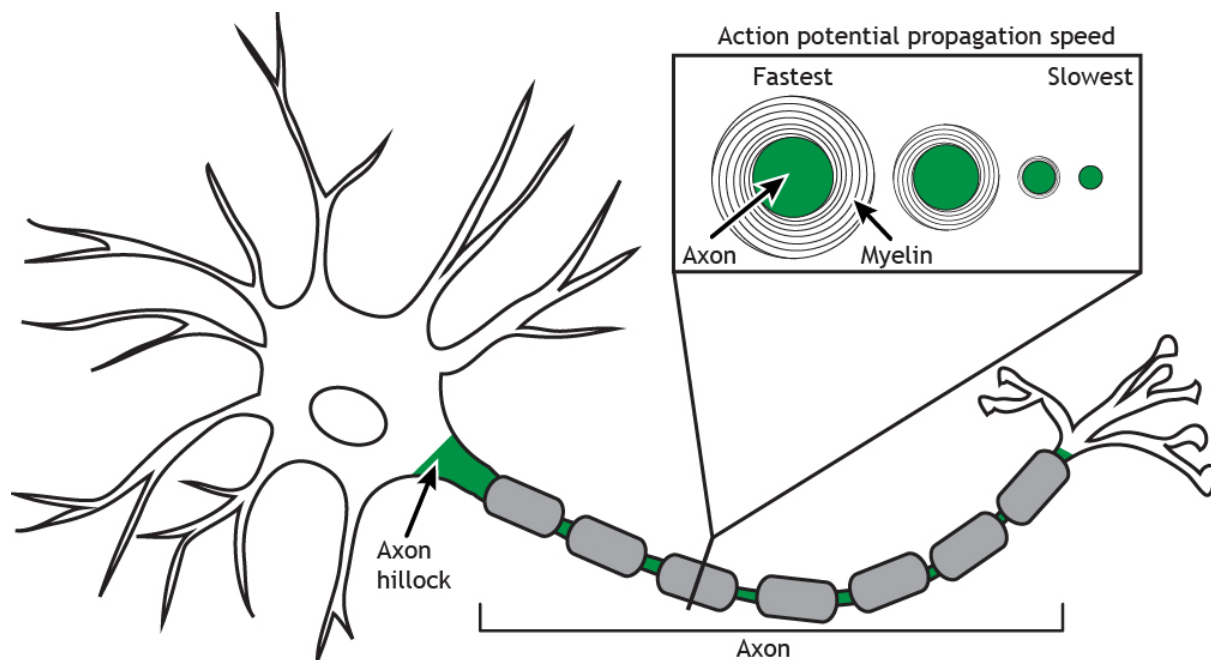


Figure 6.8. The diameter of the axon and the amount of myelination varies. Large diameter axons typically have thicker myelin sheath, which results in fast action potential speed. Small diameter axons may have no myelin present, resulting in slow action potential speed. 'Axon Diameter' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

#### Key Takeaways

- The voltage-gated ion channels are located along the axon hillock and axon; they open in response to the membrane potential reaching a threshold value
- The rising phase of the action potential is a result of sodium influx
- The falling phase of the action potential is a result of potassium efflux
- Action potentials are all-or-none (postsynaptic potentials are graded)
- Action potentials have the same height of depolarization for a given cell under typical conditions
- The neuron cannot fire a second action potential during the absolute refractory phase
- The neuron can fire a second action potential during the relative refractory phase, but it requires a stronger stimulus than when the neuron is at rest
- Stimulus strength is coded by frequency of action potential firing
- Action potential travel in one direction due to the presence of inactivated voltage-gated sodium channels
- Speed of propagation relies on presence and thickness of myelin and diameter of axon

#### Test Yourself!

How is stimulus intensity encoded by the action potential?

- ☐ The stronger the stimulus the shorter the absolute refractory period
- ☐ The stronger the stimulus the higher the action potential amplitude
- ☐ The stronger the stimulus the longer the action potential undershoot
- ☐ The stronger the stimulus the faster the action potential frequency

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## CHAPTER OVERVIEW

### 2: Neuronal Communication

2.1: Synapse Structure

2.2: Neurotransmitter Release

2.3: Neurotransmitter Clearance

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## 2.1: Synapse Structure

For the nervous system to function, neurons must be able to communicate with each other, and they do this through structures called synapses. At the synapse, the terminal of a presynaptic cell comes into close contact with the cell membrane of a postsynaptic neuron.

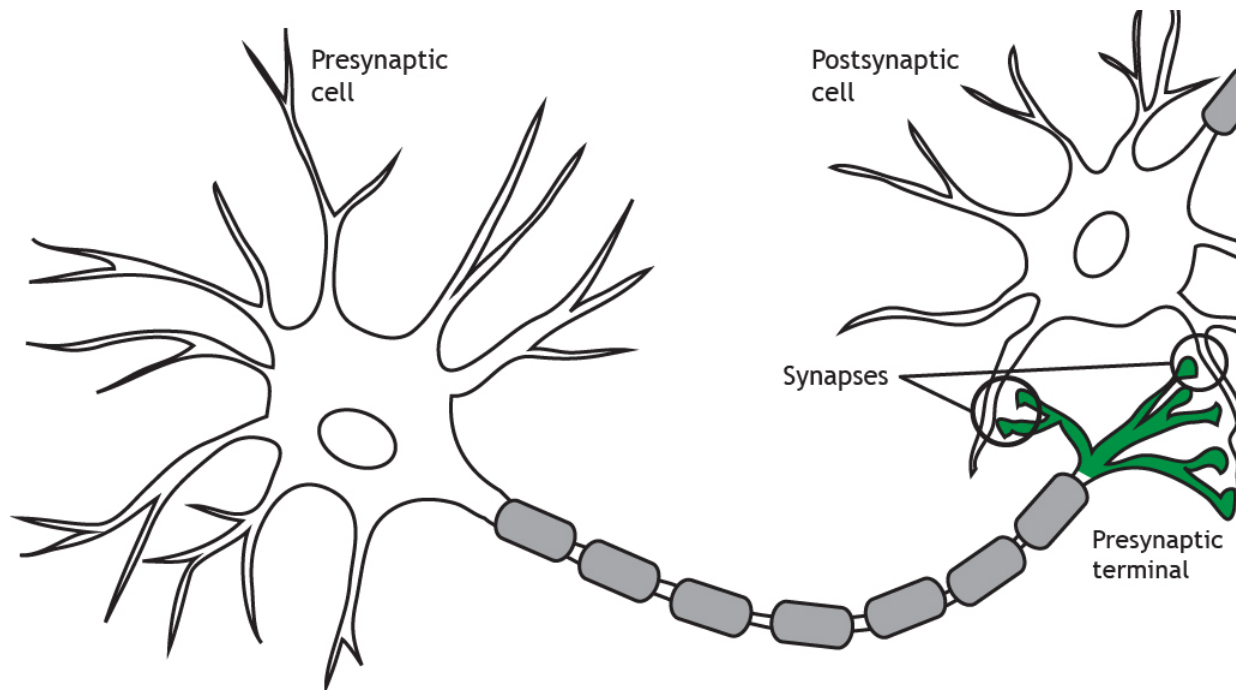


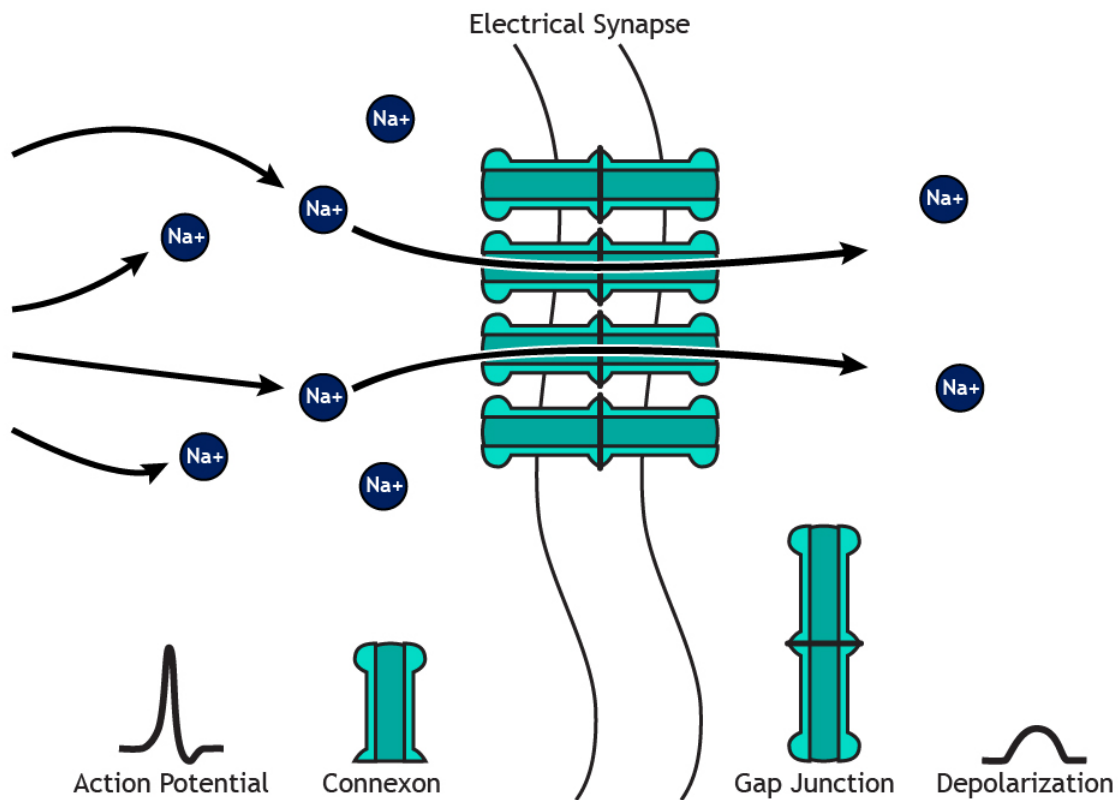
Figure 8.1. The terminal of a presynaptic neuron comes into close contact with a postsynaptic cell at the synapse. 'Synapse' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC BY-NC-SA\) 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

### Synapse Types

There are two types of synapses: electrical and chemical.

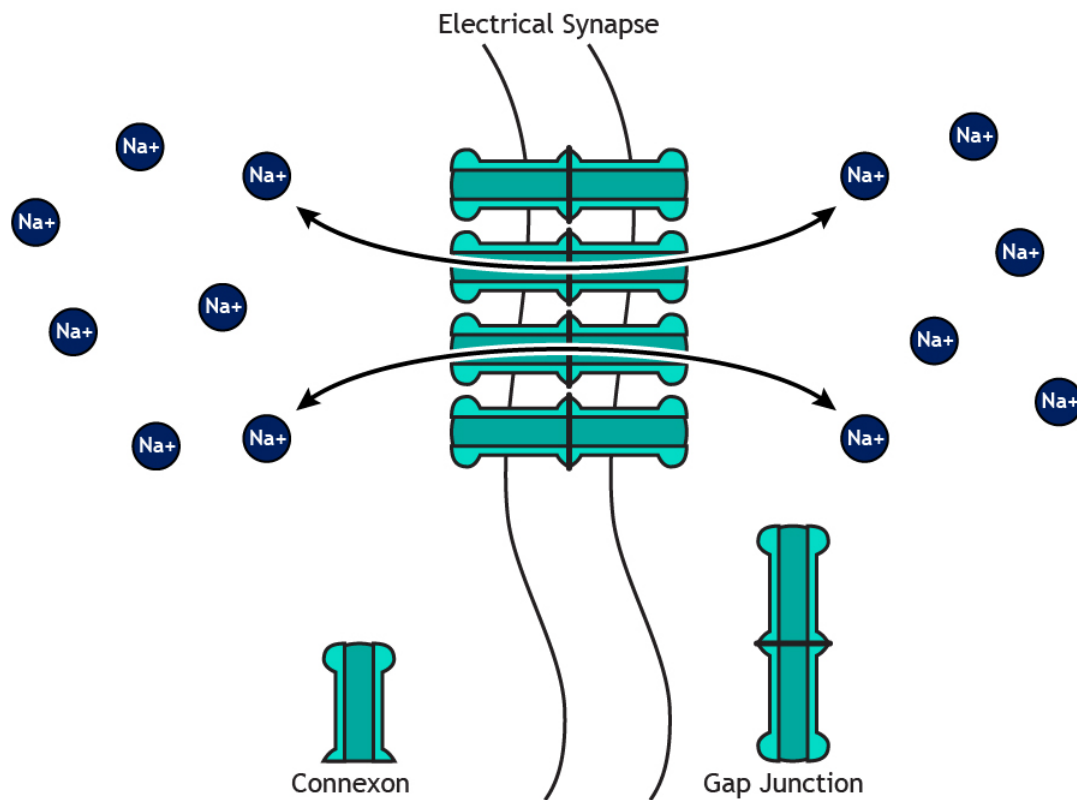
#### Electrical

Electrical synapses are a direct connection between two neurons. Cell membrane proteins called connexons form gap junctions between the neurons. The gap junctions form pores that allow ions to flow between neurons, so as an action potential propagates in the presynaptic neuron, the influx of sodium can move directly into the postsynaptic neuron and depolarize the cell. The response in the postsynaptic cell is almost immediate, with little to no delay between signaling in the pre- and postsynaptic neurons.



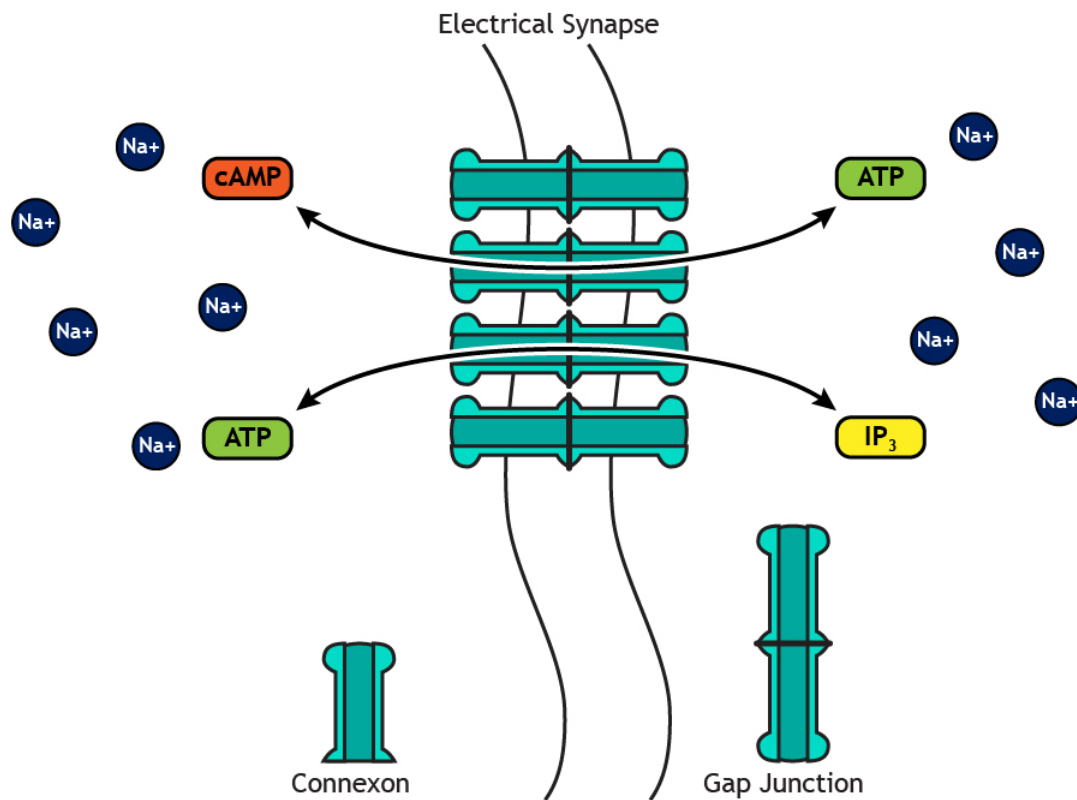
Animation 8.1. Membrane-bound proteins called connexons form gap junctions between presynaptic and postsynaptic neurons. This allows for direct exchange of ions between neurons. An action potential in the presynaptic neuron will cause an immediate depolarization of the postsynaptic membrane because the sodium ions will cross the membrane through the gap junctions. 'Electrical Synapse – Ion Flow' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC BY-NC-SA) 4.0 International License. View static image of animation.

Since the gap junctions allow diffusion of ions without any obstruction, the signal can flow bidirectionally through an electrical synapse. The electrochemical gradients will drive direction of ion flow.



Animation 8.2. Since an electrical synapse is a direct, physical connection between two neurons, ions are able to flow either direction across the gap junction. 'Bidirectional Electrical Synapse' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC BY-NC-SA) 4.0 International License. View static image of animation.

Additionally, small molecules like ATP or second messengers can also move through the gap junctions. These signaling molecules play an important role in cellular mechanisms, which we will see in a later chapter.



Animation 8.3. Gap junctions are large enough to allow the flow of small cellular molecules like ATP or second messengers. 'Electrical Synapse – Small Molecules' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC BY-NC-SA) 4.0 International License. View static image of animation.

### Chemical

Chemical synapses do not form physical connections between the pre- and postsynaptic neurons. Instead, a space called the synaptic cleft exists between the presynaptic terminal and the postsynaptic membrane.

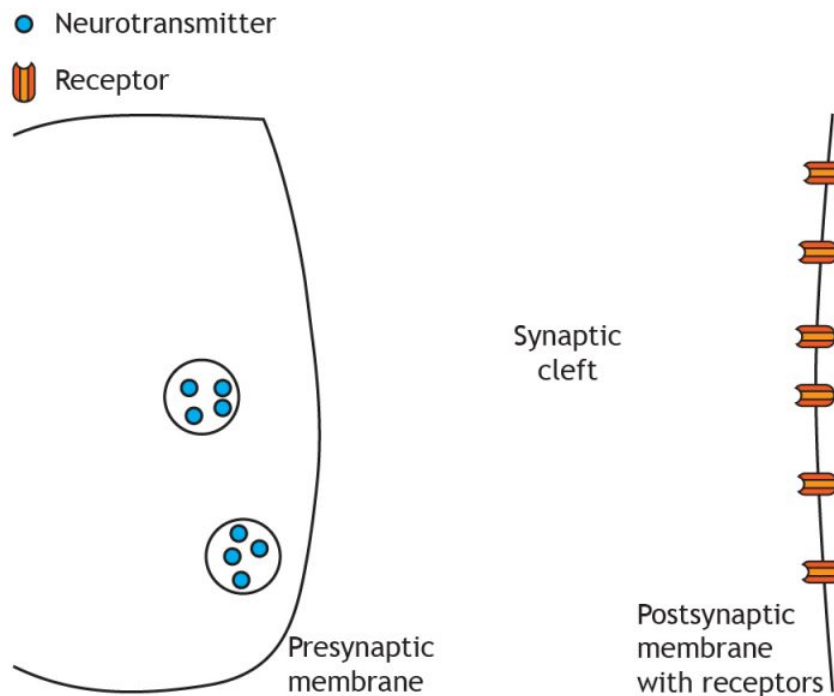
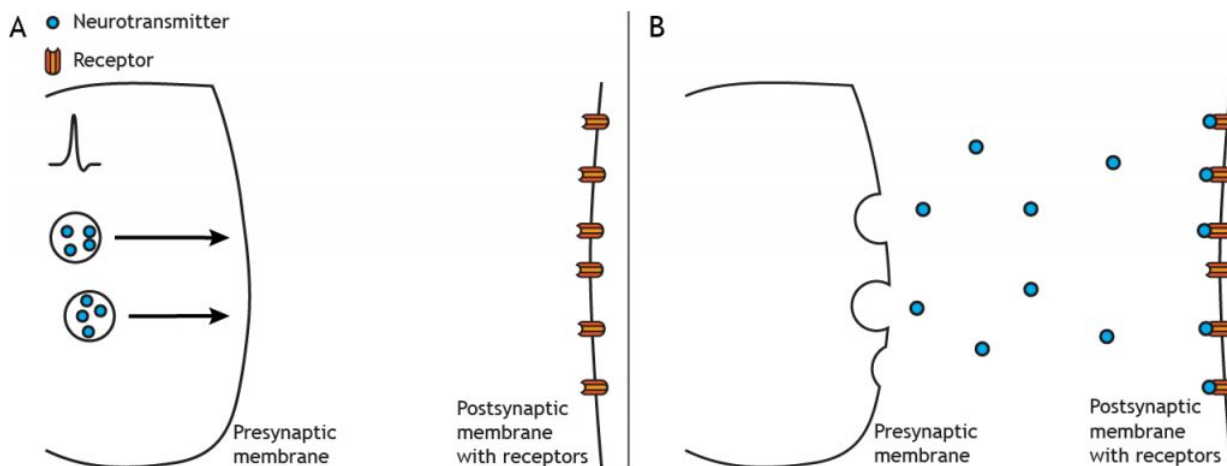


Figure 8.2. A chemical synapse does not make direct contact between the two neurons. The presynaptic terminal and the postsynaptic membrane are separated by the synaptic cleft. Neurotransmitters are stored in the presynaptic cell, and the postsynaptic cell has neurotransmitter receptors in the membrane. 'Chemical Synapse' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC BY-NC-SA\) 4.0 International License](#).

Figure 8.2. A chemical synapse does not make direct contact between the two neurons. The presynaptic terminal and the postsynaptic membrane are separated by the synaptic cleft. Neurotransmitters are stored in the presynaptic cell, and the postsynaptic cell has neurotransmitter receptors in the membrane. 'Chemical Synapse' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC BY-NC-SA\) 4.0 International License](#).

At a chemical synapse, the depolarization of an action potential reaching the presynaptic terminal causes release of neurotransmitters, which act on specialized receptors located in the cell membrane of the postsynaptic neuron. The structure and function of chemical synapses make them slower than electrical synapses and permit signaling in only one direction.



Animation 8.4. An action potential causes release of neurotransmitters from the presynaptic terminal into the synaptic cleft. The transmitters then act on neurotransmitter receptors in the postsynaptic membrane. 'Chemical Synapse – Neurotransmitter Release' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC BY-NC-SA\) 4.0 International License](#). View static image of animation.

## Synapse Location

As we discuss synaptic transmission, we will focus mainly on axodendritic synapses, in which the presynaptic terminal synapses on the dendrites of the postsynaptic cell. But synapses can also be located between the terminal and the cell body of the postsynaptic cell, called axosomatic, or even between the terminal and the axon of the postsynaptic cell, called axoaxonic.

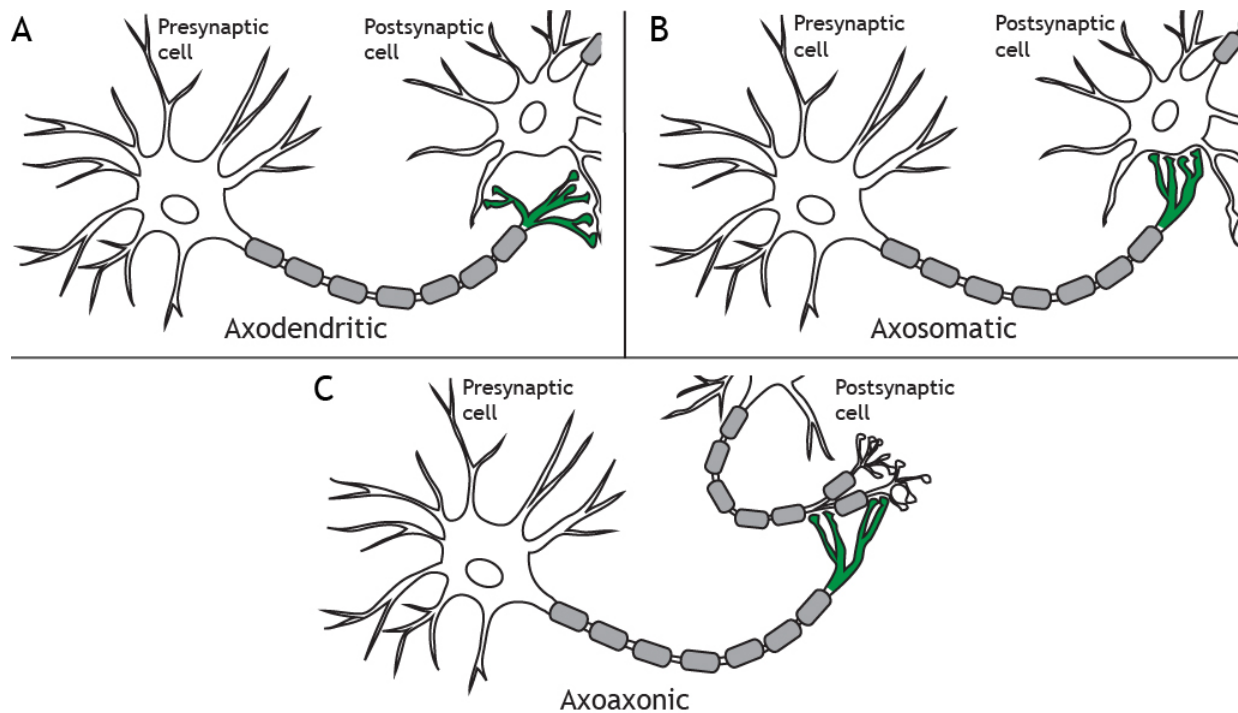


Figure 8.3. A) Axodendritic synapses occur when the presynaptic terminal makes a synaptic connection with the dendrite of a postsynaptic neuron. B) Axosomatic synapses occur when the presynaptic terminal makes a synaptic connection with the cell body of a postsynaptic neuron. C) Axoaxonic synapses occur when the presynaptic terminal makes a synaptic connection with the axon of a postsynaptic neuron. 'Chemical Synapse Types' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC BY-NC-SA) 4.0 International License.

#### Key Takeaways

- Electrical synapses make direct contact between neurons, are faster than chemical synapses, and can be bidirectional
- Chemical synapses form a synaptic cleft between the neurons and are unidirectional
- Synapses can occur between the presynaptic terminal and the postsynaptic dendrites (axodendritic), cell body (axosomatic), or axon (axoaxonic)

#### Test Yourself!

If a research team measures instantaneous transmission of signals between two neurons without any synaptic delay, they are likely recording from an electrical synapse.

☐ False

☐ True

☒ Check



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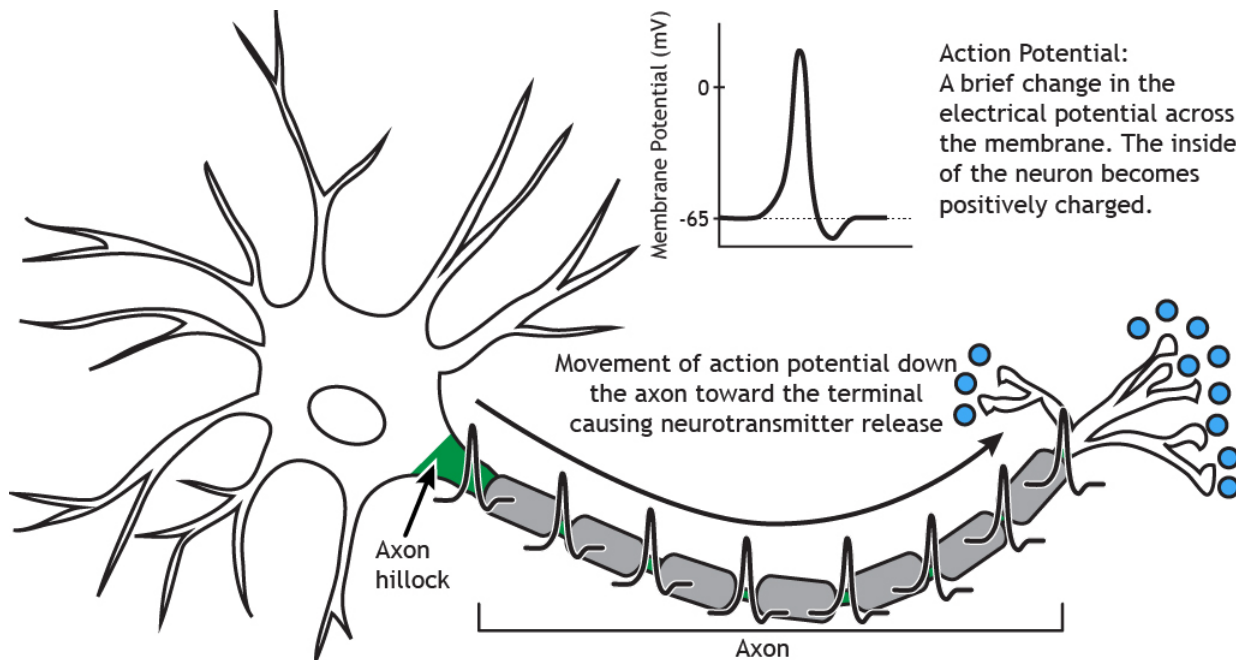
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## 2.2: Neurotransmitter Release

### Action Potential

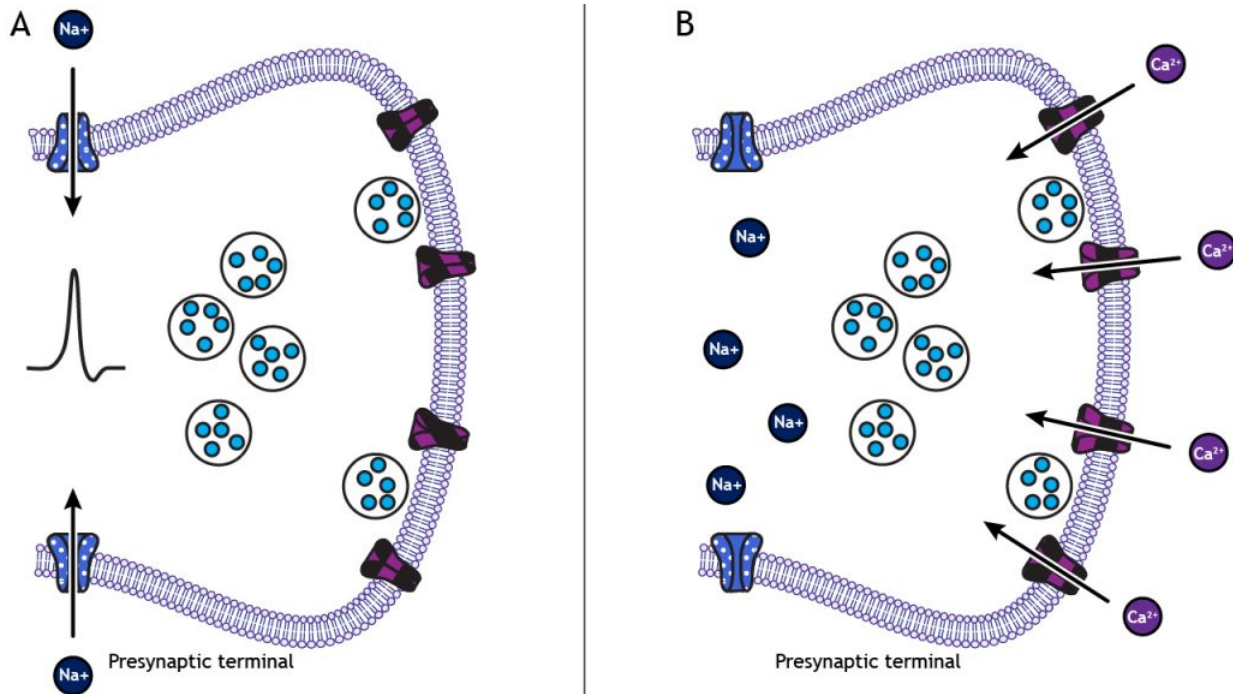
As we have covered, when an action potential propagates down the axon to the presynaptic terminal, the electrical signal will result in a release of chemical neurotransmitters that will communicate with the postsynaptic cell.



Animation 10.1. The action potential is a brief but significant change in electrical potential across the membrane. The membrane potential will move from a negative, resting membrane potential, shown here as -65 mV, and will rapidly become positive and then rapidly return to rest during an action potential. The action potential moves down the axon beginning at the axon hillock. When it reaches the synaptic terminal, it causes the release of chemical neurotransmitter. 'Action Potential Propagation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](#). View static image of animation

### Ion flow in Terminal

When the action potential reaches the terminal, there is an influx of sodium ions. This inward current causes a depolarization of the terminal, activating voltage-gated calcium channels. There is a strong electrochemical gradient that moves calcium into the terminal.



Animation 10.2. An action potential causes an influx of sodium in the terminal. The depolarization opens voltage-gated calcium channels, and calcium ions flow into the terminal down their electrochemical gradient. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. 'Terminal Calcium Influx' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/). View static image of animation.

## Active Zones

The voltage-gated calcium channels are concentrated in the presynaptic terminal at active zones, the regions of the membrane where small molecule neurotransmitters are released. At active zones, some synaptic vesicles are docked and are ready for immediate release upon arrival of the action potential. Other neurotransmitter-filled vesicles remain in a reserve pool outside of the active zone.

Vesicles filled with neuropeptides do not dock at active zones. They are located outside of the active zone, further away from the membrane and the high density of voltage-gated calcium channels and are therefore slower to release than the small molecule transmitters.

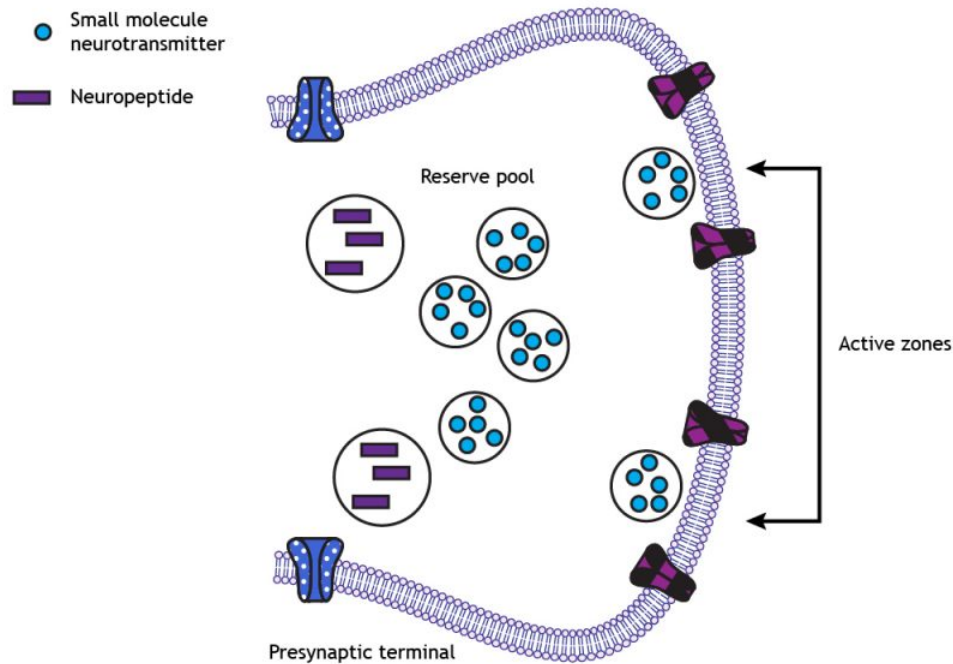


Figure 10.1. Some synaptic vesicles filled with small molecule neurotransmitters dock at active zones on the presynaptic membrane, ready for immediate release. Other synaptic vesicles remain nearby in reserve pools, ready to move into empty active zones. Neuropeptide-filled vesicles do not dock at active zones. The blue, dotted channels represent voltage-gated sodium channels, and the purple, striped channels represent voltage-gated calcium channels. 'Active Zones' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

## Vesicle Docking

Docking of synaptic vesicles packaged with small molecule neurotransmitters occurs through the interaction of three membrane-bound proteins called SNARE proteins. Synaptobrevin is called a v-SNARE because it is located on the Vesicular membrane. Syntaxin and SNAP-25 are called t-SNARES because they are located on the terminal membrane, which is the Target membrane. The interaction of these three proteins leads to vesicle docking at the active zone.

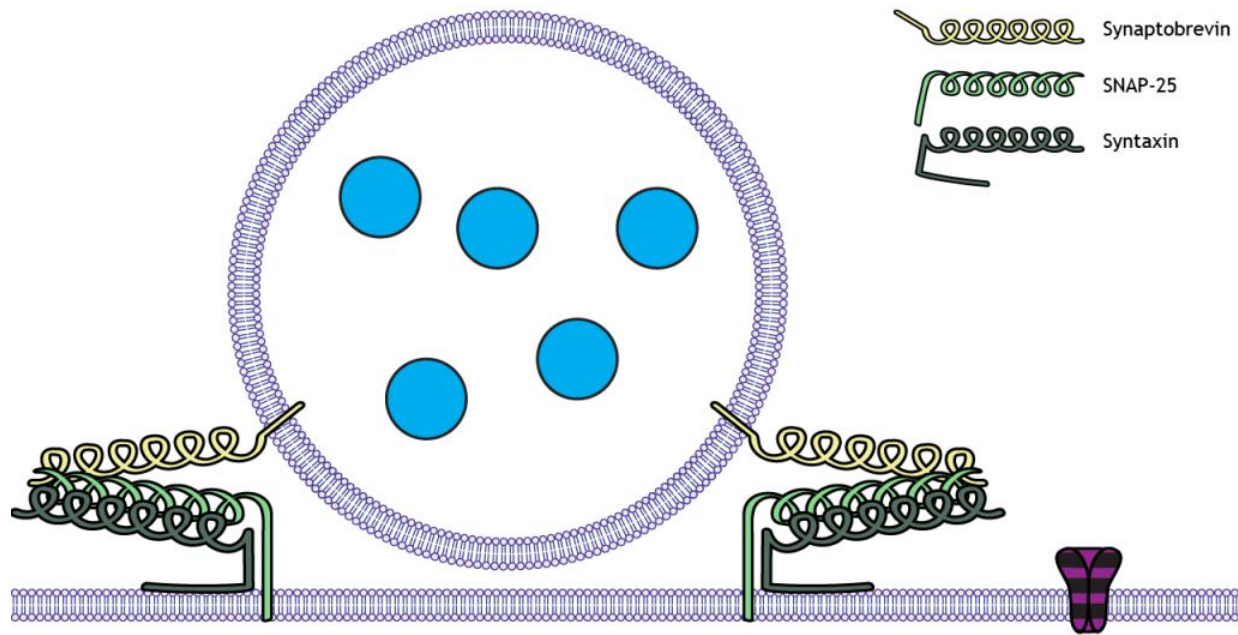
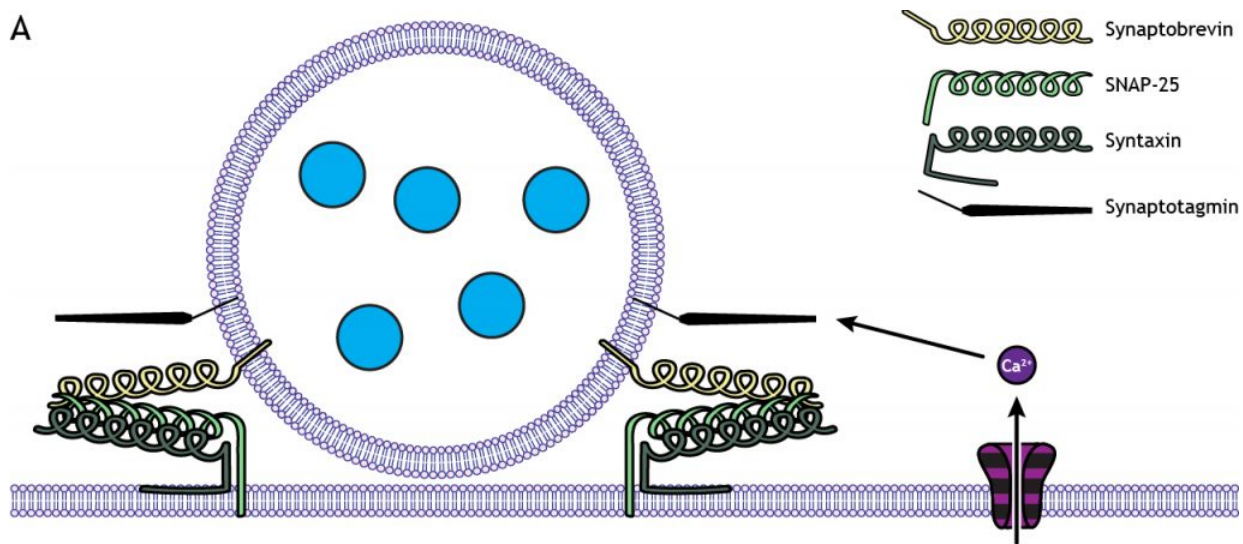


Figure 10.2. Synaptic vesicles filled with small molecule neurotransmitters are able to dock at active zones by the interaction of v- and t-SNARE proteins. Synaptobrevin is embedded in the membrane of the vesicle whereas SNAP-25 and Syntaxin are embedded in the presynaptic terminal membrane. The purple, striped channels represent voltage-gated calcium channels. 'SNARE proteins' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

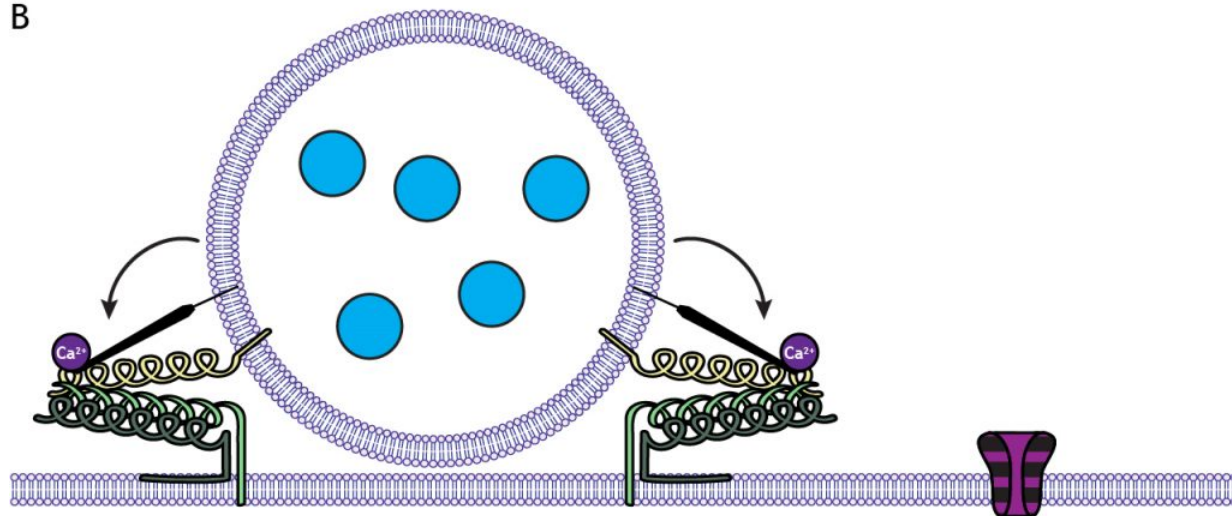
## Exocytosis

The influx of calcium through the voltage-gated calcium channels initiates the exocytosis process that leads to neurotransmitter release. Calcium enters the cell and interacts with another vesicle-bound protein called synaptotagmin. This protein is a calcium sensor, and when calcium is present at the active zone, synaptotagmin interacts with the SNARE proteins. This is the first step toward exocytosis of the synaptic vesicle.

A



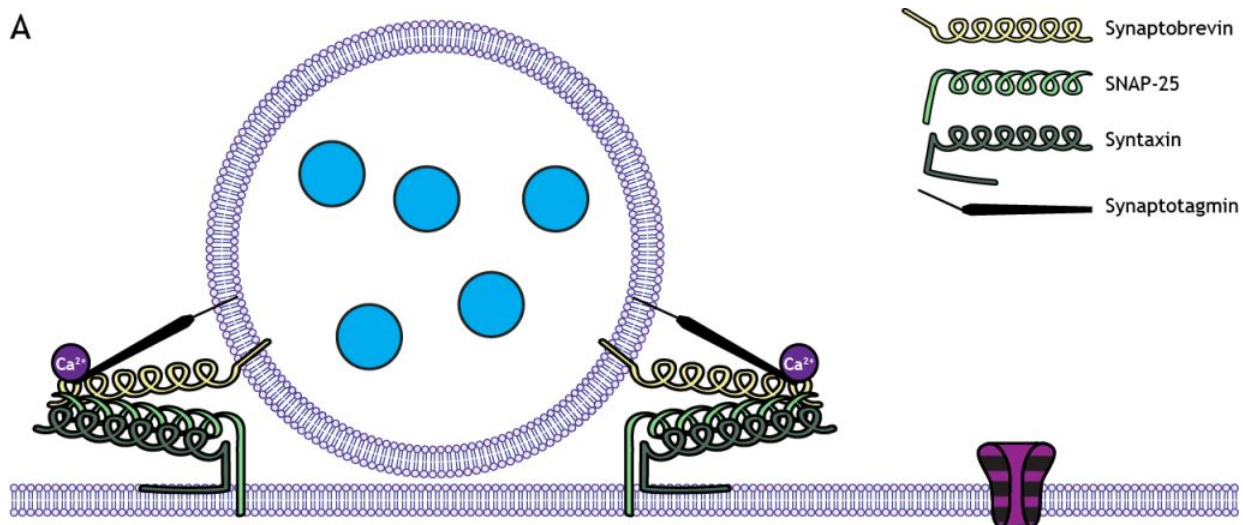
B



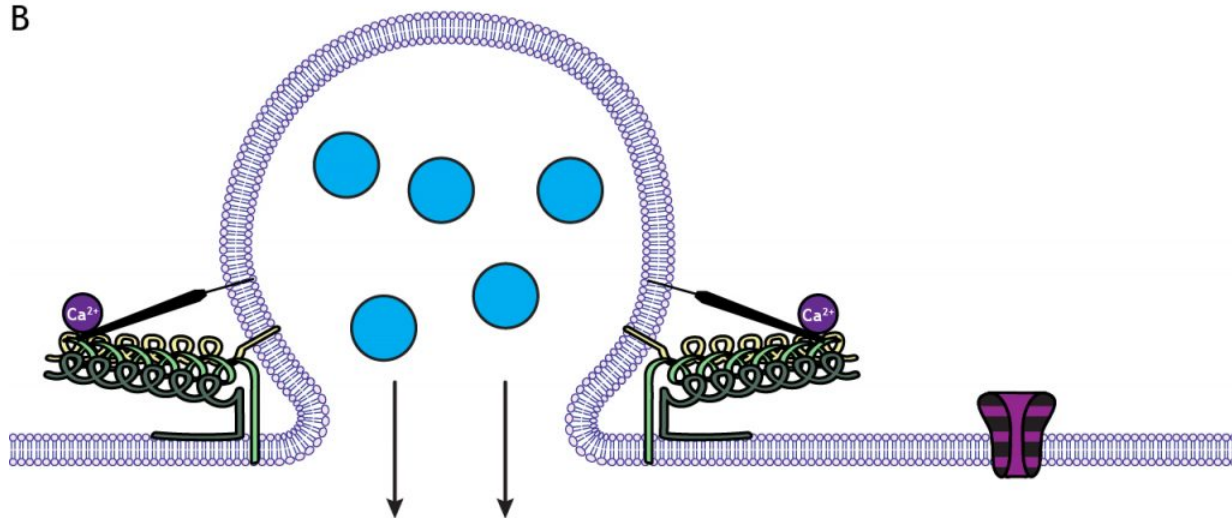
Animation 10.3. Calcium enters the cell when the voltage-gated channels open. In the presence of calcium, synaptotagmin, a protein bound to the vesicular membrane interacts with the SNARE proteins. The purple, striped channels represent voltage-gated calcium channels. 'Synaptotagmin' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License. View static image of animation

Once synaptotagmin interacts with the SNARE proteins, the synaptic vesicle membrane fuses with the presynaptic terminal membrane, exocytosis occurs, and the neurotransmitters released.

A



B



Animation 10.4. Once the synaptotagmin-SNARE protein complex forms, the synaptic vesicle membrane fuses with the terminal membrane, and the neurotransmitters are released into the synaptic cleft through exocytosis. The purple, striped channels represent voltage-gated calcium channels. 'Transmitter Exocytosis' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License. View static image of animation.

## Neurotransmitter Action

After exocytosis of the transmitter molecules, they enter the synaptic cleft and bind to receptors on the postsynaptic membrane. Receptors fall into two main categories: ligand-gated channels and G-protein coupled receptors. The next two chapters cover these receptors.

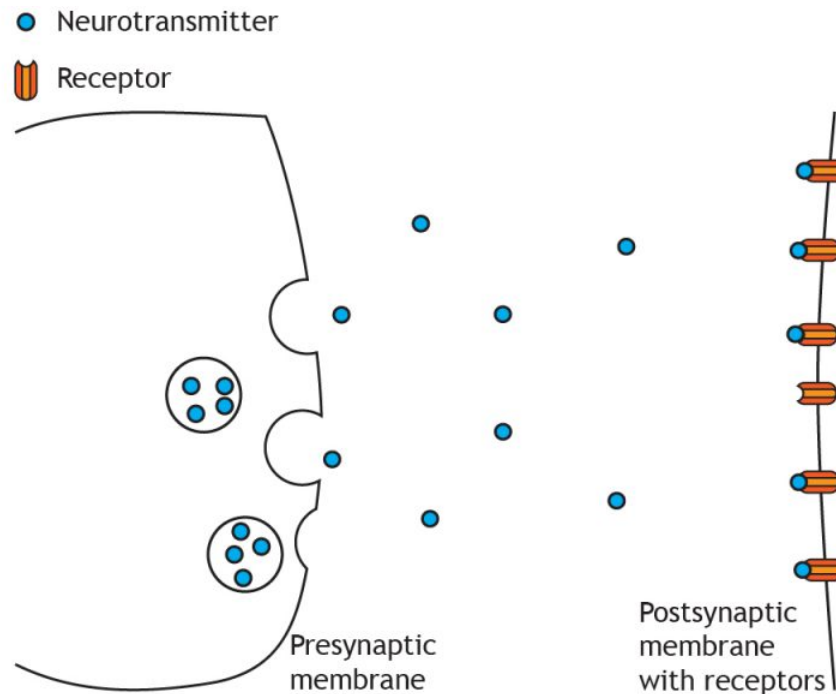


Figure 10.4. After exocytosis of the neurotransmitters into the synaptic cleft, the transmitters bind to receptors present on the postsynaptic membrane. 'Neurotransmitter in Synapse' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

#### Key Takeaways

- Neurotransmitter release is dependent on the influx of calcium into the terminal
- SNARE proteins are important for vesicle docking at active zones and exocytosis
- Synaptotagmin is a calcium sensor

#### Test Yourself!

What drives calcium ions into the presynaptic terminal when channels open?

- ☐ The strong electrochemical gradient for  $\text{Ca}^{2+}$
- ☐ Binding of calcium to vesicles before entering
- ☐ A lower concentration of  $\text{Ca}^{2+}$  outside than inside
- ☐ Active transport pumps pushing  $\text{Ca}^{2+}$  in

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## 2.3: Neurotransmitter Clearance

After neurotransmitters have been released into the synaptic cleft, they act upon postsynaptic receptors, as covered in the previous chapters. That action must be terminated in order for proper neuronal communication to continue. This is accomplished mainly through two processes: neurotransmitter transport and/or degradation. Transport physically removes the neurotransmitter molecule from the synaptic cleft. Degradation breaks down the neurotransmitter molecule by enzyme activity.

### Acetylcholine

Acetylcholine action is terminated by acetylcholinesterase, an enzyme present in the synaptic cleft. Acetylcholinesterase degrades acetylcholine into choline and acetate molecules. Choline is then transported back into the presynaptic terminal and used in the synthesis of new acetylcholine.

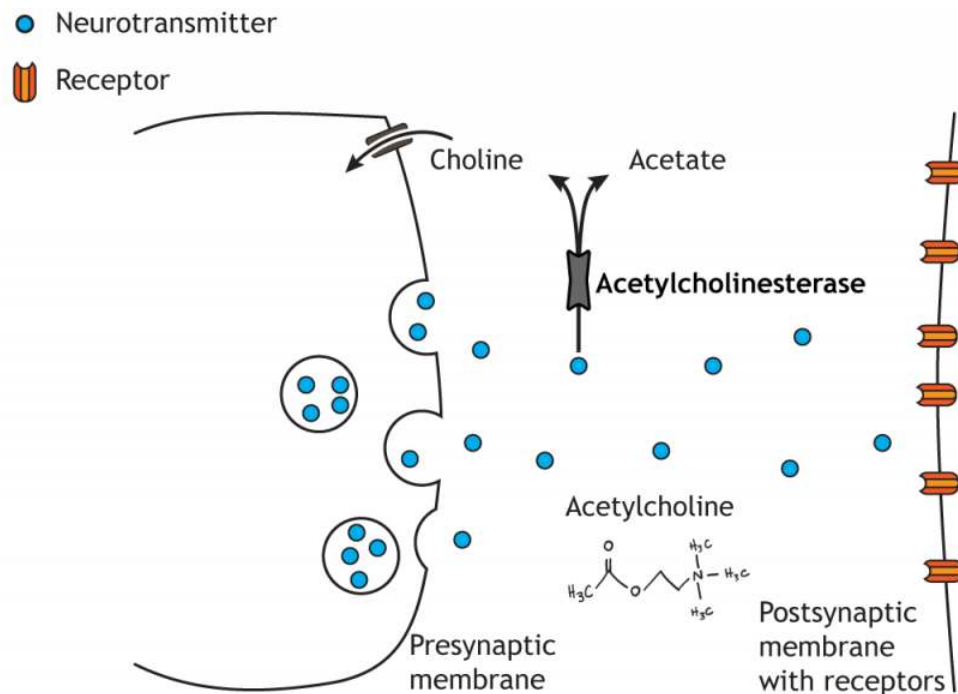


Figure 13.1. Acetylcholine is degraded into choline and acetate within the synaptic cleft via acetylcholinesterase. Choline is then transported back into the presynaptic terminal. 'Acetylcholine Degradation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

### Glutamate

Glutamate action is terminated by two mechanisms. Reuptake of glutamate molecules into the presynaptic terminal can occur, or glutamate can be transported into nearby glial cells. The excitatory amino acid transporters are sodium co-transporters and use the sodium electrochemical gradient to drive neurotransmitter transport. Within glial cells, glutamate is converted into glutamine by glutamine synthetase. Glutamine is then transported out of the glial cell and back into the presynaptic terminal for use in future glutamate synthesis. If glutamate is transported back into the presynaptic terminal, it can be repackaged in synaptic vesicles.

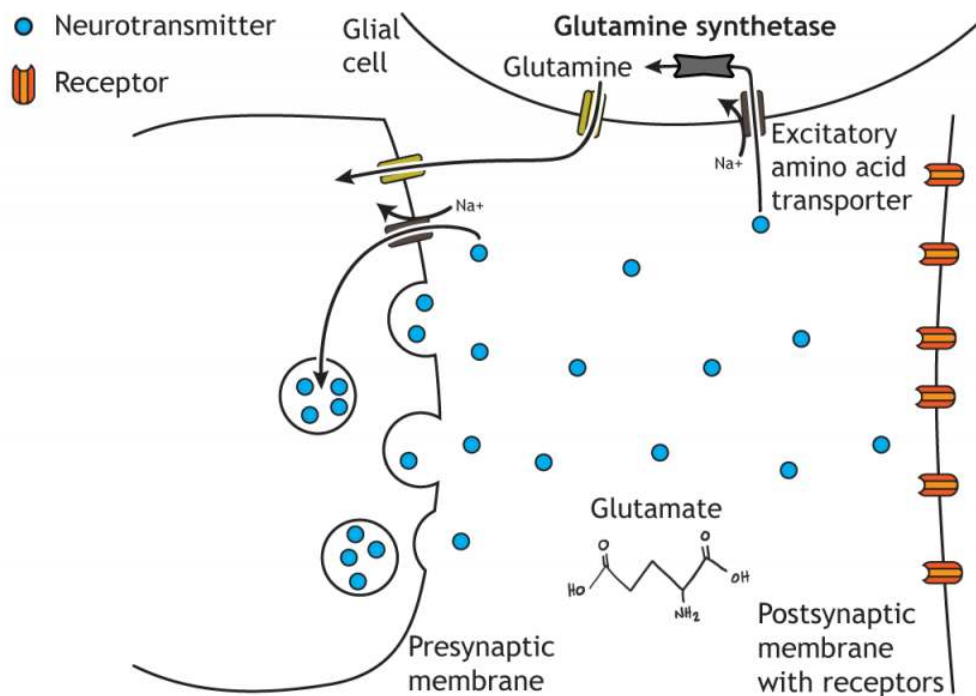


Figure 13.2. Glutamate needs to be removed from the synapse. The excitatory amino acid transporter that uses sodium to drive glutamate movement across the membrane can move glutamate into glial cells or back into the presynaptic terminal. In the terminal, glutamate is repackaged into synaptic vesicles. In the glial cells, glutamate is broken down into glutamine by glutamine synthetase. 'Glutamate Degradation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

## GABA and Glycine

Like glutamate, GABA and glycine action are terminated by either reuptake into the presynaptic terminal and packaging in synaptic vesicles or through transport into glial cells where breakdown can occur. The GABA and glycine transporter also use the sodium electrochemical gradient to drive the movement of the transmitter across the membrane.

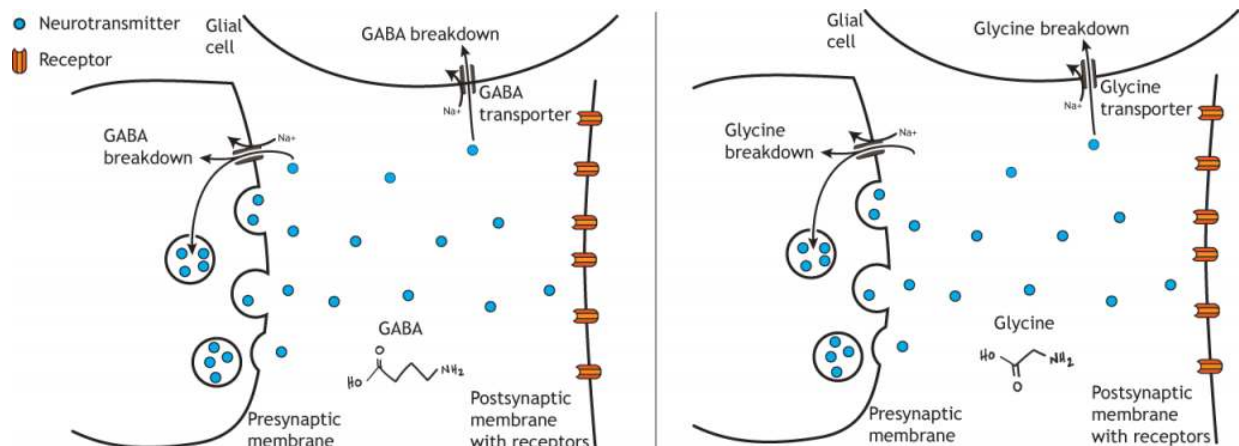


Figure 13.3. GABA and glycine action is terminated by reuptake by sodium co-transporters into either glial cells or back into the presynaptic terminal. In both locations, the neurotransmitters can be broken down by enzymes, whereas in the presynaptic terminal, the transmitters can be repackaged in synaptic vesicles. 'GABA and Glycine Degradation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

## Dopamine

Dopamine action is terminated by reuptake into the presynaptic terminal via the dopamine transporter (DAT). Once inside the cell, dopamine is either degraded via the actions of either monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT), or it is repackaged into vesicles.

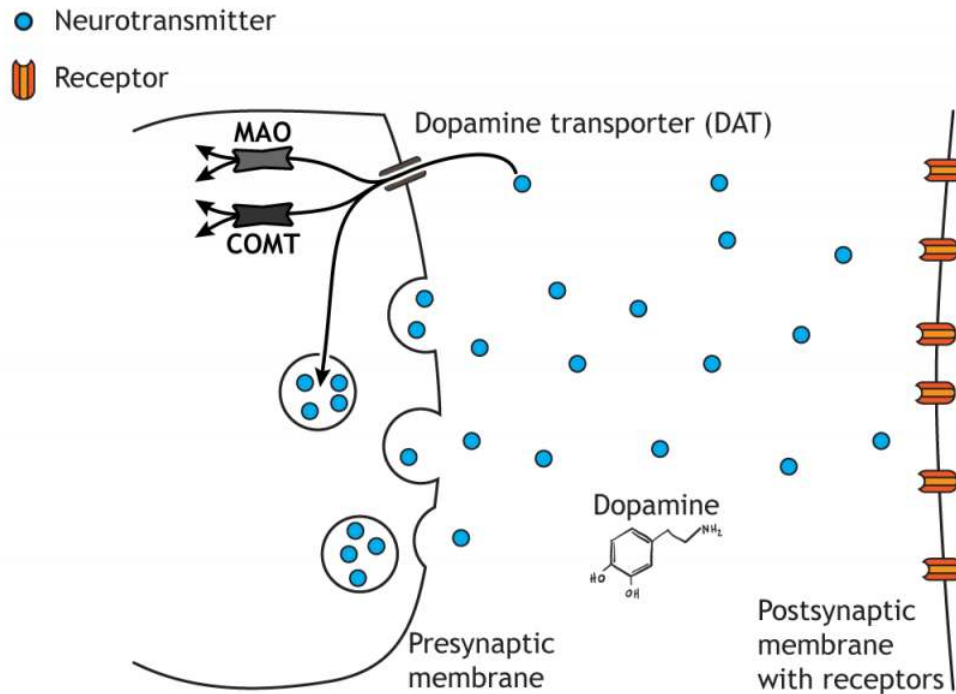


Figure 13.4. Dopamine action is terminated by reuptake into the presynaptic terminal via DAT. Dopamine is then either degraded by MAO or COMT or repackaged into synaptic vesicles. 'Dopamine Degradation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](https://creativecommons.org/licenses/by-nc-sa/4.0/) (CC-BY-NC-SA) 4.0 International License.

## Norepinephrine

Norepinephrine follows the same pathway as dopamine. Reuptake into the presynaptic terminal occurs via the norepinephrine transporter (NET), and then the transmitter is either degraded within the cell by MAO or COMT or repackaged into synaptic vesicles.

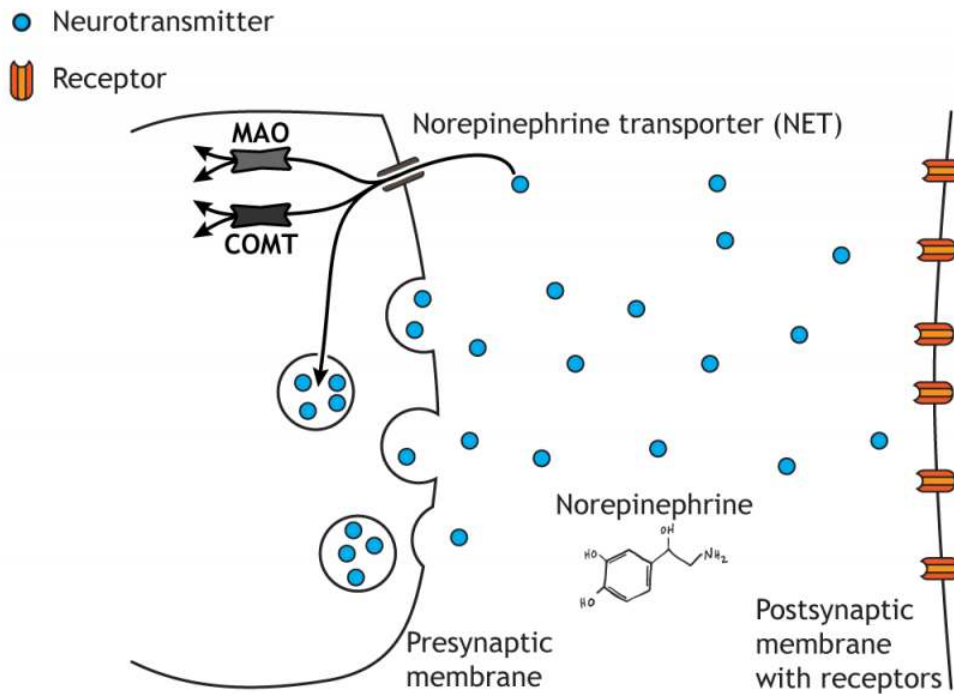


Figure 13.5. Norepinephrine action is terminated by reuptake into the presynaptic terminal via NET. Norepinephrine is then either degraded by MAO or COMT or repackaged into synaptic vesicles. 'Norepinephrine Degradation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike \(CC-BY-NC-SA\) 4.0 International License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

## Serotonin

Like the other monoamines, serotonin is transported back into the presynaptic terminal via the serotonin transporter (SERT). The difference between serotonin and the catecholamines dopamine and norepinephrine is that monoamine oxidase is the only enzyme used for degradation.

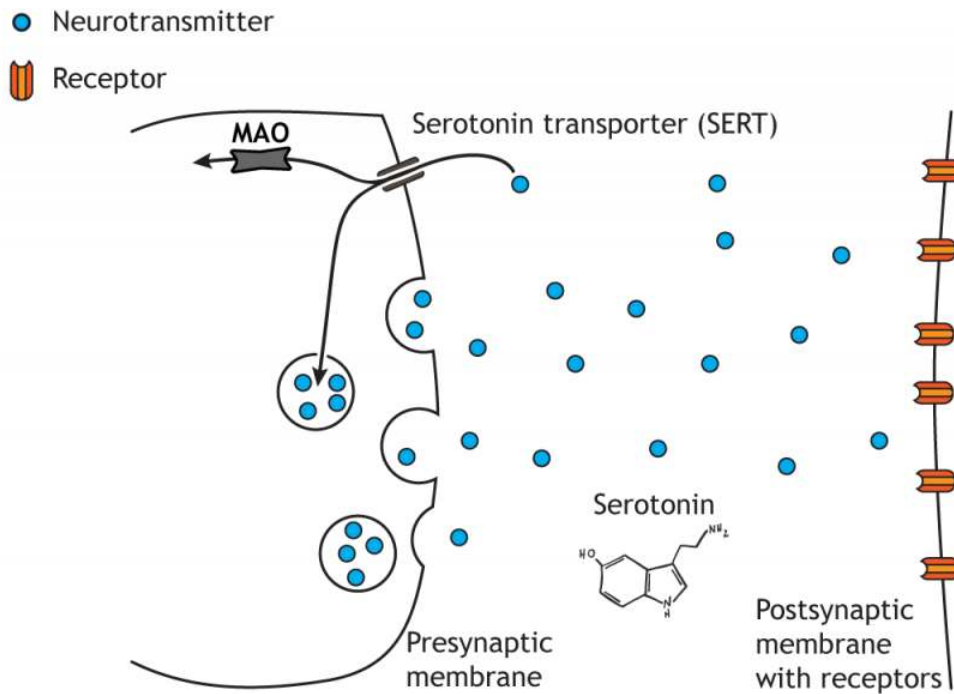


Figure 13.6. Serotonin action is terminated by reuptake into the presynaptic terminal via SERT. Serotonin is then either degraded by MAO or repackaged into synaptic vesicles. 'Serotonin Degradation' by Casey Henley is licensed under a [Creative Commons Attribution Non-Commercial Share-Alike](#) (CC-BY-NC-SA) 4.0 International License.

#### Key Takeaways

- Neurotransmitter action in the synapse must be terminated
- This occurs by either
  - reuptake into the presynaptic terminal where enzymatic degradation or repackaging into vesicles occurs
  - transport into glial cells where enzymatic degradation occurs
  - enzymatic degradation in the synapse

#### Test Yourself!

How does norepinephrine termination compare to dopamine termination?

- ☐ Cannot be repackaged into vesicles
- ☐ No overlap in pathways
- ☐ Follows the same pathway as dopamine
- ☐ Only uses MAO for degradation

✓ Check



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## CHAPTER OVERVIEW

### 3: The Nervous System

[3.1: Nervous System Structure and Terminology](#)

[3.2: The Peripheral Nervous System](#)

[3.3: The Central Nervous System](#)

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## 3.1: Nervous System Structure and Terminology

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### Learning Objectives

1. Describe anatomical position and describe the location of at least two structures using anatomical direction terms
2. Explain the difference between frontal (/coronal), transverse (/horizontal), and sagittal sectional planes
3. Understand the six common divisions of the nervous system
4. List the four major regions of the central nervous system
5. Describe the components of the ventricular system in the brain and spinal cord

### 3.1.1 Overview

This module starts with anatomical position, sectional planes and directional terms and continues with the divisions of the nervous system. Some areas and structures of the central nervous system (brain and spinal cord) are then discussed, including the four major regions, the protective coverings, and the ventricular system.

### 3.1.2 Anatomical Orientation and Directions

#### 3.1.2.1 Anatomical Position

When anatomists or health professionals identify the location of a structure in the human body, they do so in reference to a body in anatomical position. That is, they figure out the location based on the assumption that the body is starting out in anatomical position. Anatomical position for a human is when the human is standing up, facing forward, with arms extended to the sides, and palms facing out, as illustrated by two human models in Figure 3.1.1.



Figure 3.1.1:

Female (left) and male (right) **human body** in anatomical position seen from anterior (upper) and posterior (lower) views.

When referencing a structure that is on one side of the body or the other, we use the terms “anatomical right” and “anatomical left.” Anatomical right means that the structure is on the side that a person in anatomical position would consider their right-hand side (not necessarily on the right of the viewer) and anatomical left means that the structure is the side that a person in anatomical position would consider their left-hand side (which likewise is not necessarily the left side of the viewer.)

### 3.1.2.2 Anatomical Planes

To view the interior of a body, we expose the organs and structures that are visible when that body is cut open along one of three commonly used sectional planes. These planes are the different directions a body is cut to reveal different views of its internal structures.

- **Frontal (or coronal) plane**—A vertical cut that separates the front from the back of the individual/structure.
- **Transverse (or horizontal) plane**—A horizontal cut that separates the top from the bottom of the individual/structure. (May also be called cross-sections.)
- **Sagittal plane**—A vertical cut that separates the left half from the right half of the individual/structure.

- **Midsagittal (or median) plane**—A vertical cut down the exact center line of the individual/structure that separates the left half from the right half.
- **Parasagittal plane**—A vertical cut that is off-center that separates the left of the individual/structure from the right in unequal portions. It does not matter whether it is the left side or the right side that is larger, as long as they are not equal.

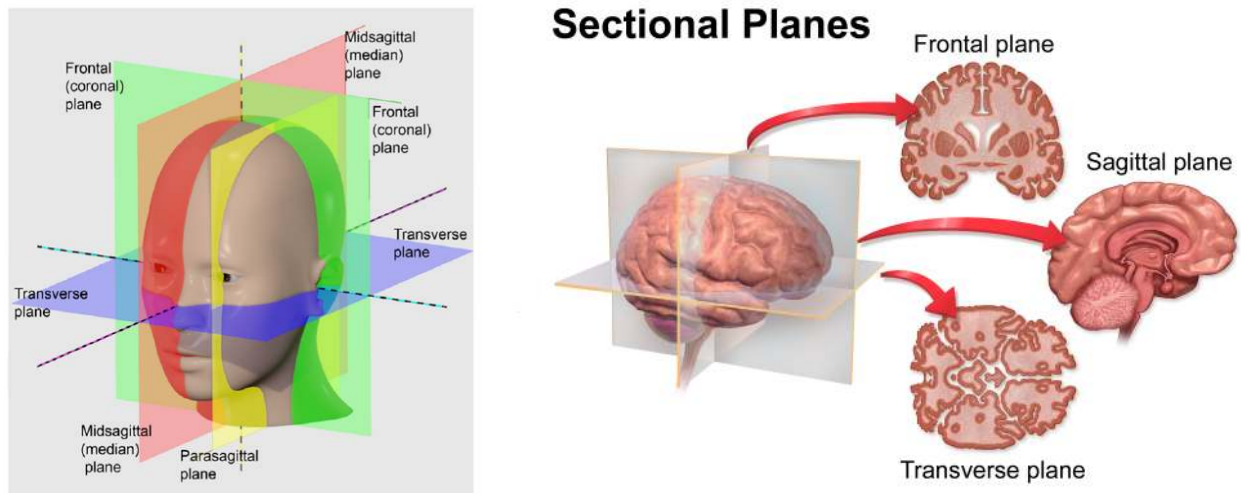


Figure 3.1.2: The different sectional planes used to expose internal structures, and examples of these planes through the human brain.

### 3.1.2.3 Anatomical Directional Terms

To be able to direct others to specific anatomical structures, or to find structures based on someone else's directions, it is useful to have specific pairs of terms that allow you to orient your search with respect to the location of another known structure. The following pairs of terms are used to make comparisons. Each term is used to orient a first structure or feature with respect to the position of a second structure or feature. All of these terms refer to the body in anatomical position, and are illustrated in Figure 3.1.3.

- **Superior/Inferior**—Equivalent to above (superior) versus below (inferior) when moving along the long axis of the body. A structure that is superior to another is above the second structure. A feature that is inferior to another is below the second feature.
- **Proximal/Distal**—Equivalent to near (proximal) versus far (distal). Usually used to orient the positions of structures and features along the limbs with respect to the trunk of the body. A feature that is proximal to something else is closer to the limb's point of attachment to the trunk. A structure that is distal to something else is farther away from the limb's point of attachment. Although less precise, these terms are occasionally used in the trunk of the body itself to indicate whether something is closer to (proximal) or farther away from (distal) something else.
- **Medial/Lateral**—Equivalent to towards the middle (medial) versus towards the edge (lateral). These terms are used with respect to the midline of the trunk of the body. A structure that is medial to another is closer to the midline of the body's trunk. A feature that is lateral to another is farther away from the midline of the trunk.
- **Anterior/Posterior**—Equivalent to the front (anterior) versus the back (posterior) of the body. A structure that is anterior to another is closer to the front of the body. A feature that is posterior to another is closer to the back of the body.
- **Ventral/Dorsal**—Equivalent to belly-side (ventral) versus back-side (dorsal) of the body. For a human in anatomical position, this pair of terms is largely equivalent to anterior versus posterior. However, for the head and brain, dorsal is on the top (superior) and ventral is on the bottom (inferior), whereas the front of the face would be anterior and the back of the head would be posterior. These terms match four-legged animals in what is considered their anatomical position, where the belly-side is not equivalent to the front of the animal. A structure below the human head that is ventral to another is closer to the belly-side of the body, whereas a feature that is dorsal to another is closer to the back of the body.
- **Superficial/Deep**—Equivalent to closer to the surface (superficial) versus farther from the surface (deep). A structure that is superficial to another is closer to the surface of the body. A feature that is deep to another is farther from the surface of the body.
- **(Cephalic/Caudal)**—Equivalent to closer to the head (cephalic) versus closer to the tail (caudal). These terms are more useful for four-legged animals with tails than for upright humans with only a few vestigial tail bones and no visible tail- an area which is

also not at the end of the body like the tail is in four-legged animals.)

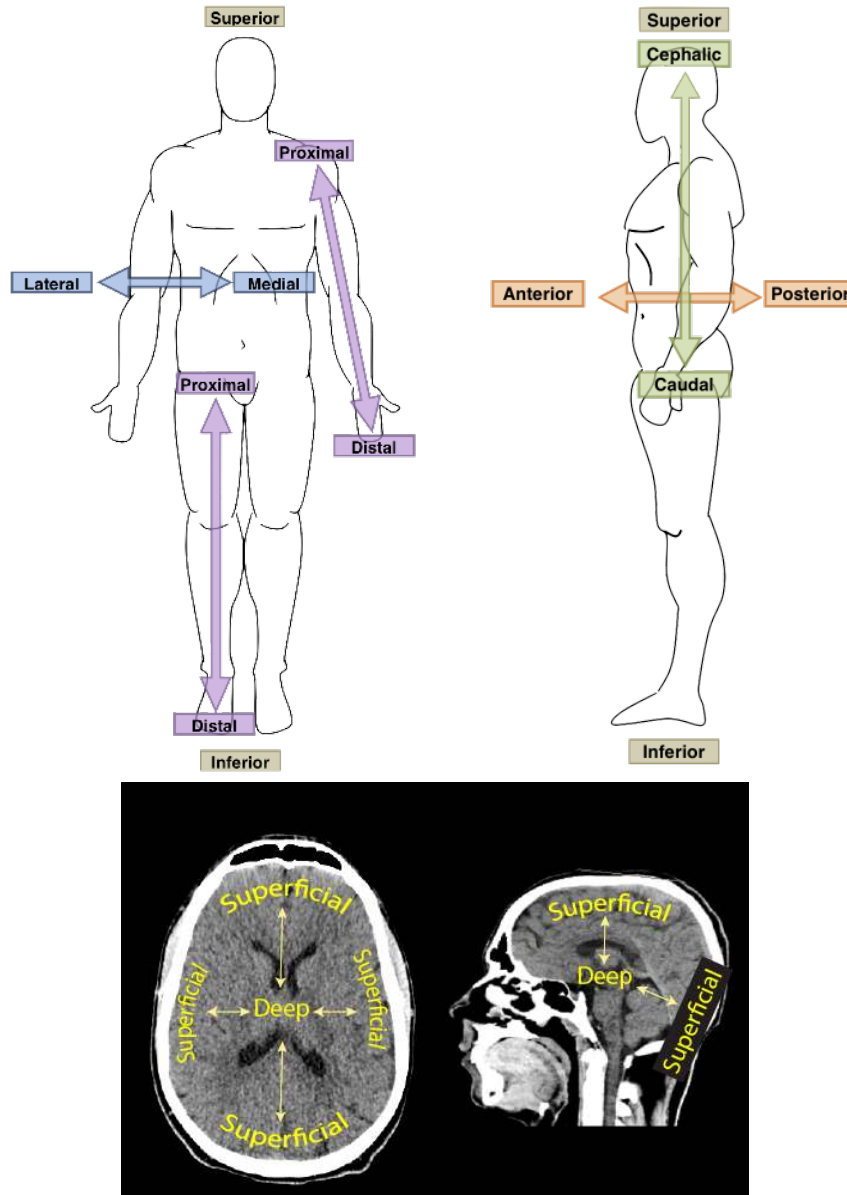


Figure 3.1.3: Pairs of terms providing anatomical direction or orientation, shown on body outlines in the first image, and in a cross-section (left) and sagittal section (right) of the brain in the second image.

### 3.1.3 Organization of the Nervous System

As you might predict, the human nervous system is very complex. It has multiple divisions, beginning with its two main parts, the **central nervous system** (CNS) and the **peripheral nervous system** (PNS), as shown in Figure 3.1.4. The CNS includes the brain and spinal cord, and the PNS consists of all other nervous tissue in the body- mainly nerves, which are bundles of axons from sensory and motor neurons. The nerves of the PNS connect the CNS to the rest of the body.

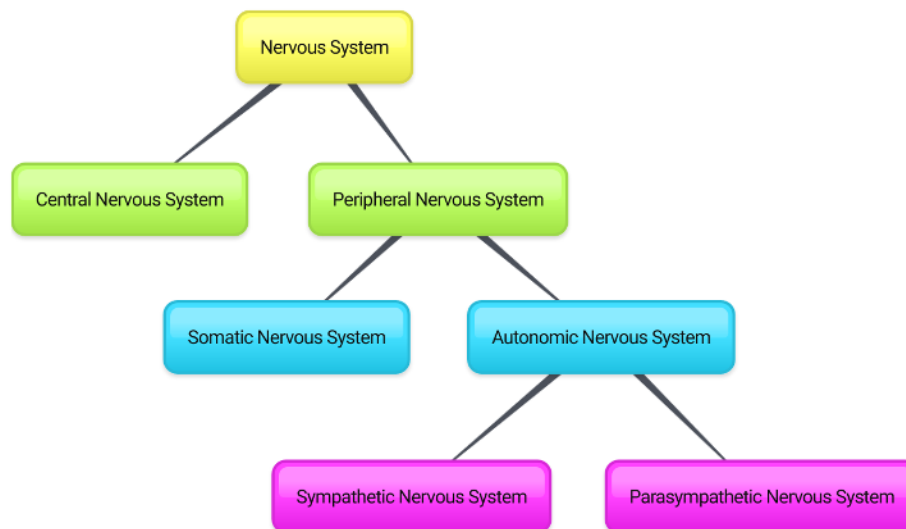


Figure 3.1.4: This concept map illustrates that the nervous system is divided into the central and peripheral systems. The peripheral nervous system is further divided into the somatic and autonomic systems. The autonomic nervous system is further divided into the sympathetic and parasympathetic systems.

The PNS is divided into two major parts, called the autonomic and somatic nervous systems. The **somatic nervous system** (SNS) is responsible for activities that are under voluntary control and awareness, such as turning a steering wheel or feeling water splashing on your hands. The **autonomic nervous system** (ANS) controls involuntary activities, such as digesting a meal or regulating your heartbeat. The autonomic nervous system also has two divisions: the sympathetic and parasympathetic nervous systems. The **sympathetic nervous system** controls the "fight-or-flight" response during emergencies, and the **parasympathetic nervous system** controls the routine "housekeeping" functions of the body (sometimes referred to as the "rest and digest" division). Generally speaking, your body is usually activating a balance of sympathetic and parasympathetic functions.

The CNS and the sympathetic and parasympathetic branches of the ANS (itself a division of the PNS) are described in greater detail in other modules of this chapter. The other division of the PNS, the SNS, is composed largely of sensory receptors and their connections (covered in the sensory system chapter) and structures related to voluntary motor control (addressed in the movement chapter).

### 3.1.4 Summary

Anatomical position for humans is standing up, facing forward, with arms extended to the sides, and palms facing out. Anatomical planes are the different directions a body is cut to reveal different views of its internal structures, which include frontal (coronal) planes, separating the front from the back, transverse (horizontal) planes, separating the top from the bottom, and sagittal planes, separating the left and right halves. A midsagittal (or median) plane is exactly on the center line and a parasagittal plane divides the left and right halves unevenly. Pairs of anatomical directional terms are used to make comparisons between one structure with respect to the position of a second structure. These include superior (above) versus inferior (below), proximal (near) versus distal (far), medial (towards the middle) versus lateral (towards the edge), anterior (front) versus posterior (back), ventral (belly-side) versus dorsal (back-side), and superficial (closer to the surface) versus deep (farther from the surface).

The organization of the nervous system includes six divisions. The CNS includes the brain and spinal cord, and the PNS consists of all other nervous tissue in the body. The nerves of the PNS connect the CNS to the rest of the body. The PNS is further divided into the autonomic and somatic nervous systems. The somatic nervous system (SNS) is responsible for activities that are under voluntary control and awareness. The autonomic nervous system (ANS) controls involuntary activities. The autonomic nervous system also has two divisions: the sympathetic and parasympathetic nervous systems. The sympathetic nervous system controls response during emergencies, and the parasympathetic nervous system controls the routine functions of the body.

### 3.1.5 References

Basinger H., & Hogg, J.P. (2021) Neuroanatomy, Brainstem. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK544297/>

### 3.1.6 Additional Resources

If you are curious about anatomical terms used to describe different areas of the body, see "Anatomical Vocabulary" on: "[Anatomical Position and Planes](#)" by LibreTexts, licensed under CC BY-SA .

For more detail on the embryological development of the brain and the primary and secondary brain vesicles, see: "[The Embryologic Perspective](#)" by OpenStax, LibreTexts, licensed under CC BY .

For more detail on the meninges and the ventricles, see: "[Support and Protection of the Brain](#)" by Whitney Menefee, Julie Jenks, Chiara Mazzasette, & Kim-Leiloni Nguyen, LibreTexts, licensed under CC BY and "[Circulation and the Central Nervous System](#)" by OpenStax, LibreTexts, licensed under CC BY .

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## 3.2: The Peripheral Nervous System

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the [ASCSC](mailto:ascsc.org) OERI ([oeri@ascsc.org](mailto:oeri@ascsc.org)).

### Learning Objectives

1. Describe the structures found in the PNS
2. Distinguish between somatic and autonomic structures
3. Explain the functions of the sympathetic and parasympathetic divisions of the autonomic system

### 3.2.1 Overview

This module discusses the peripheral nervous system (PNS) in greater depth, including nervous tissues, the two major systems the PNS divides into (the somatic nervous system and the autonomic nervous system), names and functions of the twelve cranial nerves, and characteristics of the 31 pairs of spinal nerves. The subdivisions of the autonomic nervous system (the sympathetic nervous system and the parasympathetic nervous system) and their functions are also covered, as well as a brief mention of disorders of the PNS.

### 3.2.2 What Is the Peripheral Nervous System?

The **peripheral nervous system (PNS)** consists of all the nervous tissue that lies outside of the central nervous system (CNS). The main function of the PNS is to connect the CNS to the rest of the organism. It serves as a communication relay, going back and forth between the CNS and muscles, organs, and glands throughout the body. Figure 3.2.1 illustrates both the central and peripheral nervous systems, including many representative **spinal nerves**. Although an overview of spinal nerves is discussed in greater detail below, the identification and functions of specific spinal nerves are beyond the scope of this section.

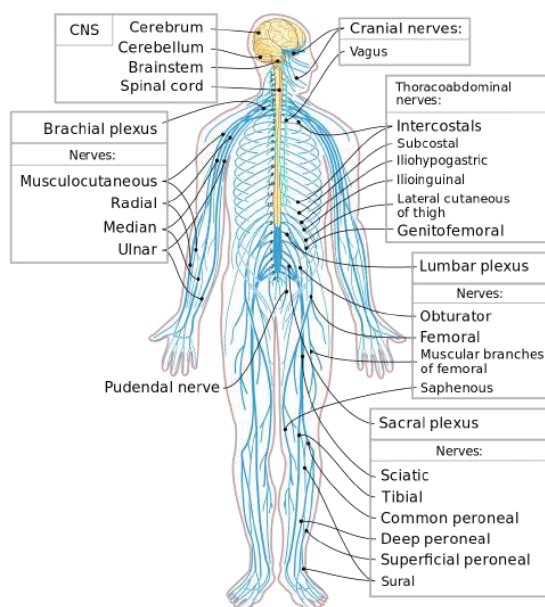


Figure 3.2.1: The central nervous system (CNS) is shown in yellow: Cerebrum, Cerebellum, Brainstem, Spinal cord. Some representative nerves of the peripheral nervous system (PNS) are shown in blue.

The representative nerves pictured are Cranial nerves: Vagus. Brachial plexus nerves: Musculocutaneous, Radial, Median, Ulnar; Thoracoabdominal nerves: Intercostals, Subcostal, Iliohypogastric, Ilioinguinal, Lateral cutaneous of thigh, Genitofemoral; Lumbar plexus nerves: Obturator, Femoral, Muscular branches of femoral, Saphenous; Sacral plexus nerves: Sciatic, Tibial, Common peroneal, Deep peroneal, Superficial peroneal, Sural. The Pudendal nerve is also pictured.

### 3.2.3 Tissues of the Peripheral Nervous System

The primary structures that make up the PNS are nerves and ganglia. Ganglia are clusters of neuron cell bodies outside the CNS; they act as relay points for messages transmitted through nerves of the PNS. Nerves are cable-like bundles of axons that make up the majority of PNS tissues. Nerves are generally classified based on the type of information they carry (which coincides with the direction in which their nerve impulses travel) as sensory, motor, or mixed nerves. See an example of a sensory and motor nerve in Figure 3.2.2. (Note that the interneuron that is usually located between the sensory and motor neuron is not shown in this figure.)

- **Sensory nerves** transmit information from sensory receptors in the body to the CNS. Sensory nerves are also called afferent nerves.
- **Motor nerves** transmit information from the CNS to muscles, organs, and glands. Motor nerves are also called efferent nerves.
- **Mixed nerves** contain axons from both sensory and motor neurons, so they transmit information in both directions and have both afferent and efferent functions.

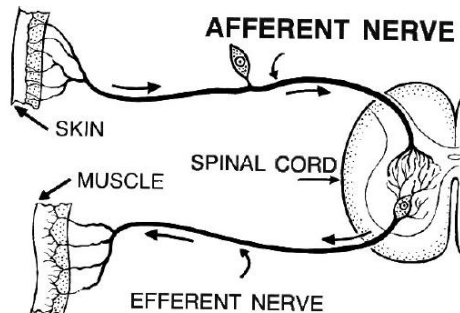


Figure 3.2.2: A sensory nerve is an afferent nerve. The one pictured here sends nerve impulses from sensory receptors in the skin to the CNS. A motor nerve is an efferent nerve. This one sends nerve impulses from the CNS to a muscle.

### 3.2.4 Divisions of the Peripheral Nervous System

The PNS is divided into two major systems, called the autonomic nervous system and the somatic nervous system. Both systems of the PNS interact with the CNS and include sensory and motor neurons, but they use different circuits of nerves and ganglia.

#### 3.2.4.1 Somatic Nervous System

The **somatic nervous system** primarily senses the external environment and controls voluntary activities for which decisions and commands come from the cerebral cortex of the brain. For example, when you feel too cold, decide to turn on the heater, and walk across the room to the thermostat, you are using your somatic nervous system. In general, the somatic nervous system is responsible for all of your conscious perceptions of the outside world, and all of the voluntary motor activities you perform in response. Whether it's playing piano, driving a car, or playing basketball, you can thank your somatic nervous system for making it possible. Structurally, the somatic nervous system consists of 12 pairs of cranial nerves and 31 pairs of spinal nerves.

#### 3.2.4.2 Autonomic Nervous System

The **autonomic nervous system** primarily senses the internal environment and controls involuntary activities. It is responsible for monitoring conditions in the internal environment and bringing about appropriate changes in them. In general, the autonomic nervous system is responsible for all the activities that go on inside your body without your conscious awareness or voluntary participation.

Structurally, the autonomic nervous system consists of sensory and motor nerves that run between the CNS (especially the hypothalamus in the brain) and internal organs (such as the heart, lungs, and digestive organs) and glands (such as the pancreas and sweat glands). Sensory neurons in the autonomic system detect internal body conditions and send messages to the brain. Motor nerves in the autonomic system function by controlling the contractions of smooth or cardiac muscle or glandular tissue. For example, when sensory nerves of the autonomic system detect a rise in body temperature, motor nerves signal both the smooth muscles in blood vessels near the body surface to undergo vasodilation, and the sweat glands in the skin to secrete more sweat, to cool the body.

The autonomic nervous system, in turn, has two subdivisions: the sympathetic division and parasympathetic division. The functions of the two subdivisions of the autonomic system are summarized in Figure 3.2.5. Both affect most of the same organs and glands, but they generally do so in opposite ways.

- The **sympathetic division** controls the fight-or-flight response. Changes occur in organs and glands throughout the body that prepare the body to fight or flee in response to a perceived danger. For example, the pupils dilate, saliva production decreases, air passages in the lungs become wider (the bronchia dilate), heart rate speeds up, more blood flows to the skeletal muscles, and the digestive system temporarily shuts down. With regard to urinary and sexual functions, the sympathetic division relaxes the urinary bladder and stimulates orgasm in both men and women.
- The **parasympathetic division** returns the body to normal after the fight-or-flight response has occurred. For example, pupils constrict, saliva production increases, air passages in the lungs narrow (the bronchia constrict), heart rate slows down, blood flow to the skeletal muscles is reduced, and the digestive system is stimulated to start working again. The parasympathetic division also maintains the internal homeostasis of the body at other times. With regard to urinary and sexual functions, the parasympathetic division constricts the urinary bladder and stimulates genital tissue erection in both men and women.

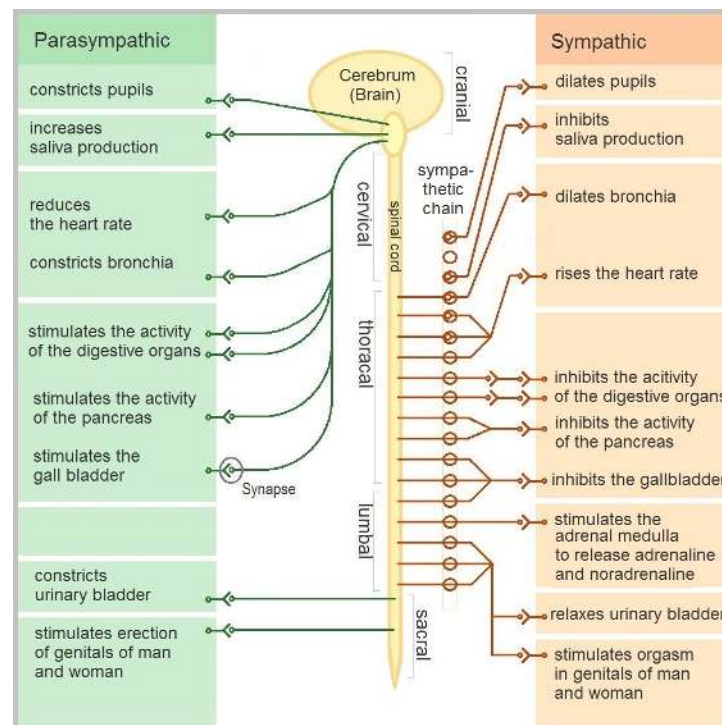


Figure 3.2.7: This diagram summarizes the structures and functions controlled by the parasympathetic and sympathetic divisions of the autonomic nervous system. The image shows how eyes, salivary gland, heart rate, bronchi, digestive system, bladder, and genitalia are affected in opposite ways by the two systems.

### 3.2.5 Disorders of the Peripheral Nervous System

Unlike the CNS, which is protected by bones, meninges, and cerebrospinal fluid (CSF), the PNS has no such protections. The PNS also has no blood-brain barrier to protect it from toxins and pathogens in the blood. Therefore, the PNS is more subject to injury and disease than is the CNS. Causes of nerve injury include diabetes, infectious diseases such as shingles, and poisoning by toxins such as heavy metals. Disorders of the PNS often have symptoms such as loss of feeling, tingling, burning sensations, or muscle weakness. If a traumatic injury results in a nerve being transected (cut all the way through), it may regenerate, but this is a very slow process and may take many months.

### 3.2.6 Summary

The peripheral nervous system (PNS) is composed of the groups of neurons (ganglia) and bundles of axons (nerves) that are outside of the brain and spinal cord. The PNS connects the CNS to the rest of the body.

Sensory (/afferent) nerves transmit information from sensory receptors in the body to the CNS. Motor (/efferent) transmit information from the CNS to muscles, organs, and glands. Mixed nerves transmit information in both directions and have both sensory (/afferent) and motor (/efferent) functions. The PNS is divided into the autonomic nervous system and the somatic nervous system.

The autonomic nervous system senses the internal environment and controls involuntary activities. It is divided into the sympathetic division and parasympathetic division. Both affect most of the same organs and glands, but in opposite ways. The sympathetic division controls the fight-or-flight response and the parasympathetic division returns the body to normal after the fight-or-flight response has occurred.

The PNS does not have the same protections (bones, meninges, CSF, blood-brain barrier) that the CNS has, so it is more prone to injury and disease. If a nerve is transacted, it may regenerate, but this is a very slow process.

### 3.2.7 Additional Resources

Interested in the effects of meditation on the brain? See [Integrative and Contemplative Neuroscience](#)

Mindfulness techniques have been shown to reduce symptoms of depression as well as those of anxiety and stress. They have also been shown to be useful for pain management and performance enhancement. Specific mindfulness programs include Mindfulness-Based Stress Reduction (MBSR) and Mindfulness Mind-Fitness Training (MMFT). You can learn more about MBSR by watching the video below.

### 3.2.8 Attributions

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## 3.3: The Central Nervous System

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the [ASCCC OERI](mailto:ASCCC_OERI@asc.cc.org) ([oeri@asc.cc.org](mailto:oeri@asc.cc.org)).

### Learning Objectives

1. Name the structures that comprise the central nervous system
2. Describe the structure and function of the spinal cord

### 3.3.1 Overview

This module defines the central nervous system (the brain and spinal cord).

#### Homunculus



Figure 3.3.1: Front and rear views of a sensory homunculus model.

Figure 3.3.1 is a very odd-looking model called a homunculus. This model shows the relative representation of different parts of the body in the primary sensory cortex, an area in the parietal lobe of the brain. As you can see, larger areas of the brain in this region are associated with the hands, face, and tongue than the arms, torso, legs and feet. Larger areas of representation in the brain result in greater sensitivity in those body areas. Given the importance of speech, manual dexterity, and face-to-face social interactions in human beings, it is not surprising that relatively large areas of the brain are needed to relay sensation from these body parts. (There is a similarly odd-looking representation of voluntary motor functions called the motor homunculus that is located in the primary motor cortex, an area in the frontal lobe of the brain.) The brain is the most complex organ in the human body and is part of the central nervous system.

### 3.3.2 What Is the Central Nervous System?

The central nervous system (CNS) is the part of the nervous system that includes the brain and spinal cord. Figure 3.3.2 shows the central nervous system both as it appears in the body dissected from the backside and also completely removed from the body. The central nervous system and the peripheral nervous system (PNS, the other main division, which is addressed in a separate module), work together to control virtually all body functions.

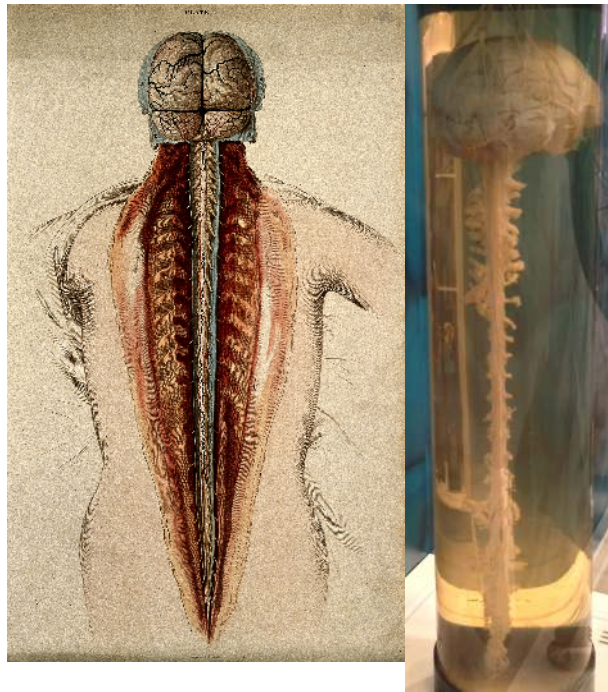


Figure 3.3.2: The human central nervous system. A back view dissection of the brain and spinal cord (colored line engraving by W.H. Lizars, circa 1827) and a preserved brain and spinal cord.

### 3.3.3 The Brain

The **brain** is the control center not only of the rest of the nervous system but of the entire organism. The adult brain makes up only about two percent of the body's weight, but it uses about 20 percent of the body's total energy. The brain contains an estimated 86 billion neurons (Lent et al., 2012), and each neuron has thousands of synaptic connections to other neurons. It is estimated that the brain also has about the same number of glial cells as neurons. No wonder the brain uses so much energy! In addition, the brain uses mostly glucose for energy. As a result, if the brain is deprived of glucose, it can lead to unconsciousness.

#### Parts of the Brain

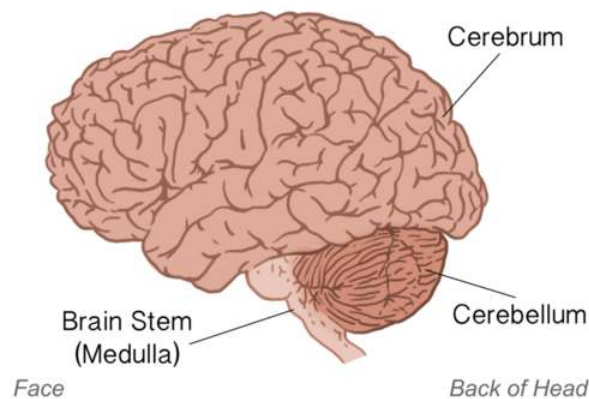


Figure 3.3.3: The major parts of the brain are the cerebrum, cerebellum, and brainstem. The medulla is part of the brainstem.

The brain controls such mental processes as reasoning, imagination, memory, and language. It also interprets information from the senses and commands the body's responses. It controls basic physiological processes such as breathing and heartbeat as well as voluntary activities such as walking and writing. The brain has three major parts: the cerebrum, cerebellum, and brainstem (Figure 3.3.3). The figure shows the brain from the left side of the head. It shows how the brain would appear if the skull and meninges were removed. The brainstem links to the spinal cord via the medulla. The cerebellum is a small structure at the back of the brain. The largest part of the brain is the cerebrum.

### 3.3.4 Spinal Cord

The spinal cord is a long, thin, tubular bundle of nervous tissues that extends from the brainstem down through the center of the back and pelvis. It is highlighted in yellow in Figure 3.3.15.



Figure 3.3.15: The spinal cord (shown in yellow) runs from the inferior aspect of the brain to the lower back. Spinal nerves are shown in black, and bones are shown in blue.

#### 3.3.4.1 Structure of the Spinal Cord

The center of the spinal cord consists of **gray matter**, which is made up mainly of neuron cell bodies, including interneurons and motor neurons. The gray matter is surrounded by **white matter** that consists mainly of myelinated axons from motor and sensory neurons. Sensory neuron axons enter the posterior side through the **dorsal (/posterior) nerve root**. Motor neuron axons emerge from the anterior side through the **ventral (/anterior) nerve root**. Note that it is common to see the terms dorsal (dorsal = back) and ventral (ventral = belly) used interchangeably with posterior and anterior, particularly in reference to nerves and the structures of the spinal cord. The **central canal** travels through the center of the spinal cord. The central canal is filled with **cerebrospinal fluid (CSF)**. Figure 3.3.16 shows the gray matter, white matter, central canal, dorsal roots and ventral roots of the spinal cord.

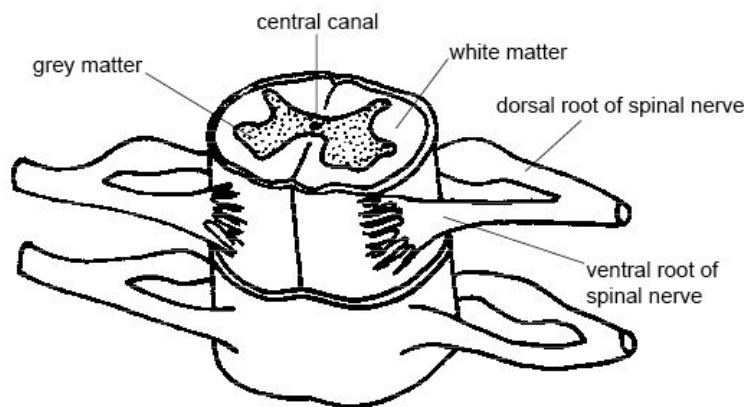


Figure 3.3.16: Cross section of spinal cord showing the central canal, gray and white matter, and the dorsal and ventral roots of the spinal nerves.

At each level of the spinal cord, the dorsal and ventral roots come together to form spinal nerves. Because the spinal cord is shorter than the vertebral column it is enclosed within, nerve roots must travel lower to exit at the associated vertebra. Spinal nerves connect the spinal cord to the PNS and enter/exit from the spinal cord between vertebrae (Figure 3.3.17).



Figure 3.3.17: This model shows three vertebrae (white) with branching spinal nerves (yellow) emerging from either side of the spinal cord between vertebrae. Also shown in yellow are pancake-like disks between vertebrae that help cushion and maintain space between adjacent bony vertebrae.

### 3.3.4.2 Gray Horns

In cross-section, the gray matter of the spinal cord has the appearance of an ink-blot test, with the spread of the gray matter on one side replicated on the other—a shape reminiscent of a bulbous capital “H” or a butterfly. As shown in Figure 3.3.18, the gray matter is subdivided into regions that are referred to as horns.

The **posterior horn** is responsible for sensory processing. The **anterior horn** sends out motor signals to the skeletal muscles. The **lateral horn**, which is only found in the thoracic, upper lumbar, and sacral regions, is the central component of the sympathetic division of the autonomic nervous system.

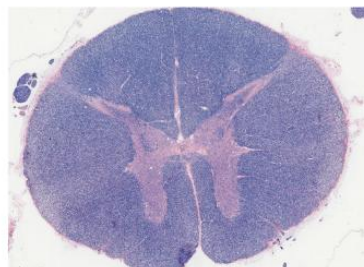
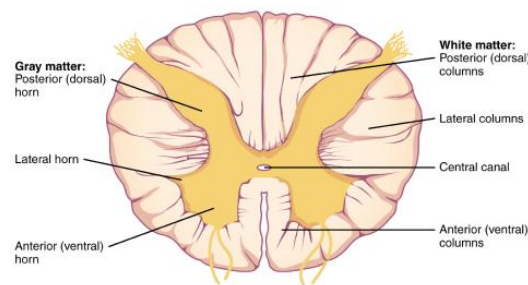


Figure 3.3.18: **Cross-section of Spinal Cord** The cross-section of a thoracic spinal cord segment shows the posterior (dorsal), anterior (ventral), and lateral horns of gray matter, as well as the posterior (dorsal), anterior (ventral), and lateral columns of white matter. Light Microscopy  $\times 40$  magnification.

### 3.3.4.3 Functions of the Spinal Cord

The spinal cord serves as an information superhighway. It passes messages from the body to the brain and from the brain to the body. Sensory (afferent) nerves carry nerve impulses to the brain from sensory receptor cells everywhere in and on the body. Motor (efferent) nerves carry nerve impulses away from the brain to glands, organs, or muscles throughout the body.

The spinal cord also independently controls certain rapid responses called **reflexes** without any input from the brain. A sensory receptor responds to a sensation and sends a nerve impulse along a sensory nerve to the spinal cord. In the spinal cord, the message passes to an interneuron and from the interneuron to a motor nerve, which carries the impulse to a muscle. The muscle contracts in response. These neuron connections form a reflex arc, which requires no input from the brain. No doubt you have experienced such

reflex actions yourself. For example, you may have reached out to touch a pot on the stove, not realizing that it was very hot. Virtually at the same moment that you feel the burning heat, you jerk your arm back and remove your hand from the pot.

#### 3.3.4.4 Injuries to the Spinal Cord

Physical damage to the spinal cord may result in **paralysis**, which is a loss of sensation and movement in part of the body. Paralysis generally affects all the areas of the body below the level of the injury because nerve impulses are interrupted and can no longer travel back and forth between the brain and body beyond that point. If an injury to the spinal cord produces nothing more than swelling, the symptoms may be transient. However, if nerve fibers (axons) in the spinal cord are badly damaged, the loss of function may be permanent. Experimental studies have shown that spinal nerve fibers attempt to regrow, but tissue destruction usually produces scar tissue that cannot be penetrated by the regrowing nerves, as well as other factors that inhibit nerve fiber regrowth in the central nervous system.

#### Feature: My Human Body

Each year, many millions of people have a stroke, and stroke is the second leading cause of death in adults. **Stroke**, also known as **cerebrovascular accident**, occurs when poor blood flow to the brain results in the death of brain cells. There are two main types of strokes:

- **Ischemic** strokes occur due to a lack of blood flow because of a blood clot in an artery going to the brain.
- **Hemorrhagic** strokes occur due to bleeding from a broken blood vessel in the brain.

Either type of stroke may result in paralysis, loss of the ability to speak or comprehend speech, loss of bladder control, personality changes, and many other potential effects, depending on the part of the brain that is injured. The effects of a stroke may be mild and transient or more severe and permanent. A stroke may even be fatal. It generally depends on the type of stroke and how extensive it is.

Are you at risk of stroke? The main risk factor for stroke is age: about two-thirds of strokes occur in people over the age of 65. There is nothing you can do about your age, but most other stroke risk factors can be reduced with lifestyle changes or medications. The risk factors include high blood pressure, tobacco smoking, obesity, high blood cholesterol, diabetes mellitus, and atrial fibrillation.

Chances are good that you or someone you know is at risk of a stroke, so it is important to recognize a stroke if one occurs. Stroke is a medical emergency, and the more quickly treatment is given, the better the outcome is likely to be. In the case of ischemic strokes, the use of clot-busting drugs may prevent permanent brain damage if administered within 3 or 4 hours of the stroke. Remembering the signs of a stroke is easy. They are summed up by the acronym FAST, as explained in Figure 3.3.19.



Figure 3.3.19: The signs of stroke are abbreviated as FAST, where F stands for droopy face, A stands for arm weakness, S stands for slurry speech, and T stands for time to call 911.

### 3.3.5 Summary

The central nervous system (CNS) includes the brain and spinal cord.

The spinal cord extends from the brainstem down through the center of the back and pelvis. Sensory neuron axons enter through the dorsal (/posterior) nerve root and motor neuron axons emerge from the ventral (/anterior) nerve root. Gray matter (containing of neuron cell bodies) is located in the center of the spinal cord, surrounded by white matter (myelinated axons). The gray matter is subdivided into the posterior, anterior, and lateral horns. The spinal cord passes messages from the body to the brain and from the brain to the body. Sensory (afferent) nerves carry nerve impulses to the brain from sensory receptor cells everywhere in and on the body. Motor (efferent) nerves carry nerve impulses away from the brain to glands, organs, or muscles throughout the body. The spinal cord also independently controls reflexes without any input from the brain. Physical damage to the spinal cord may result in paralysis, which may be permanent.

### 3.3.6 References

Basinger H., & Hogg, J.P. (2021) Neuroanatomy, Brainstem. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK544297/>

Lent, R., Azevedo, F.A., Andrade-Moraes, C.H., & Pinto, A.V. (2012) How many neurons do you have? Some dogmas of quantitative neuroscience under revision. *European Journal of Neuroscience* 35(1),1-9. doi: 10.1111/j.1460-9568.2011.07923.x. Epub 2011 Dec 13. PMID: 22151227.

### 3.3.7 Additional Resources

### 3.3.8 Attributions

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## CHAPTER OVERVIEW

### 4: Brain Anatomy

[4.1: The Central Nervous System](#)

[4.2: Anatomy of the Nervous System](#)

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## 4.1: The Central Nervous System

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### Learning Objectives

1. Identify the three main parts of the brain
2. Describe the lobes of the cerebrum and their locations
3. Identify the components of the diencephalon and describe their functions
4. Identify the regions of the brainstem and describe their functions
5. Identify the major structures of the limbic system and describe their functions
6. Describe the structure and function of the cerebellum

### 4.1.1 Overview

This module defines the central nervous system (the brain and spinal cord) and goes into detail on its components. Structures and functions of the brain are discussed, including the cerebrum: hemispheres and lateralization, the cerebral cortex, the frontal, parietal, temporal and occipital lobes; the brainstem: diencephalon, midbrain, pons and medulla; the limbic system; and the cerebellum; as well as structures, function and injury of the spinal cord.

Figure 4.1.1: Front and rear views of a sensory homunculus model.

Figure 4.1.1 is a very odd-looking model called a homunculus. This model shows the relative representation of different parts of the body in the primary sensory cortex, an area in the parietal lobe of the brain. As you can see, larger areas of the brain in this region are associated with the hands, face, and tongue than the arms, torso, legs and feet. Larger areas of representation in the brain result in greater sensitivity in those body areas. Given the importance of speech, manual dexterity, and face-to-face social interactions in human beings, it is not surprising that relatively large areas of the brain are needed to relay sensation from these body parts. (There is a similarly odd-looking representation of voluntary motor functions called the motor homunculus that is located in the primary motor cortex, an area in the frontal lobe of the brain.) The brain is the most complex organ in the human body and is part of the central nervous system.

### 4.1.2 Cerebrum

The iconic gray mantle of the human brain, which appears to make up most of the mass of the brain, is the **cerebrum**. It controls conscious, intellectual functions, such as reasoning, language, memory, sight, touch, and hearing. When you read a book, play a video game, or recognize a classmate, you are using your cerebrum. The wrinkled portion is the **cerebral cortex** (see below), and the rest of the structure is deep to that outer covering.

#### 4.1.2.1 Hemispheres and Lateralization of the Cerebrum

There is a large separation between the two sides of the cerebrum called the **longitudinal fissure**. It separates the cerebrum into two distinct halves, the right and left **cerebral hemispheres**. The two hemispheres are connected by a thick bundle of axons, known as the **corpus callosum**, which lies deep within the cerebrum. The corpus callosum is the major pathway for communication between the two hemispheres, connecting each point in the cerebral cortex to the mirror-image point in the opposite hemisphere. The location of the corpus callosum is shown with a dotted outline in Figure 4.1.4, as though you are looking through the outside and deep inside the brain. Figure 4.1.5 shows a three-dimensional image of the corpus callosum in relation to other deep brain structures and surrounded by the cerebrum.

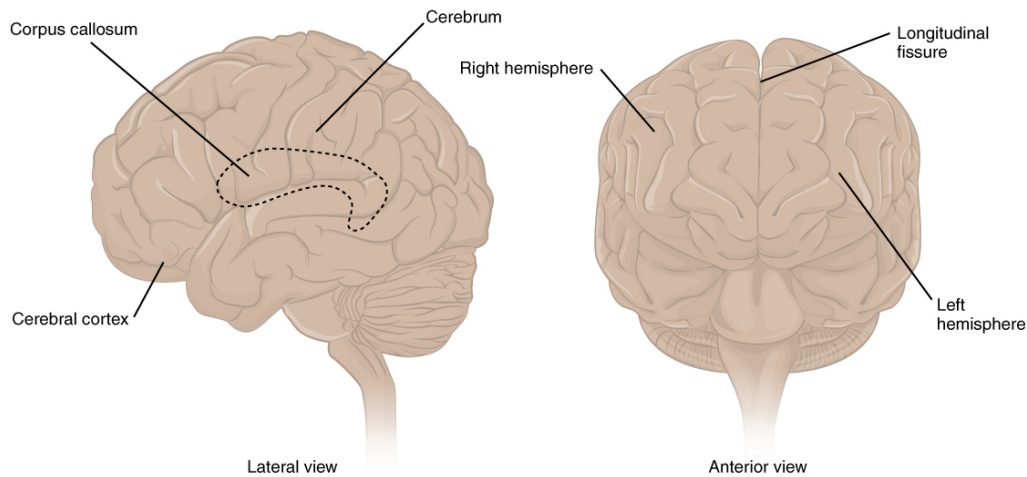


Figure 4.1.4: The cerebrum is a large component of the CNS in humans, and the most obvious aspect of it is the folded surface called the cerebral cortex.

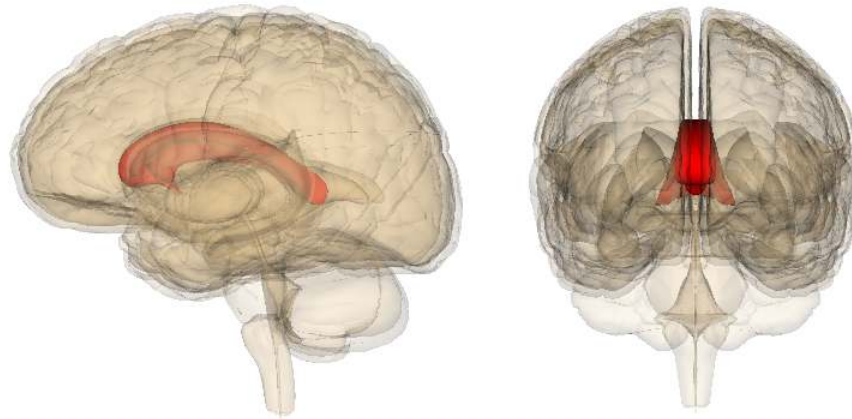


Figure 4.1.5: The corpus callosum (shown in red) is a thick bundle of axons connecting the left and right hemispheres of the brain. It is located deep within the cerebrum.

The right and left hemispheres of the cerebrum are similar in shape, and most areas of the cerebrum are found in both hemispheres. Some areas, however, show **lateralization**, or a concentration in one hemisphere or the other. For example, in most people, language functions are more concentrated in the left hemisphere, whereas abstract reasoning and visual-spatial abilities are more concentrated in the right hemisphere.

For reasons that are not yet clear, each hemisphere of the brain interacts primarily with the **contralateral** (opposite) side of the body. The left side of the brain receives messages from and sends commands to the right side of the body, and the right side of the brain receives messages from and sends commands to the left side of the body. Sensory nerves from the spinal cord to the brain and motor nerves from the brain to the spinal cord both cross to the other side of the body.

#### 4.1.2.2 Cerebral Cortex

The cerebrum is covered by a continuous layer of gray matter that wraps around either side of the forebrain—the **cerebral cortex**. This thin (just a few millimeters thick), extensive region of wrinkled gray matter is responsible for most of the information processing and higher functions of the nervous system. The cerebral cortex has many folds in it that greatly increase the surface area of the brain. A **gyrus** (plural = gyri) is the ridge of one of those wrinkles, and a **sulcus** (plural = sulci) is the groove between two gyri. The pattern of these folds of tissue indicates specific regions of the cerebral cortex. At birth, the head of the newborn is limited by the size of the birth canal, and the brain must fit inside the cranial cavity of the skull. Extensive folding in the cerebral cortex enables more gray matter to fit into this limited space. If the gray matter of the cerebral cortex in an adult were peeled off of the cerebrum and laid out flat, its surface area would be about 2,500 cm<sup>2</sup> (2.5 ft<sup>2</sup>), or about the size of the top of a card table.

### 4.1.2.3 Lobes of the Cerebral Cortex

The surface of the brain can be mapped on the basis of the locations of large gyri and sulci. Using these landmarks, the cortex can be separated into four major regions, or lobes (Figure 4.1.6). The **lateral sulcus** that separates the **temporal lobe** from the other regions is one such landmark.

Superior to the lateral sulcus are the **frontal lobe** and **parietal lobe**, which are separated from each other by the **central sulcus**. The most posterior gyrus of the frontal lobe is the **precentral gyrus**, which is where the primary motor cortex is located, while the most anterior gyrus of the parietal lobe is the **postcentral gyrus**, which is where the primary somatosensory cortex is located. (The primary somatosensory cortex is the area that the homonculus in Figure 4.1.1 represents.)

The posterior region of the cortex is the **occipital lobe**, which has no obvious anatomical border between it and the parietal or temporal lobes on the lateral surface of the brain. From the medial surface, the **parieto-occipital sulcus** separates the parietal and occipital lobes.

Figure 4.1.7 has only the four lobes labeled for quicker reference. The lobes are associated with multiple functions. The image shows one function of each lobe: frontal is associated with reasoning, parietal with touch, occipital with sight, and temporal with hearing. The lobes (found on each hemisphere of the cerebrum) are described in greater detail below.

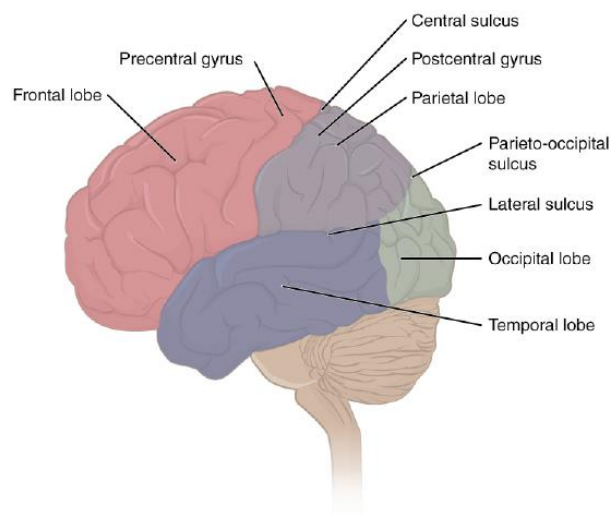


Figure 4.1.6: Major gyri, sulci and lobes of the cerebral cortex.

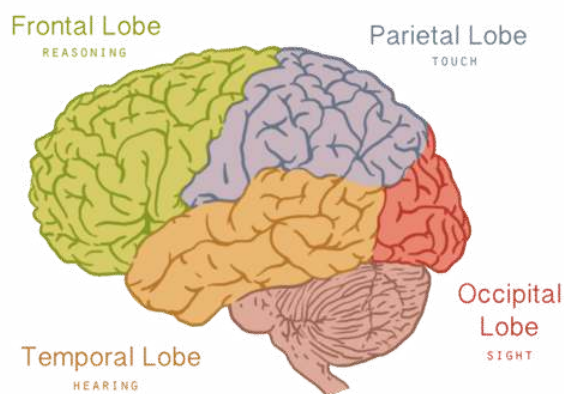


Figure 4.1.7: The four major lobes of the brain.

#### 4.1.2.3.1 Frontal Lobe

The **frontal lobes** are located at the front of the brain behind the forehead. The frontal lobes are associated with executive functions such as attention, self-control, planning, problem-solving, reasoning, abstract thought, language, and personality. Another important function of the frontal lobes is movement- as mentioned above, the precentral gyrus (indicated on Figure 4.1.6) contains

the primary motor cortex. Like the sensory homunculus pictured in the beginning of this section (Figure 4.1.1), there is a similarly disproportionate representation of voluntary motor control (the motor homunculus) located in the precentral gyrus. Figure 4.1.8 shows the areas of the primary motor cortex dedicated to movement of various body areas. Notice that like the sensory homunculus, the hands, fingers, thumb, and facial areas have a greater share of the cortex than areas with less fine-tuned movement (like the shoulders, trunk, and hips, for example).

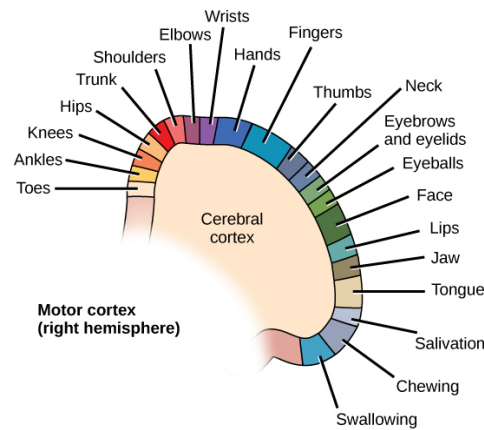


Figure 4.1.8: Different regions of the motor cortex control different muscle groups and their neighboring regions control neighboring muscle groups. Although the right hemisphere is shown, a mirror-image exists in the left hemisphere as well. Note that all areas of the body that have voluntary motor control are represented on the primary motor cortex.

#### 4.1.2.3.2 Parietal Lobe

The **parietal lobes** are located posterior to the frontal lobes at the top of the head. The parietal lobes are involved in body sensations, including temperature, touch, and pain. As mentioned above, the postcentral gyrus (indicated on Figure 4.1.6) contains the primary somatosensory cortex. The sensory homunculus model pictured in the beginning of this section (Figure 4.1.1) shows the strange character that results from making the body areas proportional to their representation in the brain. The drawing in Figure 4.1.9 shows the sensory homunculus stretched out along the postcentral gyrus of the parietal lobe. Notice that areas that have sensation but no voluntary motor control (like the genitals and the intra-abdominal organs) are present on the primary somatosensory cortex but not on the primary motor cortex (Figure 4.1.8). Reading and arithmetic are also functions of the parietal lobes.

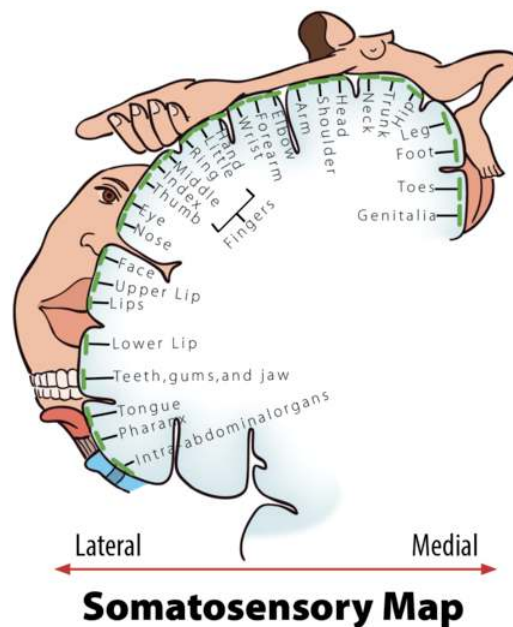


Figure 4.1.9: Somatosensory Map. The sensory map of your body represented on the primary somatosensory cortex in your brain is not proportional to the actual size of your body parts. Sensitive areas like your face (particularly your lips) and hands (particularly your fingers) occupy a larger section of cortex than less sensitive areas like your limbs (arms and legs) or trunk. Although the left hemisphere is shown, a mirror-image exists in the right hemisphere as well. Note that all areas of the body that register touch sensations are represented on the primary somatosensory cortex.

#### 4.1.2.3.3 Temporal Lobe

The **temporal lobes** are located at the sides of the head below the frontal and parietal lobes. The temporal lobes enable the formation and retrieval of memories, the integration of memories and sensations, and perception of the senses of hearing (audition), and smell (olfaction)- primary auditory cortex and primary olfactory cortex are both located in the temporal lobes.

#### 4.1.2.3.4 Occipital Lobe

The **occipital lobes** are located at the back of the head below the parietal lobes. The occipital lobes are the smallest of the four pairs of lobes. Primary visual cortex is located in the occipital lobes, and they are dedicated almost solely to vision.

### 4.1.3 Brainstem

As noted separately (see the nervous system structure module), sometimes the diencephalon is considered as a separate additional region, and sometimes it is included as the uppermost part of the brainstem (Basinger and Hogg, 2021), as it is here. The **brainstem** is the central region of the brain that connects the cerebrum (on the superior end) to the diencephalon, midbrain, pons, medulla, and ultimately joins the spinal cord (on the inferior end). The **cerebellum** is attached to the brainstem, but is considered a separate region of the adult brain.

One of the brainstem's most important roles is that of an "information highway." That is, all of the information coming from the body to the brain and the information from the cerebrum to the body go through the brainstem. Sensory pathways for such things as pain, temperature, touch, and pressure sensation go upward to the cerebrum, and motor pathways for movement and other body processes go downward to the spinal cord. Most of the axons in the motor pathways cross from one side of the CNS to the other as they pass through the medulla. As a result, the right side of the brain controls much of the movement on the left side of the body, and the left side of the brain controls much of the movement on the right side of the body. Similarly, axons in sensory pathways cross from one side of the CNS to the other either in the spinal cord or in the medulla (depending on the specific sensory information carried, such as pain versus localized touch), such that the right side of the brain receives sensation primarily from the left side of the body and vice versa.

#### 4.1.3.1 Diencephalon

The diencephalon ("through brain") is the one region of the adult brain that retains its name from embryonic development. It connects the cerebrum and the rest of the nervous system, with one exception. The brainstem, the spinal cord, and the PNS all send information to the cerebrum through the diencephalon, and output from the cerebrum then passes back through the diencephalon.

The single exception to this pattern is the sense of smell (olfaction), which connects directly to the cerebrum first. The diencephalon comprises the ventral surface of the forebrain (and connects to the tapering cone of the midbrain, pons, and medulla, the remaining structures in the brainstem).

The diencephalon is located deep within the cerebrum and constitutes the walls of the third ventricle. The diencephalon can be described as any region of the brain with “thalamus” in its name. The two major regions of the diencephalon are the thalamus itself and the hypothalamus (Figure 4.1.10). There are other structures as well, such as the epithalamus, which contains the pineal gland.

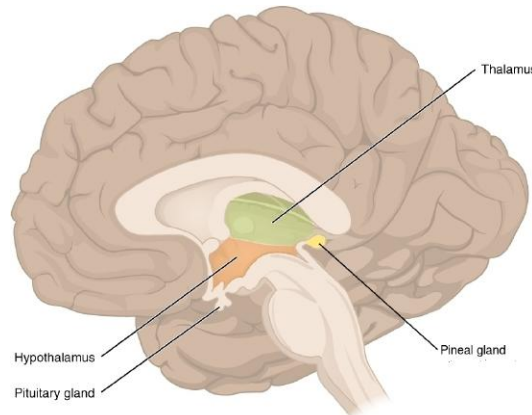


Figure 4.1.10: The diencephalon.

#### 4.1.3.1.1 Thalamus

The **thalamus**, which is located above the hypothalamus (Figure 4.1.10 and Figure 4.1.11), is a major hub for information traveling back and forth between the spinal cord, brainstem, and cerebrum. It filters sensory information traveling to the cerebrum. It relays sensory signals to the cerebral cortex and motor signals to the spinal cord. It is also involved in the regulation of consciousness, sleep, and alertness. As noted above, olfaction (smell) is the only sense that travels directly to the cortex and does not travel through the thalamus (as part of the diencephalon) first. However, olfactory messages do travel from the cortex back to the thalamus, so smell is still a participant in the "sensory relay" functions of the thalamus.

#### 4.1.3.1.2 Hypothalamus

The **hypothalamus** ("below thalamus") is about the size of an almond and is responsible for certain metabolic processes and other activities of the autonomic nervous system, including body temperature, heart rate, hunger, thirst, fatigue, sleep, wakefulness, and circadian (24-hour) rhythms. The hypothalamus is also an important emotional center of the brain. The hypothalamus can regulate so many body functions because it responds to many different internal and external signals, including messages from the brain, light, steroid hormones, stress, and invading pathogens, among others.

One way the hypothalamus influences body functions is by synthesizing hormones that directly influence body processes. For example, it synthesizes the hormone oxytocin, which stimulates penile and vaginal contractions during orgasm, uterine contractions during childbirth, and the letdown of milk during lactation. It also synthesizes the hormone vasopressin (also called antidiuretic hormone), which stimulates the kidneys to reabsorb more water and excrete more concentrated urine. These two hormones are sent from the hypothalamus via a stalk-like structure called the **infundibulum** ("pituitary stalk", see Figure 4.1.11) directly to the posterior (back) portion of the **pituitary gland**, which secretes them into the blood.

The main way the hypothalamus influences body functions is by controlling the pituitary gland, known as the "master gland" of the **endocrine system**. (The endocrine system is considered separately in the communication and the endocrine system module.) The hypothalamus synthesizes neurohormones called releasing factors that travel through the infundibulum directly to the anterior (front) part of the pituitary gland. The releasing factors generally either stimulate or inhibit the secretion of anterior pituitary hormones, most of which control other glands of the endocrine system.

Figure 4.1.11 shows where the thalamus, hypothalamus, and pituitary gland (typically considered an extension of the hypothalamus) are located in the brain. The cerebrum, hypothalamus, and thalamus exist in two halves, one in each hemisphere. The pituitary gland is a single structure in the center, connected to the hypothalamus by the infundibulum (or "pituitary stalk").

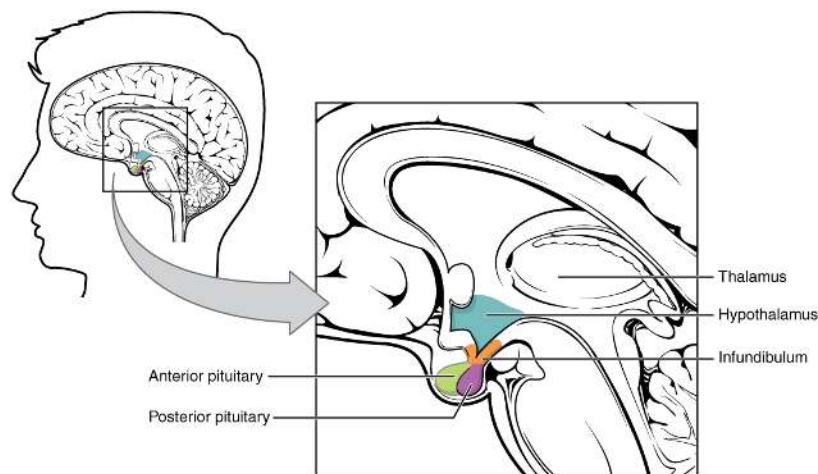


Figure 4.1.11: Just inferior (and deep) to the cerebrum is the thalamus. The hypothalamus is located a little bit anterior and inferior to the thalamus. The pituitary gland is attached to the hypothalamus via a stalk called the infundibulum.

The remaining parts to the brainstem are the midbrain, the pons, and the medulla, which are shown in Figure 4.1.12 below. These structures are primarily involved in the unconscious functions of the autonomic nervous system as well as several types of sensory information. They also help coordinate large body movements such as walking and running.

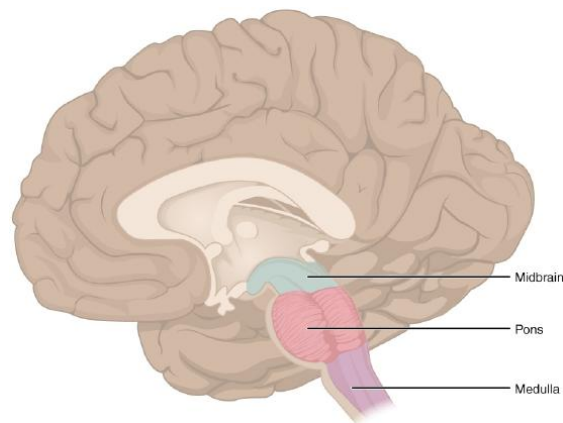


Figure 4.1.12: The brainstem includes the midbrain, pons, and medulla

#### 4.1.3.2 Midbrain

The **midbrain** coordinates sensory representations of sight (visual system- the **superior colliculi**), sound (auditory system- the **inferior colliculi**), and somatosensory perceptual spaces, translating these inputs before sending them to the forebrain.

#### 4.1.3.3 Pons

The **pons** ("bridge") is the main connection with the cerebellum. It relays messages between other parts of the brain (primarily the cerebrum and cerebellum) and sends messages to paralyze major body muscles during REM sleep. Some researchers have hypothesized that the pons plays a role in dreaming. Some of the functions of the pons are shared by the medulla, such as regulating several crucial functions including cardiovascular system and respiratory systems, and heartbeat and breathing rates.

#### 4.1.3.4 Medulla

The **medulla** (also called the medulla oblongata) controls several subconscious homeostatic functions such as breathing, heart and blood vessel activity, swallowing, and digestion.

### 4.1.4 Limbic System

The **limbic system** is a collection of structures of the cerebrum and diencephalon that are involved in emotion, motivation and memory. Although still under debate, the structures most often recognized as belonging to this system are the cingulate gyrus, hippocampus, amygdala, olfactory structures, and various nuclei of the diencephalon. Here we will focus on the cingulate gyrus, the hippocampus, and the amygdala (Figure 4.1.13). The **cingulate gyrus** (colored green in the figure) is located on the midsagittal

surface of the cortex, immediately superior to the corpus callosum and surrounding the diencephalon. The cingulate gyrus focuses attention on events that are emotionally salient. The **hippocampus** (colored purple in the figure) is a nucleus shaped like a seahorse, hence its name. The hippocampus is essential for forming memories and storing them long-term and is located deep in the temporal lobe. Lastly, the **amygdala** (also called the amygdaloid body, colored blue in the figure) is connected to the anterior end of the hippocampus and is involved in multiple aspects of emotion, including encoding memories related to highly emotional states. The amygdala is especially important for the emotion fear.

## The Limbic System

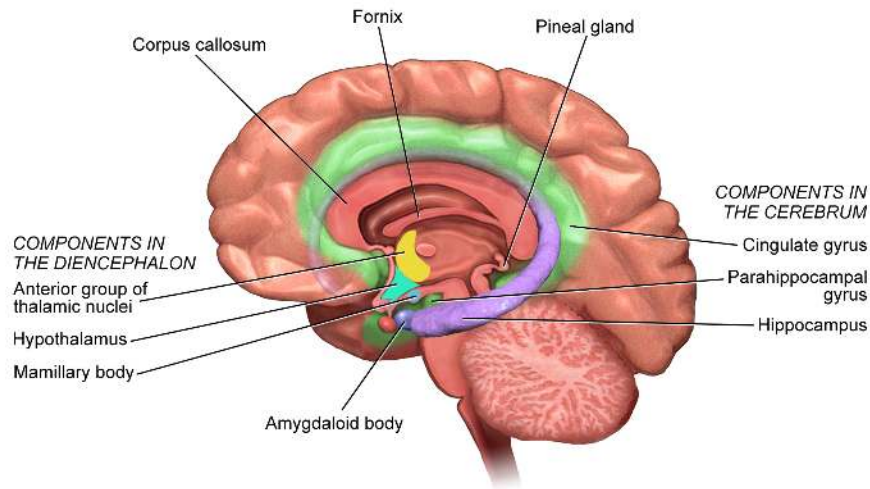


Figure 4.1.13: The Limbic System includes components from both the diencephalon (anterior group of thalamic nuclei, hypothalamus, and mammillary body) and the cerebrum (cingulate gyrus, parahippocampal gyrus, hippocampus, and amygdaloid body). Structures additionally labeled for reference are the corpus callosum, fornix, and pineal gland.

### 4.1.5 Cerebellum

The **cerebellum**, as the name suggests, is the “little brain”, just below the cerebrum and at the back of the brain behind the brainstem. It is covered in gyri and sulci like the cerebrum, and looks like a miniature version of that part of the brain Figure 4.1.14. The cerebellum is largely responsible for comparing information from the cerebrum with sensory feedback from the periphery through the spinal cord. It accounts for approximately 10 percent of the mass of the brain. The cerebellum coordinates body movements and is involved in movements that are learned with repeated practice. For example, when you hit a softball with a bat or touch type on a keyboard you are using your cerebellum. Many nerve pathways link the cerebellum with motor neurons throughout the body.

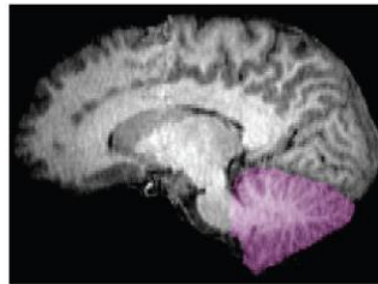
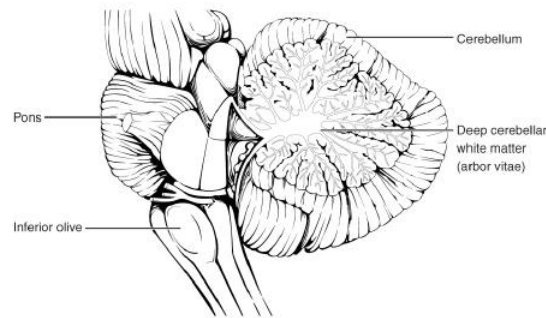


Figure 4.1.14: **The cerebellum.** The cerebellum is situated on the posterior surface of the brainstem. Descending input from the cerebellum enters through the large white matter structure of the pons. Ascending input from the periphery and spinal cord enters through the fibers of the inferior olive. Output goes to the midbrain, which sends a descending signal to the spinal cord.

#### 4.1.6 Summary

The central nervous system (CNS) includes the brain and spinal cord, described in greater detail in this module. The adult brain is separated into three major regions: the cerebrum, the brainstem, and the cerebellum. The cerebrum is the largest portion and is divided into two halves called hemispheres by the longitudinal fissure. The two hemispheres are connected by the corpus callosum, the major pathway for communication between the hemispheres.

The cerebral cortex, a continuous layer of gray matter covering the cerebrum, is the location of important cognitive functions. The cerebral cortex is separated into the frontal, parietal, temporal, and occipital lobes. The frontal lobe is responsible for executive functions and movements. The parietal lobe is involved in body sensations, reading, and arithmetic. The temporal lobe has regions crucial for memory formation, and contains cortical areas that process audition (hearing) and olfaction (smell). The occipital lobe is where visual processing begins.

The brainstem is composed of the diencephalon, midbrain, pons, and medulla. The brainstem serves as an "information highway", since all of the information coming from the body to the brain and the information from the cerebrum to the body go through the brainstem. The two major regions of the diencephalon are the thalamus and the hypothalamus. The thalamus is a relay between the cerebrum and the rest of the nervous system. The hypothalamus coordinates metabolic processes through the autonomic and endocrine systems. The midbrain coordinates sensory representations of sight, sound and somatosensation. The pons is the main connection between the cerebrum and the cerebellum. The pons and the medulla together regulate the cardiovascular and respiratory systems. The medulla also has important functions for swallowing and digestion.

The limbic system includes structures of the cerebrum and diencephalon that are responsible for emotion, motivation, and memory. The main structures are the cingulate gyrus, the hippocampus and the amygdala.

The cerebellum is connected to the brain stem and compares information from the cerebrum with sensory feedback from the spinal cord. The cerebellum coordinates body movements and is involved in movements that are learned with repeated practice.

#### 4.1.7 References

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## 4.2: Anatomy of the Nervous System

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## CHAPTER OVERVIEW

### 5: Sensation and Perception

[5.1: Sensation versus Perception](#)

[5.2: Vision](#)

[5.3: Hearing](#)

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## 5.1: Sensation versus Perception

### Learning Objectives

- Distinguish between sensation and perception
- Describe the concepts of absolute threshold and difference threshold
- Discuss the roles attention, motivation, and sensory adaptation play in perception

### Sensation

What does it mean to sense something? Sensory receptors are specialized neurons that respond to specific types of stimuli. When sensory information is detected by a sensory receptor, **sensation** has occurred. For example, light that enters the eye causes chemical changes in cells that line the back of the eye. These cells relay messages, in the form of action potentials (as you learned when studying biopsychology), to the central nervous system. The conversion from sensory stimulus energy to action potential is known as **transduction**.

You have probably known since elementary school that we have five senses: vision, hearing (audition), smell (olfaction), taste (gustation), and touch (somatosensation). It turns out that this notion of five senses is oversimplified. We also have sensory systems that provide information about balance (the vestibular sense), body position and movement (proprioception and kinesthesia), pain (nociception), and temperature (thermoception).

The sensitivity of a given sensory system to the relevant stimuli can be expressed as an absolute threshold. **Absolute threshold** refers to the minimum amount of stimulus energy that must be present for the stimulus to be detected 50% of the time. Another way to think about this is by asking how dim can a light be or how soft can a sound be and still be detected half of the time. The sensitivity of our sensory receptors can be quite amazing. It has been estimated that on a clear night, the most sensitive sensory cells in the back of the eye can detect a candle flame 30 miles away (Okawa & Sampath, 2007). Under quiet conditions, the hair cells (the receptor cells of the inner ear) can detect the tick of a clock 20 feet away (Galanter, 1962).

It is also possible for us to get messages that are presented below the threshold for conscious awareness—these are called **subliminal messages**. A stimulus reaches a physiological threshold when it is strong enough to excite sensory receptors and send nerve impulses to the brain: This is an absolute threshold. A message below that threshold is said to be subliminal: We receive it, but we are not consciously aware of it. Over the years there has been a great deal of speculation about the use of subliminal messages in advertising, rock music, and self-help audio programs. Research evidence shows that in laboratory settings, people can process and respond to information outside of awareness. But this does not mean that we obey these messages like zombies; in fact, hidden messages have little effect on behavior outside the laboratory (Kunst-Wilson & Zajonc, 1980; Rensink, 2004; Nelson, 2008; Radel, Sarrazin, Legrain, & Gobancé, 2009; Loersch, Durso, & Petty, 2013).

Absolute thresholds are generally measured under incredibly controlled conditions in situations that are optimal for sensitivity. Sometimes, we are more interested in how much difference in stimuli is required to detect a difference between them. This is known as the **just noticeable difference (jnd)** or **difference threshold**. Unlike the absolute threshold, the difference threshold changes depending on the stimulus intensity. As an example, imagine yourself in a very dark movie theater. If an audience member were to receive a text message that caused the cell phone screen to light up, chances are that many people would notice the change in illumination in the theater. However, if the same thing happened in a brightly lit arena during a basketball game, very few people would notice. The cell phone brightness does not change, but its ability to be detected as a change in illumination varies dramatically between the two contexts. Ernst Weber proposed this theory of change in difference threshold in the 1830s, and it has become known as Weber's law: The difference threshold is a constant fraction of the original stimulus, as the example illustrates.

### Perception

While our sensory receptors are constantly collecting information from the environment, it is ultimately how we interpret that information that affects how we interact with the world. **Perception** refers to the way sensory information is organized, interpreted, and consciously experienced. Perception involves both bottom-up and top-down processing. **Bottom-up processing** refers to sensory information from a stimulus in the environment driving a process, and **top-down processing** refers to knowledge and expectancy driving a process, as shown in [Figure 5.2](#) (Egeth & Yantis, 1997; Fine & Minnery, 2009; Yantis & Egeth, 1999).

The figure includes two vertical arrows. The first arrow comes from the word "Top" and points downward to the word "Down." The explanation reads, "Top-down processing occurs when previous experience and expectations are first used to recognize stimuli." The second arrow comes from the word "bottom" and points upward to the word "up." The explanation reads, "Bottom-up processing occurs when we sense basic features of stimuli and then integrate them."

Figure 5.2 Top-down and bottom-up are ways we process our perceptions.

Imagine that you and some friends are sitting in a crowded restaurant eating lunch and talking. It is very noisy, and you are concentrating on your friend's face to hear what she is saying, then the sound of breaking glass and clang of metal pans hitting the floor rings out. The server dropped a large tray of food. Although you were attending to your meal and conversation, that crashing sound would likely get through your attentional filters and capture your attention. You would have no choice but to notice it. That attentional capture would be caused by the sound from the environment: it would be bottom-up.

Alternatively, top-down processes are generally goal directed, slow, deliberate, effortful, and under your control (Fine & Minnery, 2009; Miller & Cohen, 2001; Miller & D'Esposito, 2005). For instance, if you misplaced your keys, how would you look for them? If you had a yellow key fob, you would probably look for yellowness of a certain size in specific locations, such as on the counter, coffee table, and other similar places. You would not look for yellowness on your ceiling fan, because you know keys are not normally lying on top of a ceiling fan. That act of searching for a certain size of yellowness in some locations and not others would be top-down—under your control and based on your experience.

One way to think of this concept is that sensation is a physical process, whereas perception is psychological. For example, upon walking into a kitchen and smelling the scent of baking cinnamon rolls, the *sensation* is the scent receptors detecting the odor of cinnamon, but the *perception* may be “Mmm, this smells like the bread Grandma used to bake when the family gathered for holidays.”

Although our perceptions are built from sensations, not all sensations result in perception. In fact, we often don't perceive stimuli that remain relatively constant over prolonged periods of time. This is known as **sensory adaptation**. Imagine going to a city that you have never visited. You check in to the hotel, but when you get to your room, there is a road construction sign with a bright flashing light outside your window. Unfortunately, there are no other rooms available, so you are stuck with a flashing light. You decide to watch television to unwind. The flashing light was extremely annoying when you first entered your room. It was as if someone was continually turning a bright yellow spotlight on and off in your room, but after watching television for a short while, you no longer notice the light flashing. The light is still flashing and filling your room with yellow light every few seconds, and the photoreceptors in your eyes still sense the light, but you no longer perceive the rapid changes in lighting conditions. That you no longer perceive the flashing light demonstrates sensory adaptation and shows that while closely associated, sensation and perception are different.

There is another factor that affects sensation and perception: attention. Attention plays a significant role in determining what is sensed versus what is perceived. Imagine you are at a party full of music, chatter, and laughter. You get involved in an interesting conversation with a friend, and you tune out all the background noise. If someone interrupted you to ask what song had just finished playing, you would probably be unable to answer that question.

#### Link to Learning

See for yourself how inattentional blindness works by checking out this [selective attention test](#) from Simons and Chabris (1999).

One of the most interesting demonstrations of how important attention is in determining our perception of the environment occurred in a famous study conducted by Daniel Simons and Christopher Chabris (1999). In this study, participants watched a video of people dressed in black and white passing basketballs. Participants were asked to count the number of times the team dressed in white passed the ball. During the video, a person dressed in a black gorilla costume walks among the two teams. You would think that someone would notice the gorilla, right? Nearly half of the people who watched the video didn't notice the gorilla at all, despite the fact that he was clearly visible for nine seconds. Because participants were so focused on the number of times the team dressed in white was passing the ball, they completely tuned out other visual information. **Inattentional blindness** is the failure to notice something that is completely visible because the person was actively attending to something else and did not pay attention to other things (Mack & Rock, 1998; Simons & Chabris, 1999).

In a similar experiment, researchers tested inattentional blindness by asking participants to observe images moving across a computer screen. They were instructed to focus on either white or black objects, disregarding the other color. When a red cross passed across the screen, about one third of subjects did not notice it ([Figure 5.3](#)) (Most, Simons, Scholl, & Chabris, 2000).



Figure 5.3 Nearly one third of participants in a study did not notice that a red cross passed on the screen because their attention was focused on the black or white figures. (credit: Cory Zanker)

Motivation can also affect perception. Have you ever been expecting a really important phone call and, while taking a shower, you think you hear the phone ringing, only to discover that it is not? If so, then you have experienced how motivation to detect a meaningful stimulus can shift our ability to discriminate between a true sensory stimulus and background noise. The ability to identify a stimulus when it is embedded in a distracting background is called **signal detection theory**. This might also explain why a mother is awakened by a quiet murmur from her baby but not by other sounds that occur while she is asleep. Signal detection theory has practical applications, such as increasing air traffic controller accuracy. Controllers need to be able to detect planes among many signals (blips) that appear on the radar screen and follow those planes as they move through the sky. In fact, the original work of the researcher who developed signal detection theory was focused on improving the sensitivity of air traffic controllers to plane blips (Swets, 1964).

Our perceptions can also be affected by our beliefs, values, prejudices, expectations, and life experiences. As you will see later in this chapter, individuals who are deprived of the experience of binocular vision during critical periods of development have trouble perceiving depth (Fawcett, Wang, & Birch, 2005). The shared experiences of people within a given cultural context can have pronounced effects on perception. For example, Marshall Segall, Donald Campbell, and Melville Herskovits (1963) published the results of a multinational study in which they demonstrated that individuals from Western cultures were more prone to experience certain types of visual illusions than individuals from non-Western cultures, and vice versa. One such illusion that Westerners were more likely to experience was the Müller-Lyer illusion (Figure 5.4): The lines appear to be different lengths, but they are actually the same length.

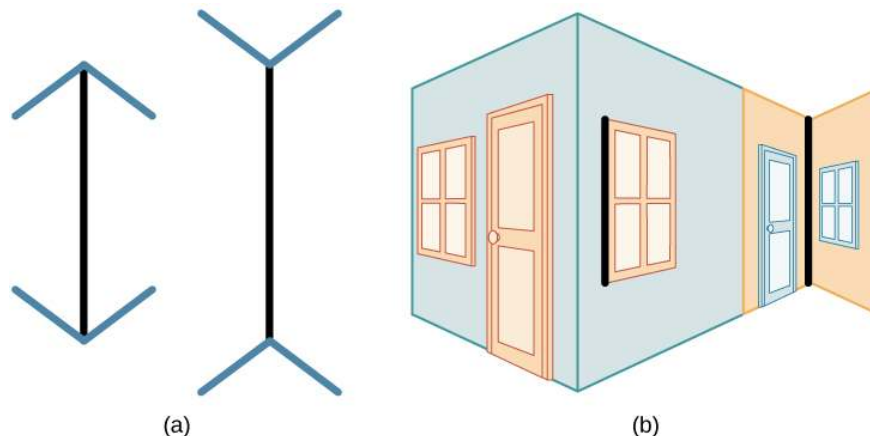


Figure 5.4 In the Müller-Lyer illusion, lines appear to be different lengths although they are identical. (a) Arrows at the ends of lines may make the line on the right appear longer, although the lines are the same length. (b) When applied to a three-dimensional image, the line on the right again may appear longer although both black lines are the same length.

These perceptual differences were consistent with differences in the types of environmental features experienced on a regular basis by people in a given cultural context. People in Western cultures, for example, have a perceptual context of buildings with straight lines, what Segall's study called a carpentered world (Segall et al., 1966). In contrast, people from certain non-Western cultures with an uncarpentered view, such as the Zulu of South Africa, whose villages are made up of round huts arranged in circles, are less susceptible to this illusion (Segall et al., 1999). It is not just vision that is affected by cultural factors. Indeed, research has

demonstrated that the ability to identify an odor, and rate its pleasantness and its intensity, varies cross-culturally (Ayabe-Kanamura, Saito, Distel, Martínez-Gómez, & Hudson, 1998).

Children described as thrill seekers are more likely to show taste preferences for intense sour flavors (Liem, Westerbeek, Wolterink, Kok, & de Graaf, 2004), which suggests that basic aspects of personality might affect perception. Furthermore, individuals who hold positive attitudes toward reduced-fat foods are more likely to rate foods labeled as reduced fat as tasting better than people who have less positive attitudes about these products (Aaron, Mela, & Evans, 1994).

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## 5.2: Vision

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### 5.2.1 Vision

#### Learning Objectives

- Identify the key structures of the eye and the role they play in vision.
- Summarize how the eye and the visual cortex work together to sense and perceive the visual stimuli in the environment, including processing colors, shape, depth, and motion.
- Explain the benefit of having two eyes.
- Understand differences in color vision.
- Understand depth perception and vision.
- Understand motion detection.

Humans rely largely on vision and seeing the world around them through sight. Most non human organisms rely more on the other senses to interpret the world around them. Research indicates that a large part of the cerebral cortex in humans is dedicated to vision. As the information reaches the visual cortex in the brain, multiple neurons identify shapes, colors, and motions. When light falls on the eyes, sensory receptors begin the process of transduction. As this process occurs, individuals begin to perceive the environment around them.

Think about entering a dark theater or room if you have been outside on a sunny day; often times it takes time to adjust to the change of light intensity in the environment. The muscles in the iris of the eye adjust to allow more light to enter the pupil (**the round opening in the center of the iris**). The iris of the eye is the colored part of the eye that constricts and dilates the pupil to adjust for different light intensities that we may encounter throughout the day. Photoreceptors help distinguish the different characteristics of different objects. The types of photoreceptors in the human eye include rods and cones; rods are typically more prevalent than cones. Rods give us sensitivity under dim lighting conditions and allow us to see at night. Cones allow us to see fine details in bright light and give us the ability to distinguish color. Cones are tightly packed around the fovea (the small central region located at the back of the retina) and more sparsely elsewhere. Rods populate the periphery (the region surrounding the fovea) and are almost absent from the fovea. As organisms move about their environment throughout the day the information by light from objects both near and far is encoded by the brain and the identification of colors, shapes, and motion occurs (see Figure 5.2.1).

#### **Anatomy of the Human Eye**

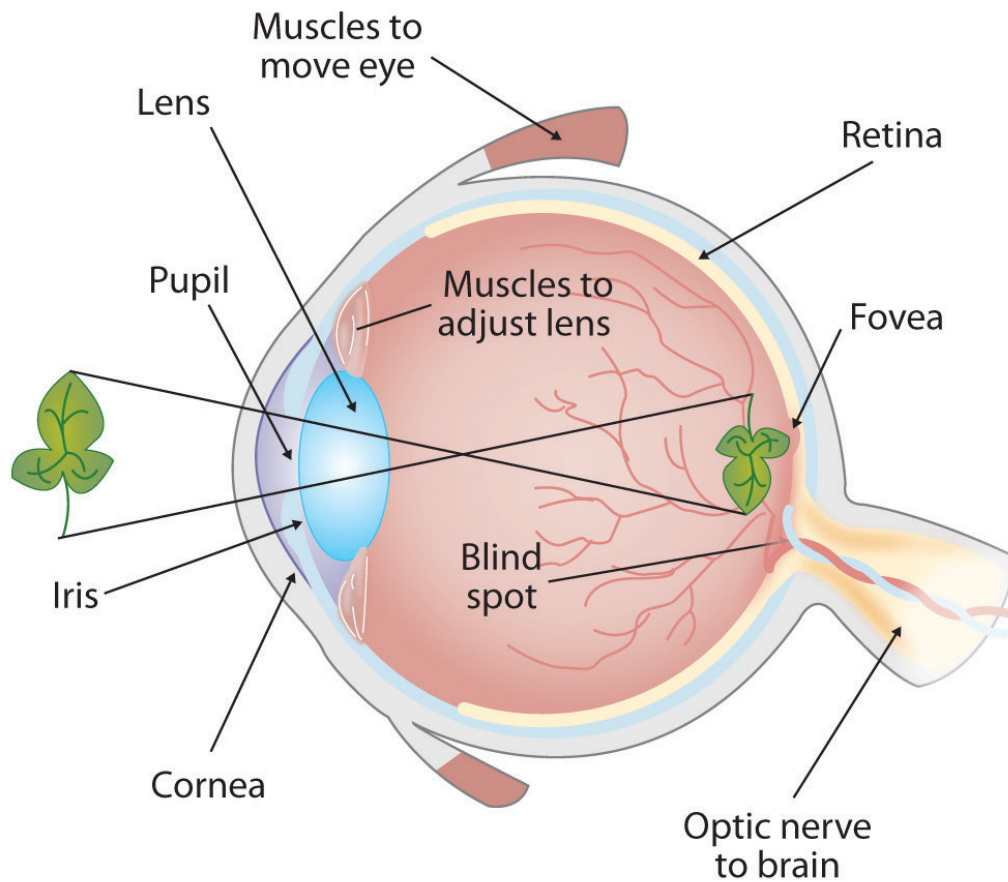


Figure 5.2.1: Light enters the eye through the transparent cornea, passing through the pupil at the center of the iris. The lens adjusts to focus the light on the retina, where it appears upside down and backward. Receptor cells on the retina send information via the optic nerve to the visual cortex. [https://open.lib.umn.edu/intropsyc/c...04\\_s02\\_s01\\_f02](https://open.lib.umn.edu/intropsyc/c...04_s02_s01_f02)

**Normal, Nearsighted, and Farsighted Eyes Figure 5.2.2**

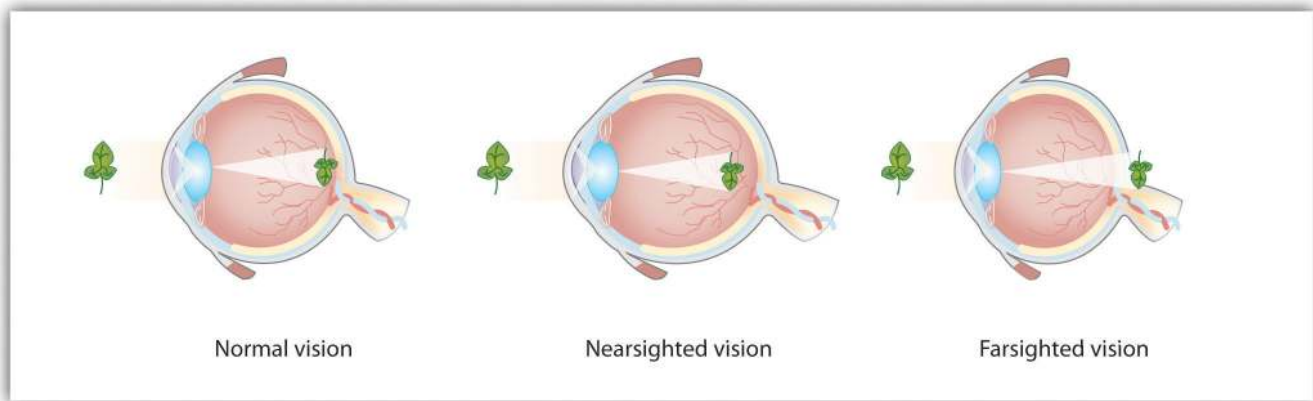


Figure 5.2.2 For people with normal vision (left), the lens properly focuses incoming light on the retina. For people who are nearsighted (center), images from far objects focus too far in front of the retina, whereas for people who are farsighted (right), images from near objects focus too far behind the retina. Eyeglasses solve the problem by adding a secondary, corrective, lens.  
[https://open.lib.umn.edu/intropsych/chapter/4-2-seeing/#stangor-ch04\\_s02\\_s01\\_f02](https://open.lib.umn.edu/intropsych/chapter/4-2-seeing/#stangor-ch04_s02_s01_f02)

Research indicates that humans can distinguish between millions of different color variations (Gerald , 1972). Although humans can distinguish between a wide variety of variations there are three primary colors that form the base of these variations; red, green, and blue. The ability for these colors to form these variations is based on the hue or shade of the colors. The electromagnetic spectrum illustrated below shows that visible light for humans is just a small slice of the entire spectrum, which includes radiation that we cannot see as light because it is below the frequency of visible red light and above the frequency of visible violet light.

The Electromagnetic Spectrum Figure 5.2.3

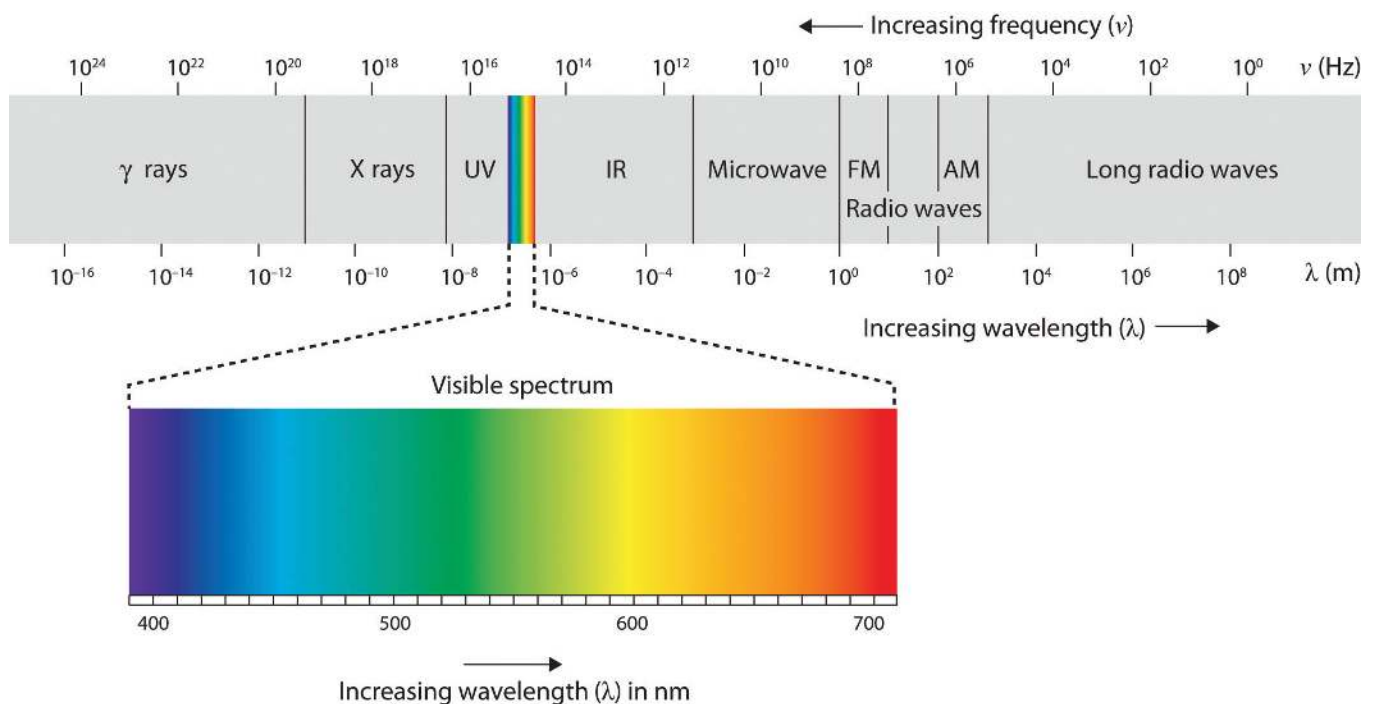


Figure 5.2.3: Only a small fraction of the electromagnetic energy that surrounds us (the visible spectrum) is detectable by the human eye.

In his important research on color vision, Hermann von Helmholtz theorized that color is perceived because the cones in the retina come in three types. One type of cone reacts primarily to blue light (short wavelengths), another reacts primarily to green light (medium wavelengths), and a third reacts primarily to red light (long wavelengths). The visual cortex then detects and compares the strength of the signals from each of the three types of cones, creating the experience of color. According to this Young-

Helmholtz trichromatic color theory, *what color we see depends on the mix of the signals from the three types of cones*. If the brain is receiving primarily red and blue signals, for instance, it will perceive purple; if it is receiving primarily red and green signals it will perceive yellow; and if it is receiving messages from all three types of cones it will perceive white.

The different functions of the three types of cones are apparent in people who experience color blindness. Color blindness can be defined as having decreased capacity to see color or distinguish differences between colors. Red–green color blindness is the most common form, followed by blue–yellow color blindness and total color blindness. Red–green color blindness affects up to 8% of males and 0.5% of females of Northern European descent. Red-green color blindness is a result of an absence of long or medium wavelength cones or to the production of abnormal opsin pigments in these cones that affect red-green color vision (see Figure 5.2.4).

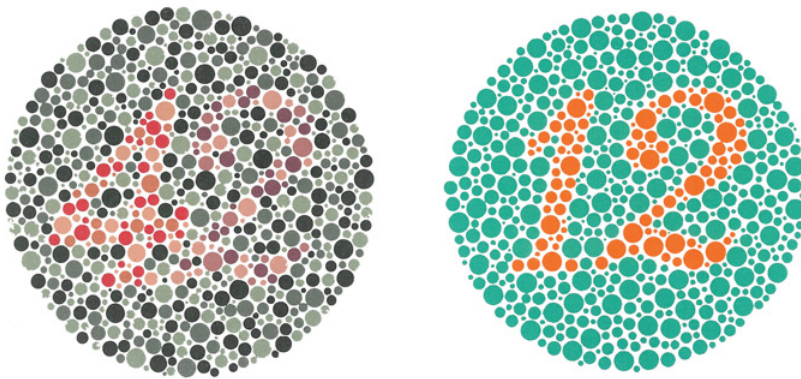


Figure 5.2.4: People with normal color vision can see the number 42 in the first image and the number 12 in the second (they are vague but apparent). However, people who are color blind cannot see the numbers at all. [Wikimedia Commons](#).

An alternative approach to the Young-Helmholtz theory, known as the opponent-process color theory, *proposes that we analyze sensory information not in terms of three colors but rather in three sets of “opponent colors”*: red-green, yellow-blue, and white-black. Evidence for the opponent-process theory comes from the fact that some neurons in the retina and in the visual cortex are excited by one color (e.g., red) but inhibited by another color (e.g., green).

One example of opponent processing occurs in the experience of an afterimage. If you stare at the flag on the left for about 30 seconds (the longer you look, the better the effect), and then move your eyes to the blank area to the right of it, you will see the afterimage. When we stare at the green stripes, our green receptors habituate and begin to process less strongly, whereas the red receptors remain at full strength. When we switch our gaze, we see primarily the red part of the opponent process. Similar processes create blue after yellow and white after black (see Figure 5.2.5).



Figure 5.2.5: U.S. Flag. The presence of an afterimage is best explained by the opponent-process theory of color perception. Stare at the flag for a few seconds, and then move your gaze to the blank space next to it. Do you see the afterimage? Mike Swanson – [U.S. Flag \(inverted\)](#) – public domain.

## Depth Perception

**Depth perception** is the ability to perceive three-dimensional space and to accurately judge distance. Without depth perception, we would be unable to drive a car, thread a needle, or simply navigate our way around the supermarket (Howard & Rogers, 2001). Research has found that depth perception is in part based on innate capacities and in part learned through experience (Witherington, 2005).

Psychologists Eleanor Gibson and Richard Walk (1960) tested the ability to perceive depth in 6- to 14-month-old infants by placing them on a **visual cliff**, a mechanism that gives the perception of a dangerous drop-off, in which infants can be safely tested for their perception of depth (see Figure 5.2.6). The infants were placed on one side of the “cliff,” while their mothers called to them from the other side. Gibson and Walk found that most infants either crawled away from the cliff or remained on the board and cried because they wanted to go to their mothers, but the infants perceived a chasm that they instinctively could not cross. Further research has found that even very young children who cannot yet crawl are fearful of heights (Campos, Langer, & Krowitz, 1970). On the other hand, studies have also found that infants improve their hand-eye coordination as they learn to better grasp objects and as they gain more experience in crawling, indicating that depth perception is also learned (Adolph, 2000).

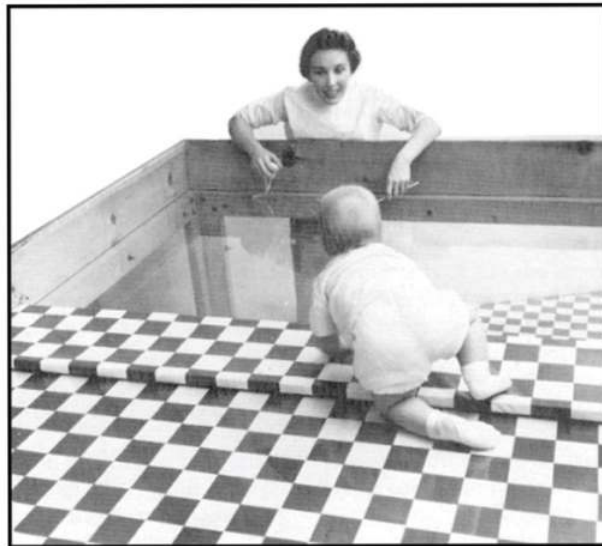


Figure 5.2.6: **Visual Cliff**- A mother urging her child from across the deep side of the visual cliff. Despite a transparent surface covering the cliff, the child hesitates to move forward. (From Gibson and Walk (1960). Copyright 1960 Nature Publishing Group., CC BY 4.0 <<https://creativecommons.org/licenses/by/4.0/>>, via Wikimedia Commons)

Depth perception is the result of our use of **depth cues**, messages from our bodies and the external environment that supply us with information about space and distance. **Binocular depth cues** are depth cues that are created by retinal image disparity—that is, the space between our eyes, and thus which require the coordination of both eyes. One outcome of retinal disparity is that the images projected on each eye are slightly different from each other. The visual cortex automatically merges the two images into one, enabling us to perceive depth. Three-dimensional movies make use of retinal disparity by using 3-D glasses that the viewer wears to create a different image on each eye. The perceptual system quickly, easily, and unconsciously turns the disparity into 3-D.

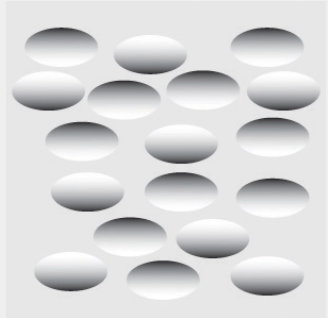
An important binocular depth cue is **convergence**, the inward turning of our eyes that is required to focus on objects that are less than about 50 feet away from us. The visual cortex uses the size of the convergence angle between the eyes to judge the object’s distance. You will be able to feel your eyes converging if you slowly bring a finger closer to your nose while continuing to focus on it. When you close one eye, you no longer feel the tension—convergence is a binocular depth cue that requires both eyes to work.

The visual system also uses **accommodation** to help determine depth. As the lens changes its curvature to focus on distant or close objects, information relayed from the muscles attached to the lens helps us determine an object’s distance. Accommodation is only effective at short viewing distances, however, so while it comes in handy when threading a needle or tying shoelaces, it is far less effective when driving or playing sports.

Although the best cues to depth occur when both eyes work together, we are able to see depth even with one eye closed. **Monocular depth cues** are depth cues that help us perceive depth using only one eye (Sekuler & Blake, 2006). Some of the most important are summarized in Table 5.2.1 “**Monocular Depth Cues That Help Us Judge Depth at a Distance**”.

Table 5.2.1 Monocular Depth Cues That Help Us Judge Depth at a Distance

|  |
|--|
|  |
|--|

| Name               | Description                                                                                                                                 | Example                                                                                                                                  | Image                                                                                                                                                                                                                 |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Position           | We tend to see objects higher up in our field of vision as farther away.                                                                    | The fence posts at right appear farther away not only because they become smaller but also because they appear higher up in the picture. | <p>Figure</p>  <p>Andrew Huff – <a href="#">Rotted Fence</a> – CC BY 2.0.</p>                                                      |
| Relative size      | Assuming that the objects in a scene are the same size, smaller objects are perceived as farther away.                                      | At right, the cars in the distance appear smaller than those nearer to us.                                                               | <p>Figure</p>  <p>Allan Ferguson – <a href="#">Trolley Crosses Freeway</a> – CC BY 2.0.</p>                                        |
| Linear perspective | Parallel lines appear to converge at a distance.                                                                                            | We know that the tracks at right are parallel. When they appear closer together, we determine they are farther away.                     | <p>Figure</p>  <p>Bo Insogna, TheLightningMan.com – <a href="#">Lightning Striking By The Train Tracks</a> – CC BY-NC-ND 2.0.</p> |
| Light and shadow   | The eye receives more reflected light from objects that are closer to us. Normally, light comes from above, so darker images are in shadow. | We see the images at right as extending and indented according to their shadowing. If we invert the picture, the images will reverse.    | <p>Figure</p>                                                                                                                    |

| Name               | Description                                                                           | Example                                                                                                                                   | Image                                                                                                                                                                             |
|--------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Interposition      | When one object overlaps another object, we view it as closer.                        | At right, because the blue star covers the pink bar, it is seen as closer than the yellow moon.                                           | <p>Figure</p>                                                                                  |
| Aerial perspective | Objects that appear hazy, or that are covered with smog or dust, appear farther away. | The artist who painted the picture on the right used aerial perspective to make the distant hills more hazy and thus appear farther away. | <p>Figure</p>  <p>Frans Koppelaar – <a href="#">Landscape near Bologna</a> – CC BY-SA 2.5.</p> |

## Motion

Many animals, including human beings, have very sophisticated perceptual skills that allow them to coordinate their own motion with the motion of moving objects in order to create a collision with that object. Bats and birds use this mechanism to catch up with prey, dogs use it to catch a Frisbee, and humans use it to catch a moving football. The brain detects motion partly from the changing size of an image on the retina (objects that look bigger are usually closer to us) and in part from the relative brightness of objects.

We also experience motion when objects near each other change their appearance. The **beta effect** refers to *the perception of motion that occurs when different images are presented next to each other in succession* (see [Note “Beta Effect and Phi Phenomenon”](#)). The visual cortex fills in the missing part of the motion and we see the object moving. The beta effect is used in movies to create the experience of motion. A related effect is the **phi phenomenon**, in which *we perceive a sensation of motion caused by the appearance and disappearance of objects that are near each other*. The phi phenomenon looks like a moving zone or cloud of background color surrounding the flashing objects. The beta effect and the phi phenomenon are other examples of the importance of the gestalt—our tendency to “see more than the sum of the parts.”

### 5.2.1.0.1 Beta Effect and Phi Phenomenon

In the beta effect, our eyes detect motion from a series of still images, each with the object in a different place. This is the fundamental mechanism of motion pictures (movies). In the phi phenomenon, the perception of motion is based on the momentary hiding of an image.

Phi phenomenon: <http://upload.wikimedia.org/Wikipedia/commons/6/6e/Lilac-Chaser.gif>

Beta effect: [http://upload.wikimedia.org/Wikipedia/commons/0/09/Phi\\_phenomenom\\_no\\_watermark.gif](http://upload.wikimedia.org/Wikipedia/commons/0/09/Phi_phenomenom_no_watermark.gif)

## 5.2.2 Attribution

- Vision sections adapted by Isaias Hernandez from "NOBA-Vision"; <https://nobaproject.com/modules/vision>
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- Vision sections adapted by Isaias Hernandez from "Introduction to Psychology-University of Minnesota";  
[https://open.lib.umn.edu/intropsyc/c...04\\_s02\\_s01\\_f02](https://open.lib.umn.edu/intropsyc/c...04_s02_s01_f02)

### 5.2.3 References

<https://www.nei.nih.gov/learn-about-...olor-blindness>

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## 5.3: Hearing

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the [ASCCC OERI \(oeri@asccc.org\)](mailto:asccc@oeri.org).

### 5.3.1 Hearing

#### Learning Objectives

1. Label key structures of the ear, identify their functions, and describe the role they play in hearing.
2. Explain how we encode and perceive pitch.
3. Explain how we localize sound.
4. Describe how hearing and the vestibular system are associated.

This section will provide an overview of the basic anatomy and function of the auditory system, how we perceive pitch, and how we know where sound is coming from. It has been argued that the human ear can hear a variety of sounds and can distinguish between a large variation of these sounds. The complex anatomy of the ear in humans can be divided into three sections (the three sections are shown in the image below). The neural impulses of these sound waves are sent to the brain and our past experiences integrate with those sound waves to help us make sense of the sounds we are hearing. The auditory system converts the sound waves into electrical signals that the brain interprets. The illustration below shows the complex system of the ear and how the anatomical structures lead to the ability to hear the sounds of nature, appreciate beauty of music and utilize language to communicate with others who speak the same language (see Figure 5.3.1).

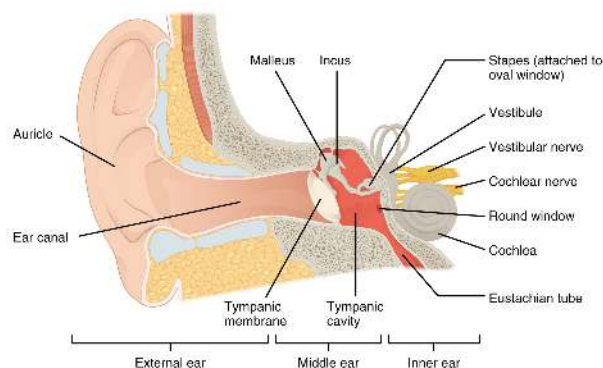


Figure 5.3.1 – **Structures of the Ear:** The external ear contains the auricle, ear canal, and tympanic membrane. The middle ear contains the ossicles and is connected to the pharynx by the Eustachian tube. The inner ear contains the cochlea and vestibule, which are responsible for audition and equilibrium, respectively <https://open.oregonstate.edu/a.../15-3-hearing/>.

In particular, the human ear is most responsive to sounds that are in the same frequency as the human voice. This is why parents and mothers in particular are able to pick out the sound of their children's voice amongst other children's voices and we are often able to identify another person from the sound of their voice without having to see them physically. The complex system of the ear allows us to process sounds almost instantly.

Unlike light waves which travel in a vacuum, sound waves are transferred when molecules bump into each other in the air and produce sound waves that allow us to identify the source of the sounds that we encounter. These sound waves create different frequencies, with low frequency sounds being lower pitched and higher frequency sounds being higher pitched. There are a few theories that have been proposed to help account as to why individuals can distinguish between pitch perception and frequencies.

The **temporal theory** of pitch perception asserts that frequency is coded by the activity level of a sensory neuron. This would mean that a given hair cell would fire action potentials related to the frequency of the sound wave. While this is a very intuitive explanation, we detect such a broad range of frequencies (20–20,000 Hz) that the frequency of action potentials fired by hair cells cannot account for the entire range. Because of properties related to sodium channels on the neuronal membrane that are involved in action potentials, there is a point at which a cell cannot fire any faster (Shamma, 2001).

The **place theory** of pitch perception suggests that different portions of the basilar membrane (**a stiff structural element within the cochlea of the inner ear**) moves up and down in response to incoming sound waves. More specifically, the base of the basilar

membrane responds best to high frequencies and the tip of the basilar membrane responds best to low frequencies. Therefore, hair cells that are in the base portion would be labeled as high-pitch receptors, while those in the tip of basilar membrane would be labeled as low-pitch receptors (Shamma, 2001). In reality, both theories explain different aspects of pitch perception. At frequencies up to about 4000 Hz, it is clear that both the rate of action potentials and place contribute to our perception of pitch. However, much higher frequency sounds can only be encoded using place cues (Shamma, 2001).

Similar to the need for recognizing different pitches and frequencies, knowing where particular sounds are coming from (sound localization) is an important part of navigating the environment around us. The auditory system has the ability to use monaural (one ear) and binaural (two ears) cues to locate where a particular sound might be coming from. Each pinna interacts with incoming sound waves differently, depending on the sound's source relative to our bodies. This interaction provides a monaural cue that is helpful in locating sounds that occur above or below and in front or behind us. The sound waves received by your two ears from sounds that come from directly above, below, in front, or behind you would be identical; therefore, monaural cues are essential (Grothe, Pecka, & McAlpine, 2010).

Binaural cues, on the other hand, provide information on the location of a sound along a horizontal axis by relying on differences in patterns of vibration of the eardrum between our two ears. If a sound comes from an off-center location, it creates two types of binaural cues: interaural level differences and interaural timing differences. **Interaural level difference** refers to the fact that a sound coming from the right side of your body is more intense at your right ear than at your left ear because of the attenuation of the sound wave as it passes through your head. **Interaural timing difference** refers to the small difference in the time at which a given sound wave arrives at each ear, illustrated in Figure 5.3.2. Certain brain areas monitor these differences to construct where along a horizontal axis a sound originates (Grothe et al., 2010).

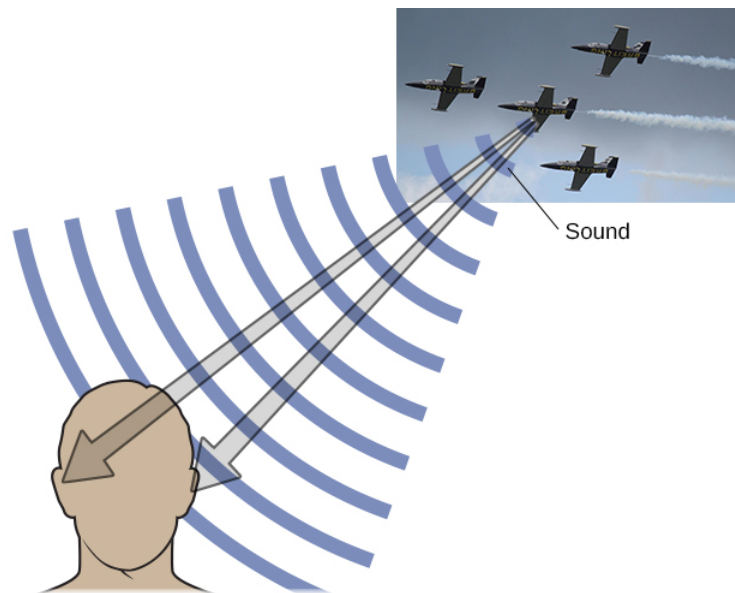


Figure 5.3.2: Localizing sound involves the use of both monaural and binaural cues. (credit "plane": modification of work by Max Pfandl)

### 5.3.1.1 Hearing Loss

#### Hearing Loss

- About 2 to 3 out of every 1,000 children in the United States are born with a detectable level of hearing loss in one or both ears (<https://www.nidcd.nih.gov/health/statistics-hearing>).
- More than 90 percent of deaf children are born to hearing parents (<https://www.nidcd.nih.gov/health/statistics-hearing>).
- Approximately 15% of American adults (37.5 million) aged 18 and over report some trouble hearing (<https://www.nidcd.nih.gov/health/statistics/quick-statistics-hearing>)

Conductive hearing loss can be caused by physical damage to the ear (such as to the eardrums); this condition reduces the ability of the ear to transfer vibrations from the outer ear to the inner ear. Conductive hearing loss can also be a result of fusion of the ossicles (**three bones in the middle ear**). Sensorineural hearing loss, which is caused by damage to the cilia (of the hair cells) or to the auditory nerve, is not as common as conductive hearing loss but the likelihood of this condition increases with age (Tennessee,

2007). As we continue to get older damage to the cilia increases; by the age of 65 years old 40% of individuals will have had damage to the cilia (Chisolm, Willott, & Lister, 2003).

Individuals who have experienced sensorineural hearing loss may benefit from a cochlear implant. Data From the National Institutes of Health shows that as of December 2019, approximately 736,900 cochlear implants have been implanted worldwide. In the United States, roughly 118,100 devices have been implanted in adults and 65,000 in children The following video explains the process of a cochlear implant.

Cochlear implant surgeries and how they work:

<https://www.youtube.com/watch?v=AqXBrKwB96E>

## Deafness and Deaf Culture

In most modern nations people who are born or become deaf at an early age have developed their own system of communication and culture amongst themselves and people close to them. It has been argued that encouraging deaf people to sign is a more appropriate adjustment as opposed to encouraging them to speak, read lips or have cochlear implant surgeries. However, more recent studies suggest that due to advancements in technology, cochlear implants increase the likelihood of a person being able to have and engage in some auditory and speaking activities if implanted early enough (Dettman, Pinder, Briggs, Dowell, & Leigh, 2007; Dorman & Wilson, 2004). As a result parents often face the difficult decision of whether to take advantage of new technologies and approaches of providing support to deaf students in mainstream classroom settings or utilizing American Sign Language (ASL) schools and encouraging more immersion in those settings.

## Hearing and the Vestibular System

The vestibular system has some similarities with the auditory system. It utilizes hair cells just like the auditory system, but it excites them in different ways. There are five vestibular receptor organs in the inner ear: the utricle, the saccule, and three semicircular canals. Together, they make up what's known as the vestibular labyrinth that is shown in Figure 5.3.3. The utricle and saccule respond to acceleration in a straight line, such as gravity. The roughly 30,000 hair cells in the utricle and 16,000 hair cells in the saccule lie below a gelatinous layer, with their stereocilia projecting into the gelatin. Embedded in this gelatin are calcium carbonate crystals—like tiny rocks. When the head is tilted, the crystals continue to be pulled straight down by gravity, but the new angle of the head causes the gelatin to shift, thereby bending the stereocilia. The bending of the stereocilia stimulates the neurons, and they signal to the brain that the head is tilted, allowing the maintenance of balance. It is the vestibular branch of the vestibulocochlear cranial nerve that deals with balance.

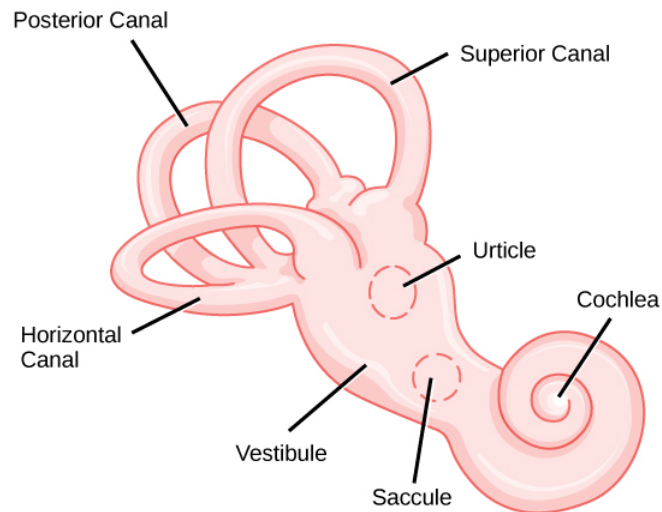


Figure 5.3.3 The structure of the vestibular labyrinth is shown. (credit: modification of work by NIH)

## 5.3.2 Attributions

- Hearing sections adapted by Isaias Hernandez from "Anatomy and Physiology from Oregon State University"; <https://open.oregonstate.edu/aandp/chapter/15-3-hearing/>

- Hearing sections adapted by Isaias Hernandez from "Psychology 2e from OpenStax"; <https://openstax.org/books/psychology-2e/pages/5-4-hearing>

### 5.3.3 References

<https://www.nidcd.nih.gov/health/statistics-hearing>

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## CHAPTER OVERVIEW

### 6: Pain and Stress

6.1: Touch and Pain

6.2: Protective and damaging effects of stress mediators- central role of the brain

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## 6.1: Touch and Pain

By Guro E. Løseth, Dan-Mikael Ellingson, and Siri Leknes

University of Oslo, University of Gothenburg

The sensory systems of touch and pain provide us with information about our environment and our bodies that is often crucial for survival and well-being. Moreover, touch is a source of pleasure. In this module, we review how information about our environment and our bodies is coded in the periphery and interpreted by the brain as touch and pain sensations. We discuss how these experiences are often dramatically shaped by top-down factors like motivation, expectation, mood, fear, stress, and context. When well-functioning, these circuits promote survival and prepare us to make adaptive decisions. Pathological loss of touch can result in perceived disconnection from the body, and insensitivity to pain can be very dangerous, leading to maladaptive hazardous behavior. On the other hand, chronic pain conditions, in which these systems start signaling pain in response to innocuous touch or even in the absence of any observable sensory stimuli, have tremendous negative impact on the lives of the affected. Understanding how our sensory-processing mechanisms can be modulated psychologically and physiologically promises to help researchers and clinicians find new ways to alleviate the suffering of chronic-pain patients.

### learning objectives

- Describe the transduction of somatosensory signals: The properties of the receptor types as well as the difference in the properties of C-afferents and A-afferents and what functions these are thought to have.
- Describe the social touch hypothesis and the role of affective touch in development and bonding.
- Explain the motivation–decision model and descending modulation of pain, and give examples on how this circuitry can promote survival.
- Explain how expectations and context affect pain and touch experiences.
- Describe the concept of chronic pain and why treatment is so difficult.

### Introduction

Imagine a life free of pain. How would it be—calm, fearless, serene? Would you feel invulnerable, invincible? Getting rid of **pain** is a popular quest—a quick search for “pain-free life” on Google returns well over 4 million hits—including links to various bestselling self-help guides promising a pain-free life in only 7 steps, 6 weeks, or 3 minutes. Pain management is a billion-dollar market, and involves much more than just pharmaceuticals. Surely a life with no pain would be a better one?



Figure 8.5.1: Patient with HSAN-V genetic mutation affecting pain nerve growth. Severely affected 12-year-old boy with damages to his left knee and ankles. (Minde et al., 2004) [Used with permission]

Well, consider one of the “lucky few”: 12-year-old “Thomas” has never felt deep pain. Not even when a fracture made him walk around with one leg shorter than the other, so that the bones of his healthy leg were slowly crushed to destruction underneath the knee joint (see Figure 8.5.1 ). For Thomas and other members of a large Swedish family, life without pain is a harsh reality because of a mutated gene that affects the growth of the nerves conducting deep pain. Most of those affected suffer from joint damage and frequent fractures to bones in their feet and hands; some end up in wheelchairs even before they reach puberty (Minde et al., 2004). It turns out pain—generally—serves us well.

Living without a sense of touch sounds less attractive than being free of pain—touch is a source of pleasure and essential to how we feel. Losing the sense of touch has severe implications—something patient G. L. experienced when an antibiotics treatment damaged the type of nerves that signal touch from her skin and the position of her joints and muscles. She reported feeling like she’d lost her physical self from her nose down, making her “disembodied”—like she no longer had any connection to the body attached to her head. If she didn’t look at her arms and legs they could just “wander off” without her knowing—initially she was unable to walk, and even after she relearned this skill she was so dependent on her visual attention that closing her eyes would cause her to land in a hopeless heap on the floor. Only light caresses like those from her children’s hands can make her feel she has a body, but even these sensations remain vague and elusive (Olausson et al., 2002; Sacks, 1985).

## Sensation

### Cutaneous Senses of the Skin Connect the Brain to the Body and the Outside World

Touch and pain are aspects of the somatosensory system, which provides our brain with information about our own body (**interoception**) and properties of the immediate external world (**exteroception**) (Craig, 2002). We have somatosensory receptors located all over the body, from the surface of our skin to the depth of our joints. The information they send to the central nervous system is generally divided into four modalities: **cutaneous senses**(senses of the skin), proprioception (body position), kinesthesia (body movement), and **nociception** (pain, discomfort). We are going to focus on the cutaneous senses, which respond to tactile, thermal, and pruritic (itchy) stimuli, and events that cause tissue damage (and hence pain). In addition, there is growing evidence for a fifth modality specifically channeling *pleasant* touch (McGlone & Reilly, 2010).

### Different Receptor Types Are Sensitive to Specific Stimuli

The skin can convey many sensations, such as the biting cold of a wind, the comfortable pressure of a hand holding yours, or the irritating itch from a woolen scarf. The different types of information activate specific receptors that convert the stimulation of the skin to electrical nerve impulses, a process called **transduction**. There are three main groups of receptors in our skin:

*mechanoreceptors*, responding to mechanical stimuli, such as stroking, stretching, or vibration of the skin; *thermoreceptors*, responding to cold or hot temperatures; and *chemoreceptors*, responding to certain types of chemicals either applied externally or released within the skin (such as histamine from an inflammation). For an overview of the different receptor types and their properties, see Box 1. The experience of *pain* usually starts with activation of **nociceptors**—receptors that fire specifically to potentially tissue-damaging stimuli. Most of the nociceptors are subtypes of either chemoreceptors or mechanoreceptors. When tissue is damaged or inflamed, certain chemical substances are released from the cells, and these substances activate the chemosensitive nociceptors. Mechanoreceptive nociceptors have a high threshold for activation—they respond to mechanical stimulation that is so intense it might damage the tissue.

### Box 1. Categories of low-threshold mechanoreceptors\*

| Identity of receptor  | Size of receptor*      | Type of skin where found | Speed of adaptation* | Adequate stimulus* |
|-----------------------|------------------------|--------------------------|----------------------|--------------------|
| Merkel's disks        | Small, sharp borders   | Glabrous*                | Slow                 | Pressure           |
| Meissner's corpuscles | Small, sharp borders   | Glabrous                 | Rapid                | Indentation        |
| Ruffini corpuscles    | Large, diffuse borders | Hairy + glabrous         | Slow                 | Stretching         |
| Pacinian corpuscles   | Large, diffuse borders | Hairy + glabrous         | Rapid                | Vibration          |

\* **Adequate stimulus:** The type of stimulus that the receptor is specialized to receive and respond to.

\* **Glabrous Skin:** The hairless skin found on our palms and the soles of our feet. This skin has a higher density of receptors of a more complex range, which reflects the fact that we use these areas of our body to actively explore our surroundings and to discriminate tactile properties of objects we're interacting with.

\* **Low-threshold mechanoreceptors:** Mechanoreceptors that respond to stimulus that is so light it doesn't threaten to damage the tissue around it. High-threshold mechanoreceptors respond to stimulation of higher intensity, and are a type of nociceptor.

\* **Receptive field:** The space of skin or tissue in which stimulation will elicit a response in the receptor. Smaller receptive fields make the receptor more sensitive to details.

\* **Speed adaptation:** Slowly adapting mechanoreceptors continue to fire action potentials during sustained stimulation. Rapidly adapting mechanoreceptors fire action potentials in response to stimulus onset and offset (i.e. to stimuli changes), and help detect stimulus movement on the skin.

### Action Potentials in the Receptor Cells Travel as Nerve Impulses with Different Speeds

When you step on a pin, this activates a host of mechanoreceptors, many of which are nociceptors. You may have noticed that the sensation changes over time. First you feel a sharp stab that propels you to remove your foot, and only then you feel a wave of more aching pain. The sharp stab is signaled via fast-conducting **A-fibers**, which project to the **somatosensory cortex**. This part of the cortex is **somatotopically organized**—that is, the sensory signals are represented according to where in the body they stem from (see illustrations, Figure 8.5.2). The unpleasant ache you feel after the sharp pin stab is a separate, simultaneous signal sent from the nociceptors in your foot via thin **C-pain or Aδ-fibers** to the insular cortex and other brain regions involved in processing of emotion and interoception (see Figure 8.5.3 for a schematic representation of this pathway). The experience of stepping on a pin is, in other words, composed by two separate signals: one discriminatory signal allowing us to localize the touch stimulus and distinguish whether it's a blunt or a sharp stab; and one affective signal that lets us know that stepping on the pin is bad. It is common to divide pain into sensory–discriminatory and affective–motivational aspects (Auvray, Myin, & Spence, 2010). This distinction corresponds, at least partly, to how this information travels from the peripheral to the central nervous system and how it is processed in the brain (Price, 2000).

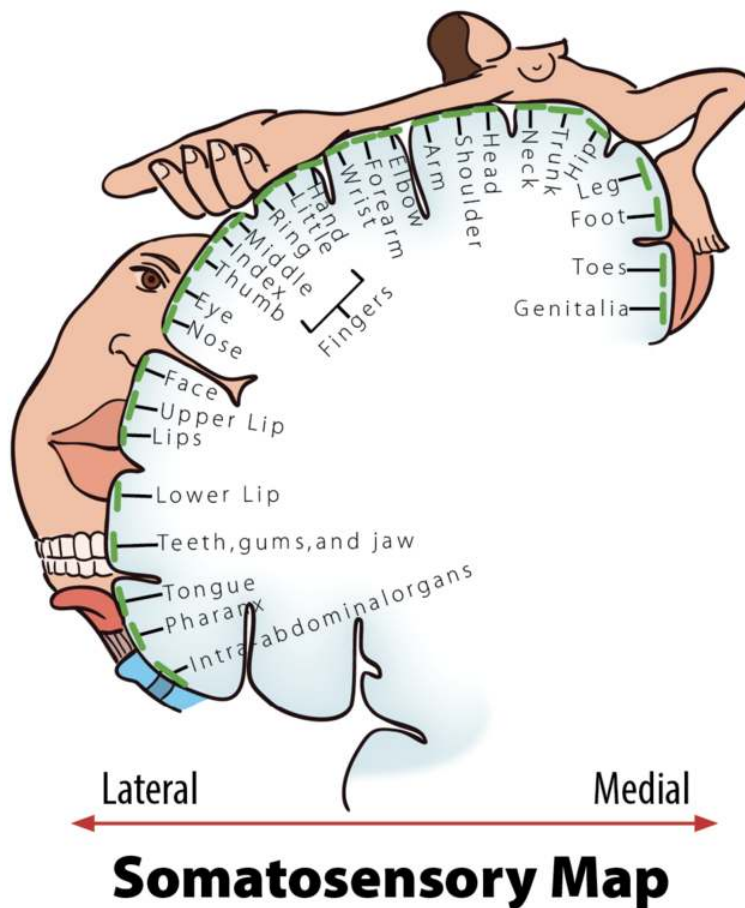


Figure 8.5.2: Somatosensory map: Body parts are represented in specific locations on the somatosensory cortex. Representations map out somatotopically, with the feet located medially and shoulders and arms laterally to the interhemispheric fissure. Facial structures are represented in a different location to the scalp and head; the face oriented upside down with the forehead pointing towards the shoulders.

### Affective Aspects of Touch Are Important for Development and Relationships

Touch senses are not just there for discrimination or detection of potentially painful events, as Harlow and Suomi (1970) demonstrated in a series of heartbreaking experiments where baby monkeys were taken from their mothers. The infant monkeys could choose between two artificial surrogate mothers—one “warm” mother without food but with a furry, soft cover; and one cold, steel mother with food. The monkey babies spent most of their time clinging to the soft mother, and only briefly moved over to the hard, steel mother to feed, indicating that touch is of “overpowering importance” to the infant (Harlow & Suomi, 1970, p. 161). Gentle touch is central for creating and maintaining social relationships in primates; they groom each other by stroking the fur and removing parasites—an activity important not only for their individual well-being but also for group cohesion (Dunbar, 2010; Keverne, Martensz, & Tuite, 1989). Although people don’t groom each other in the same way, gentle touch is important for us, too.

The sense of touch is the first to develop while one is in the womb, and human infants crave touch from the moment they’re born. From studies of human orphans, we know that touch is also crucial for human development. In Romanian orphanages where the babies were fed but not given regular attention or physical contact, the children suffered cognitive and neurodevelopmental delay (Simons & Land, 1987). Physical contact helps a crying baby calm down, and the soothing touch a mother gives to her child is thought to reduce the levels of stress hormones such as cortisol. High levels of cortisol have negative effects on neural development, and they can even lead to cell loss (Feldman, Singer, & Zagoory, 2010; Fleming, O’Day, & Kraemer, 1999; Pechtel & Pizzagalli, 2011). Thus, stress reduction through hugs and caresses might be important not only for children’s well-being, but also for the development of the infant brain.

The skin senses are similar across species, likely reflecting the evolutionary advantage of being able to tell what is touching you, where it's happening, and whether or not it's likely to cause tissue damage. An intriguing line of touch research suggests that humans, cats, and other animals have a special, evolutionarily preserved system that promotes gentle touch because it carries social and emotional significance. On a peripheral level, this system consists of a subtype of **C-fibers** that responds not to painful stimuli, but rather to gentle stroking touch—called **C-tactile** fibers. The firing rate of the C-tactile fibers correlates closely with how pleasant the stroking feels—suggesting they are coding specifically for the gentle caresses typical of social affiliative touch (Löken, Wessberg, Morrison, McGlone, & Olausson, 2009). This finding has led to the **social touch hypothesis**, which proposes that C-tactile fibers form a system for touch perception that supports social bonding (Morrison, Löken, & Olausson, 2010; Olausson, Wessberg, Morrison, McGlone, & Vallbo, 2010). The discovery of the C-tactile system suggests that touch is organized in a similar way to pain; fast-conducting A-fibers contribute to sensory–discriminatory aspects, while thin C-fibers contribute to affective–motivational aspects (Löken, Wessberg, Morrison, McGlone, & Olausson, 2009). However, while these “hard-wired” afferent systems often provide us with accurate information about our environment and our bodies, how we experience touch or pain depends very much on top-down sources like motivation, expectation, mood, fear, and stress.

## Modulation

### Pain Is Necessary for Survival, but Our Brain Can Stop It if It Needs To

In April 2003, the climber Aron Ralston found himself at the floor of Blue John Canyon in Utah, forced to make an appalling choice: face a slow but certain death—or amputate his right arm. Five days earlier he fell down the canyon—since then he had been stuck with his right arm trapped between an 800-lb boulder and the steep sandstone wall. Weak from lack of food and water and close to giving up, it occurred to him like an epiphany that if he broke the two bones in his forearm he could manage to cut off the rest with his pocket knife. The thought of freeing himself and surviving made him so excited he spent the next 40 minutes completely engrossed in the task: first snapping his bones using his body as a lever, then sticking his fingers into the arm, pinching bundles of muscle fibers and severing them one by one, before cutting the blue arteries and the pale “noodle-like” nerves. The pain was unimportant. Only cutting through the thick white main nerve made him stop for a minute—the flood of pain, he describes, was like thrusting his entire arm “into a cauldron of magma.” Finally free, he rappelled down a cliff and walked another 7 miles until he was rescued by some hikers (Ralston, 2010). How is it possible to do something so excruciatingly painful to yourself, and still manage to walk, talk, and think rationally afterwards? The answer lies within the brain, where signals from the body are interpreted. When we perceive somatosensory and nociceptive signals from the body, the experience is highly subjective and malleable by motivation, attention, emotion, and context.

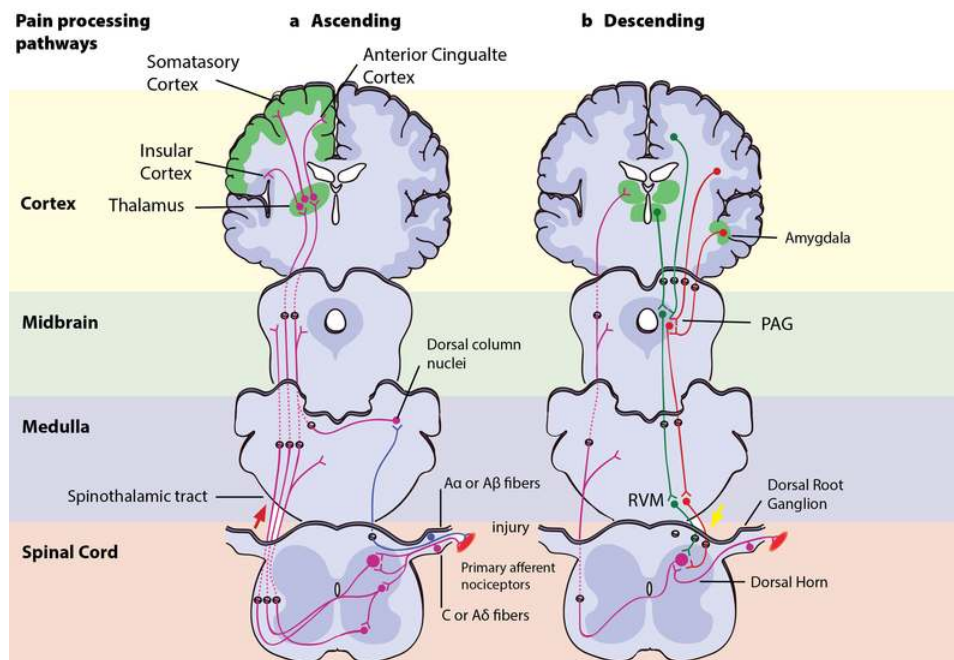


Figure 8.5.3: Pain processing pathways

Left - Ascending pain pathways: An injury is signaled simultaneously via fast-conducting Aα or Aβ-fibers and slow-conducting C-pain or Aδ-fibers. The fast A-fibers signal pressure, stretching and other tissue movements to the somatosensory cortex via the dorsal column nuclei. The C-pain and Aδ-fibers send pain information from nociceptors in the tissue or skin, and transmit these signals to second order neurons in the dorsal horn of the spinal cord. The second order neurons then cross over to the opposite side, where they form the ascending spinothalamic tract. This tract projects signals to nuclei in the medulla and midbrain on the way up to the thalamus (T). The thalamus relays the information to the somatosensory and insular cortex, as well as cortical regions mediating different aspects of the pain experience such as affective responses in the cingulate cortex.

Right - Descending pain modulation pathways: Information from the environment and certain motivational states can activate this top-down pathway. Several areas in the limbic forebrain including the anterior cingulate and insular cortex, nuclei in the amygdala and the hypothalamus (H), project to the midbrain periaqueductal grey (PAG), which then modulates ascending pain transmission from the afferent pain system indirectly through the rostral ventromedial medulla (RVM) in the brainstem. This modulating system produces analgesia by the release of endogenous opioids, and uses ON- and OFF-cells to exert either inhibitory (green) or facilitatory (red) control of nociceptive signals at the spinal dorsal horn.

### The Motivation–Decision Model and Descending Modulation of Pain

According to the *motivation–decision model*, the brain automatically and continuously evaluates the pros and cons of any situation—weighing impending threats and available rewards (Fields, 2004, 2006). Anything more important for survival than avoiding the pain activates the brain’s **descending pain modulatory system**—a top-down system involving several parts of the brain and brainstem, which inhibits nociceptive signaling so that the more important actions can be attended to. In Aron’s extreme case, his actions were likely based on such an unconscious decision process—taking into account his homeostatic state (his hunger, thirst, the inflammation and decay of his crushed hand slowly affecting the rest of his body), the sensory input available (the sweet smell of his dissolving skin, the silence around him indicating his solitude), and his knowledge about the threats facing him (death, or excruciating pain that won’t kill him) versus the potential rewards (survival, seeing his family again). Aron’s story illustrates the evolutionary advantage to being able to shut off pain: The descending pain modulatory system allows us to go through with potentially life-saving actions. However, when one has reached safety or obtained the reward, healing is more important. The very same descending system can then “crank up” nociception from the body to promote healing and motivate us to avoid potentially painful actions. To facilitate or inhibit nociceptive signals from the body, the descending pain modulatory system uses a set of ON- or OFF-cells in the brainstem, which regulates how much of the nociceptive signal reaches the brain. The descending system is dependent on opioid signaling, and **analgesics** like morphine relieve pain via this circuit (Petrovic, Kalso, Petersson, & Ingvar, 2002).



Social rewards, like holding the hands or just seeing the picture of a loved one, can reduce sensations of pain. [Image: rogerl01, CC0 Public Domain, [goo.gl/m25gce](https://goo.gl/m25gce)]

Thinking about the good things, like his loved ones and the life ahead of him, was probably pivotal to Aron’s survival. The promise of a reward can be enough to relieve pain. Expecting pain relief (getting less pain is often the best possible outcome if you’re in pain, i.e., it is a reward) from a medical treatment contributes to the **placebo effect**—where pain relief is due at least partly to your brain’s descending modulation circuit, and such relief depends on the brain’s own opioid system (Eippert et al., 2009; Eippert, Finsterbusch, Bingel, & Buchel, 2009; Levine, Gordon, & Fields, 1978). Eating tasty food, listening to good music, or feeling pleasant touch on your skin also decreases pain in both animals and humans, presumably through the same mechanism in the brain (Leknes & Tracey, 2008). In a now classic experiment, Dum and Herz (1984) either fed rats normal rat food or let them feast on highly rewarding chocolate-covered candy (rats love sweets) while standing on a metal plate until they learned exactly what to expect when placed there. When the plate was heated up to a noxious/painful level, the rats that expected candy endured the temperature for twice as long as the rats expecting normal chow. Moreover, this effect was completely abolished when the rats’ opioid (endorphin) system was blocked with a drug, indicating that the analgesic effect of reward anticipation was caused by **endorphin** release.

For Aron the climber, both the stress from knowing that death was impending and the anticipation of the reward it would be to survive probably flooded his brain with endorphins, contributing to the wave of excitement and euphoria he experienced while he carried out the amputation “like a five-year-old unleashed on his Christmas presents” (Ralston, 2010). This altered his experience of the pain from the extreme tissue damage he was causing and enabled him to focus on freeing himself. Our brain, it turns out, can modulate the perception of how unpleasant pain is, while still retaining the ability to experience the intensity of the sensation (Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Rainville, Feine, Bushnell, & Duncan, 1992). Social rewards, like holding the hand of your boyfriend or girlfriend, have pain-reducing effects. Even looking at a picture of him/her can have similar effects—in fact, seeing a picture of a person we feel close to not only reduces subjective pain ratings, but also the activity in pain-related brain

areas (Eisenberger et al., 2011). The most common things to do when wanting to help someone through a painful experience—being present and holding the person’s hand—thus seems to have a measurably positive effect.

### When Touch Becomes Painful or Pain Becomes Chronic

Chances are you’ve been sunburned a few times in your life and have experienced how even the lightest pat on the back or the softest clothes can feel painful on your over-sensitive skin. This condition, where innocuous touch gives a burning, tender sensation, is similar to a chronic condition called **allodynia**—where neuronal disease or injury makes touch that is normally pleasant feel unpleasantly painful. In allodynia, neuronal injury in the spinal dorsal horn causes A $\beta$ -afferents, which are activated by non-nociceptive touch, to access nociceptive pathways (Liljencrantz et al., 2013). The result is that even gentle touch is interpreted by the brain as painful. While an acute pain response to **noxious stimuli** has a vital protective function, allodynia and other **chronic pain** conditions constitute a tremendous source of unnecessary suffering that affects millions of people. Approximately 100 million Americans suffer from chronic pain, and annual economic cost associated is estimated to be \$560–\$635 billion (Committee on Advancing Pain Research, Care, & Institute of Medicine, 2011). Chronic pain conditions are highly diverse, and they can involve changes on peripheral, spinal, central, and psychological levels. The mechanisms are far from fully understood, and developing appropriate treatment remains a huge challenge for pain researchers.

Chronic pain conditions often begin with an injury to a peripheral nerve or the tissue surrounding it, releasing hormones and inflammatory molecules that *sensitize* nociceptors. This makes the nerve and neighboring afferents more excitable, so that also uninjured nerves become hyperexcitable and contribute to the persistence of pain. An injury might also make neurons fire nonstop regardless of external stimuli, providing near-constant input to the pain system. **Sensitization** can also happen in the brain and in the descending modulatory system of the brainstem (Zambreanu, Wise, Brooks, Iannetti, & Tracey, 2005). Exactly on which levels the pain perception is altered in chronic pain patients can be extremely difficult to pinpoint, making treatment an often exhausting process of trial and error. Suffering from chronic pain has dramatic impacts on the lives of the afflicted. Being in pain over a longer time can lead to depression, anxiety (fear or anticipation of future pain), and immobilization, all of which may in turn exacerbate pain (Wiech & Tracey, 2009). Negative emotion and attention to pain can increase sensitization to pain, possibly by keeping the descending pain modulatory system in facilitation mode. Distraction is therefore a commonly used technique in hospitals where patients have to undergo painful treatments like changing bandages on large burns. For chronic pain patients, however, diverting attention is not a long-term solution. Positive factors like social support can reduce the risk of chronic pain after an injury, and so they can help to adjust to bodily change as a result of injury. We have already talked about how having a hand to hold might alleviate suffering. Chronic pain treatment should target these emotional and social factors as well as the physiological.

### The Power of the Mind



How powerful is the mind really? Well, the next time you have dental work done, know that some people opt for no Novocain, using only the power of their minds to overcome the pain. [Image: HypnoArt, CC0 Public Domain, [goo.gl/m25gce](https://goo.gl/m25gce)]

The context of pain and touch has a great impact on how we interpret it. Just imagine how different it would feel to Aron if someone amputated his hand against his will and for no discernible reason. Prolonged pain from injuries can be easier to bear if the incident causing them provides a positive context—like a war wound that testifies to a soldier’s courage and commitment—or **phantom pain** from a hand that was cut off to enable life to carry on. The relative meaning of pain is illustrated by a recent experiment, where the same moderately painful heat was administered to participants in two different contexts—one control context where the alternative was a nonpainful heat; and another where the alternative was an intensely painful heat. In the control context, where the moderate heat was the least preferable outcome, it was (unsurprisingly) rated as painful. In the other context it was the best possible outcome, and here the exact same moderately painful heat was actually rated as *pleasant*—because it meant the intensely painful heat had been avoided. This somewhat surprising change in perception—where pain becomes pleasant because it represents relief from something worse—highlights the importance of the meaning individuals ascribe to their pain, which can have decisive effects in pain treatment (Leknes et al., 2013). In the case of touch, knowing who or what is stroking your skin can make all the difference—try thinking about slugs the next time someone strokes your skin if you want an illustration of this point. In a recent study, a group of heterosexual males were told that they were about to receive sensual caresses on the leg by either a male experimenter or by an attractive female experimenter (Gazzola et al., 2012). The study participants could not see who was touching them. Although it was always the female experimenter who performed the caress, the heterosexual males rated the otherwise pleasant sensual caresses as clearly unpleasant when they believed the male experimenter did it. Moreover, brain responses to the “male touch” in somatosensory cortex were reduced, exemplifying how top-down regulation of touch resembles top-down pain inhibition.

Pain and pleasure not only share modulatory systems—another common attribute is that we don’t need to be on the receiving end of it ourselves in order to experience it. How did you feel when you read about Aron cutting through his own tissue, or “Thomas” destroying his own bones unknowingly? Did you cringe? It’s quite likely that some of your brain areas processing affective aspects of pain were active even though the nociceptors in your skin and deep tissue were not firing. Pain can be experienced vicariously,

as can itch, pleasurable touch, and other sensations. Tania Singer and her colleagues found in an fMRI study that some of the same brain areas that were active when participants felt pain on their own skin (anterior cingulate and insula) were also active when they were given a signal that a loved one was feeling the pain. Those who were most “empathetic” also showed the largest brain responses (Singer et al., 2004). A similar effect has been found for pleasurable touch: The posterior insula of participants watching videos of someone else’s arm being gently stroked shows the same activation as if they were receiving the touch themselves (Morrison, Bjornsdotter, & Olausson, 2011).

### Summary

Sensory experiences connect us to the people around us, to the rest of the world, and to our own bodies. Pleasant or unpleasant, they’re part of being human. In this module, we have seen how being able to inhibit pain responses is central to our survival—and in cases like that of climber Aron Ralston, that ability can allow us to do extreme things. We have also seen how important the ability to feel pain is to our health—illustrated by young “Thomas,” who keeps injuring himself because he simply doesn’t notice pain. While “Thomas” has to learn to avoid harmful activities without the sensory input that normally guides us, G. L. has had to learn how to keep approaching and move about in a world she can hardly feel at all, with a body that is practically disconnected from her awareness. Too little sensation or too much of it leads to no good, no matter how pleasant or unpleasant the sensation usually feels. As long as we have nervous systems that function normally, we are able to adjust the volume of the sensory signals and our behavioral reactions according to the context we’re in. When it comes to sensory signals like touch and pain, we are interpreters, not measuring instruments. The quest for understanding how our sensory–processing mechanisms can be modulated, psychologically and physiologically, promises to help researchers and clinicians find new ways to alleviate distress from chronic pain.

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## 6.2: Protective and damaging effects of stress mediators- central role of the brain

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## CHAPTER OVERVIEW

### 7: Psychoactive Drugs

[7.1: Psychopharmacology and Psychoactive Drug Classification](#)

[7.2: Mechanisms of Psychoactive Drug Action](#)

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## 7.1: Psychopharmacology and Psychoactive Drug Classification

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the [ASCCC OERI \(oeri@asccc.org\)](mailto:ASCCC_OERI@asccc.org).

### Learning Objectives

1. Describe the general principles of psychopharmacology.
2. Explain the criteria for psychoactive drugs and the various types of classification systems.
3. Differentiate drug types based on their neurochemical effects on neurotransmission and behavioral impacts.

### 7.1.1 Overview

**Psychopharmacology** is the study of how drugs affect how we think, feel, or behave most often through their actions on the nervous system. Understanding some of the basics about psychopharmacology can help us better explain a wide range of issues that interest psychologists and others. For example, the pharmacological treatment of certain neurodegenerative diseases such as Parkinson's and Alzheimer's disease tells us something about the disease itself. The pharmacological treatments used to treat psychiatric conditions such as schizophrenia or depression have undergone amazing development since the 1950s, and the drugs used to treat these disorders provide clues to what is happening in the brain of individuals with these conditions. Finally, understanding something about the actions of drugs of abuse on the nervous system and the way they are processed by the body can help us understand why some psychoactive drugs are so likely to be abused. In this chapter, we will provide an overview of some of these topics as well as discuss some current controversial areas in the field of psychopharmacology.

### 7.1.2 Psychopharmacology

Psychopharmacology, the study of how drugs affect the brain and behavior, is a relatively new science, although people have probably been taking drugs to change how they feel from early in human history (consider the eating of fermented fruit, ancient beer recipes, chewing on the leaves of the cocaine plant for stimulant properties as just some examples). The word *psychopharmacology* itself tells us that this is a field that bridges our understanding of behavior, brain function, and pharmacology. Additionally, the topics included within this field are extremely broad including the influence of expectations of drug effects, how the drug is processed by the body, and ultimately, to how the drug impacts various systems, particularly the central nervous system.

#### 7.1.2.1 Psychoactive Drugs

If a drug changes the way you feel, think, or behave it is often doing so by acting on your brain and other parts of your nervous system. We call these **psychoactive drugs**, and almost everyone has used them at some point (yes, caffeine counts). Virtually all psychoactive drugs cause psychological or behavioral changes by altering how neurons communicate with each other. It is important to recall that neurons communicate with each other by releasing **neurotransmitters** across the **synapse**. When the neurotransmitter crosses the synapse, it binds to a postsynaptic receptor (protein) on the receiving neuron and the message may then be transmitted onward. Neurotransmission is far more complicated than this, but the first step is understanding that virtually all **psychoactive drugs** alter how neurons communicate with each other in one way or another. While some drugs, such as most antidepressants and many stimulants, have well-defined effects at the level of the neuron, others, like alcohol, have more widespread and less-clear effects.

Some of the most important in terms of psychopharmacological treatment and drugs of abuse are outlined in Table 1. The neurons that release these neurotransmitters, for the most part, are localized within specific circuits of the brain that mediate specific types of behaviors.

Table 1: Key Neurotransmitters and Highlights of Their Neural, Behavioral, and Psychological Effects

| Neurotransmitter | Abbreviation | Behaviors or Diseases Related to These Neurotransmitters                                             |
|------------------|--------------|------------------------------------------------------------------------------------------------------|
| Acetylcholine    | ACh          | Learning and memory; Alzheimer's disease; Voluntary muscle movement in the peripheral nervous system |

| Neurotransmitter   | Abbreviation            | Behaviors or Diseases Related to These Neurotransmitters                    |
|--------------------|-------------------------|-----------------------------------------------------------------------------|
| Dopamine           | DA                      | Reward circuits; Motor control; Parkinson's disease; Schizophrenia          |
| Norepinephrine     | NE                      | Arousal; Depression                                                         |
| Serotonin          | 5-HT                    | Depression; Aggression; Schizophrenia                                       |
| Glutamate          | GLU                     | Learning; Major excitatory neurotransmitter in the brain                    |
| GABA               | GABA                    | Anxiety disorders; Epilepsy; Major inhibitory neurotransmitter in the brain |
| Endogenous Opioids | Endorphins, Enkephalins | Pain; Analgesia; Reward                                                     |

Psychoactive drugs can either increase the typical effect of neurotransmitters at the synapse (these are called **agonists**) or decrease it (**antagonists**). It is important to remember that the "typical" effect of a neurotransmitter can be either excitatory or inhibitory depending on the type of receptor it binds to. For example, stimulant drugs, such as amphetamine, methamphetamine, or ADHD medications like Adderall are agonists for dopamine and norepinephrine systems and can increase the "typical" *excitation* that occurs at certain dopamine or norepinephrine receptors. Other agonistic drugs, such as morphine and fentanyl will increase the typical *inhibitory* effect at many of our endogenous opioid (endorphin) synapses. In other words, acting as an agonist at an inhibitory receptor will cause even more inhibition than without the drug present. Antagonists for these same systems will have the opposite effects, such as the effect of the opioid receptor blocker, naloxone (Narcan) which results in less inhibition at endogenous opioid synapses. Yes, this is complicated, but you just need to remember that agonist drugs increase and antagonist drugs decrease whatever the typical effect is at a particular synapse, be it excitatory or inhibitory.

There are various ways that drugs can effect the steps of synaptic communication and, thus produce their agonistic and antagonistic effects. Some of these are more intuitive than others. For example, antidepressants such as Prozac or Celexa are selective serotonin reuptake inhibitors (commonly referred to as SSRIs) are agonists for the serotonin system. However, they achieve increased serotonin activity at the synapse by *blocking* the reuptake of serotonin back into the presynaptic axon terminal from which it was released. In other words, they increase serotonin activity by interfering with the mechanism that normally turns its activity off (i.e., reuptake). As you can see, the basic distinction of whether a drug is an agonist or antagonist can get quite complicated very quickly. More examples of agonists and antagonists for various neurotransmitter systems are presented in Table 2. For each example, the drug's trade name, which is the name of the drug provided by the drug company, and generic name (in parentheses) are provided.

Table 2 provides examples of drugs and their primary mechanism of action, but it is very important to realize that drugs can also have effects on other neurotransmitters or even hormones. Sometimes these varied effects can change the potency and/or effectiveness of a drug. This could prove useful when trying to find just the right combination of transmitter action to treat an individual's psychological disorder. Or it could be problematic if it leads to unwanted side effects. The reality is that most drugs currently available work only where we would like them to in the brain or only on a specific neurotransmitter. In many cases, individuals are sometimes prescribed one drug but then may also have to take additional drugs to reduce the side effects. Sometimes individuals stop taking medication because the side effects are so profound.

Table 2: Drug function and mechanism

| Drug                  | Mechanism                                               | Use                                       | Agonist/Antagonist      |
|-----------------------|---------------------------------------------------------|-------------------------------------------|-------------------------|
| Seroquel (quetiapine) | Blocks DA and 5-HT receptors                            | Schizophrenia, bipolar disorder           | Antagonist for DA, 5-HT |
| L-dopa                | Increase synthesis of DA                                | Parkinson's disease                       | Agonist for DA          |
| Prozac (fluoxetine)   | Blocks removal of 5-HT from synapse (prevents reuptake) | Depression, obsessive compulsive disorder | Agonist 5-HT            |
| Aricept (donepezil)   | Blocks removal of ACh from synapse                      | Alzheimer's disease                       | Agonist for ACh         |

| Drug                               | Mechanism                                                | Use                          | Agonist/Antagonist        |
|------------------------------------|----------------------------------------------------------|------------------------------|---------------------------|
| Revia (naltrexone)                 | Blocks opioid post-synaptic receptors                    | Alcoholism, opioid addiction | Antagonist (for opioids)  |
| Adderall (mixed salts amphetamine) | Increase release of DA, NE                               | ADHD                         | Agonist for DA, NE        |
| Ritalin (methylphenidate)          | Blocks removal of DA, NE, and lesser (5-HT) from synapse | ADHD                         | Agonist for DA, NE mostly |

### 7.1.3 Drug Classifications

#### Art in a Cup

Who knew that a cup of coffee could also be a work of art? A talented barista can make coffee look as good as it tastes. If you are a coffee drinker, you probably know that coffee can also affect your mental state. It can make you more alert and may improve your concentration. That's because the caffeine in coffee is a psychoactive drug. In fact, caffeine is the most widely consumed psychoactive substance in the world. In North America, for example, 90 percent of adults consume caffeine daily.

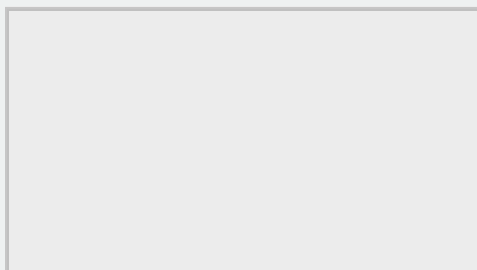


Figure 7.1.1: Murano Coffee with decoration on the surface.

Besides caffeine, other examples of psychoactive drugs include anti-anxiety medications (Xanax, Valium), antidepressants (Prozac, Celexa), alcohol, tobacco, marijuana, cocaine, psilocybin, oxycodone, and morphine. Organizing the wide range of different drugs into distinct categories is no easy task. One of the challenges is their various and, sometimes overlapping, pharmacological effects and mechanisms of action. Another challenge is that psychoactive drugs may be used for a variety of purposes, including therapeutic, ritual, and/or recreational.

In addition, many of these drugs may be legal prescription medications (e.g., oxycodone and morphine), legal nonprescription drugs (e.g., alcohol and tobacco), or illegal drugs (cocaine and psilocybin). To further complicate matters, some of these drugs, legal or not can be both therapeutic and abused. The status of cannabis (or marijuana), for example, is in flux, at least in the United States. Depending on where you are, cannabis may be used recreationally and/or medically, and it may be either legal or illegal. Legal prescription medications, such as opioids are also used illegally by alarmingly large numbers of people, resulting in a tragically high number of overdose deaths.

Although classification of psychoactive drugs is clearly complicated, there are some general categorizations that can prove useful.

#### 7.1.3.1 Classification Based on Psychopharmacological Effects

Psychoactive drugs can be divided into different classes according to their psychopharmacological effects. Several classes are listed below, along with examples of commonly used drugs in each class.

- **Stimulants:** Stimulate the brain and increase alertness and wakefulness. Examples of stimulants include caffeine, nicotine, cocaine, and amphetamines.
- **Depressants:** Calm the brain, reduce anxious feelings, and induce sleepiness. Examples of depressants include ethanol (in alcoholic beverages) and opioids such as oxycodone and heroin.
- **Anxiolytics:** Have a tranquilizing (calming) effect and inhibit anxiety. Examples of anxiolytic drugs include benzodiazepines such as diazepam (Valium), barbiturates such as phenobarbital, opioids, cannabis, and antidepressant drugs such as sertraline (Zoloft).

- **Euphoriant:** Cause a state of euphoria, or intense feelings of well-being and happiness. Examples of euphoriant include the so-called club drug MDMA (ecstasy), amphetamines, ethanol, and opioids such as morphine.
- **Hallucinogens:** Cause hallucinations and other perceptual anomalies. They also cause subjective changes in thoughts, emotions, and consciousness. Examples of hallucinogens include LSD, mescaline, nitrous oxide, and psilocybin.
- **Empathogens:** Produce feelings of empathy, or sympathy with other people. Examples of empathogens include MDMA (Ecstasy).



Figure 7.1.2: Ecstasy (MDMA) is most commonly taken in tablet form, like the colorful and decorated tablets shown

Many psychoactive drugs have multiple effects so they may be placed in more than one class. For example, many stimulants also have euphoriant properties, such as MDMA (Ecstasy). Furthermore, MDMA may also act as an empathogen or hallucinogen. As of 2016, MDMA had no accepted medical uses, but is undergoing testing for use in the treatment of post-traumatic stress disorder and certain other types of anxiety disorders (Mitchell et al., 2021). As you can tell, drug classification can get a bit complicated.

#### 7.1.3.2 Classification Based on Synaptic Mechanisms of Action

As previously stated, psychoactive drugs generally produce their effects by affecting brain chemistry, which in turn may cause changes in a person's mood, thinking, perception, and/or behavior. Each drug tends to have a specific action on one or more neurotransmitters or neurotransmitter receptors in the brain. Generally, they act as either agonists or antagonists.

- **Agonists** are drugs that mimic or increase the activity of particular neurotransmitters. They might act by promoting the synthesis of the neurotransmitters, reducing their reuptake from synapses, or mimicking their action by binding to receptors for the neurotransmitters.
- **Antagonists** are drugs that decrease the activity of particular neurotransmitters. They might act by interfering with the synthesis of the neurotransmitters or by blocking their receptors so the neurotransmitters cannot bind to them.

Consider the example of the neurotransmitter GABA. This is one of the most common neurotransmitters in the brain, and it normally has an inhibitory effect on cells. GABA *agonists*, which increase its effect at the synapse, include ethanol, depakote (anti-convulsant/bipolar medication), benzodiazepines (anti-anxiety medication), and other psychoactive drugs. All of these drugs work in different ways at the synapse, but ultimately increase the postsynaptic effect of GABA in the brain.

#### 7.1.3.3 Classification Based on Type of Use

You may have been prescribed psychoactive drugs by your doctor. For example, you may have been prescribed a drug to treat anxiety or depression or an opioid, drug such as codeine for pain (most likely in the form of Tylenol with added codeine). You may also use nonprescription psychoactive drugs, such as caffeine for mental alertness or cannabis (CBD or Marijuana) to treat pain or anxiety. These are just some of the many possible uses of psychoactive drugs.

#### 7.1.3.4 Medical Uses

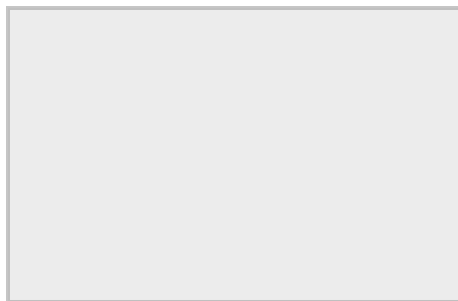


Figure 7.1.3: This child is being prepared to receive a general anesthetic prior to surgery

Medical uses of psychoactive drugs include general anesthesia, in which pain is blocked and unconsciousness is induced. General anesthetics are most often used during surgical procedures and may be administered in gaseous form. General anesthetics include the drugs halothane and ketamine. Other psychoactive drugs are used to manage pain without affecting consciousness. They may be prescribed either for acute pain in cases of trauma such as broken bones; or for chronic pain such as pain caused by arthritis, cancer, or fibromyalgia. Most often, the drugs used for pain control are opioids, such as morphine and codeine. Their pain inhibitory actions rest with their ability to enhance our endogenous opioid activity in the brain, which ultimately will lead to a reduction of incoming pain signals from the body.

Many psychiatric disorders are also managed with psychoactive drugs. For example, antidepressants such as Sertraline or Celexa are used to treat depression, anxiety, and eating disorders. These drugs act as agonists for serotonin systems in key circuits of the brain which play an important role in mood regulation. Anxiety disorders may also be treated with anxiolytic drugs, such as buspirone and diazepam. Diazepam is from the benzodiazepine class of drugs which are agonists of the GABA system and can inhibit limbic areas of the brain involved with the anxiety and fear response.

Stimulants such as amphetamines are agonists for monoamine transmitters and can be effective treatments for attention deficit disorder and certain sleep disorders. Antipsychotics such as clozapine and risperidone, as well as mood stabilizers such as lithium, are used to treat schizophrenia and bipolar disorder. These drugs act on a variety of transmitter systems in order to treat a variety of symptoms. Although controversial, relatively recent studies on the therapeutic, controlled use of hallucinogens such as MDMA and Psilocybin to treat disorders such as PTSD have been conducted.

#### 7.1.3.5 Ritual Uses

Certain psychoactive drugs, particularly hallucinogens, have been used for ritual purposes since prehistoric times. For example, Native Americans have used the mescaline-containing peyote cactus (pictured below) for religious ceremonies for as long as 5,700 years. In prehistoric Europe, the mushroom *Amanita muscaria*, which contains a hallucinogenic drug called muscimol, was used for similar purposes. Various other psychoactive drugs — including jimsonweed, psilocybin mushrooms, and cannabis — have also been used by various peoples for ritual purposes for millennia.

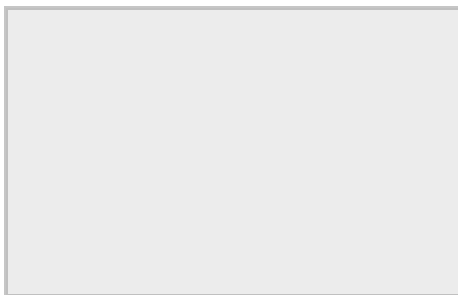


Figure 7.1.4: The peyote cactus contains a hallucinogenic drug that is still used by some Native Americans for religious rituals.

#### 7.1.3.6 Recreational Uses

The most typical recreational uses of psychoactive drugs have the purpose of altering one's consciousness and creating a feeling of euphoria commonly called a "high." Some of the drugs used most commonly for these purposes include cannabis, ethanol, opioids, and stimulants such as nicotine, amphetamine, or cocaine. Hallucinogens are also used recreationally, primarily for the alterations in thinking and perception that they cause.

Some investigators have suggested that the urge to alter one's state of consciousness is a universal human drive, similar to the drive to satiate thirst, hunger, or sexual desire. They think that the drive to alter one's state of mind is even present in children, who may attain an altered state by repetitive motions such as spinning or swinging. Some nonhuman animals also exhibit a drive to experience altered states. For example, they may consume fermented berries or fruit and become intoxicated. The way cats respond to catnip (Figure 7.1.6) is another example.

A variety of information on specific drugs used for recreational purposes is provided in section 6.3: Drugs of Abuse.

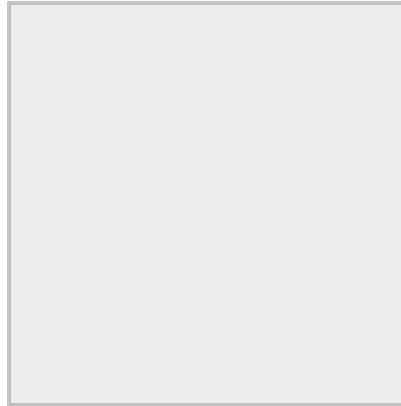


Figure 7.1.5: This cat is holding a catnip toy and apparently enjoying its psychoactive effects.

#### 7.1.4 Summary

It is probably clear now that psychoactive drugs can have profound and quite varied effects on how we think, feel, perceive the world, and behave. This range of effects depends on a multitude of factors including the particular neurotransmitter systems affected, the general pharmacology of the drug, and its specific synaptic effects. As described, the ability for drugs to act as either agonists or antagonists at synapses and the role of receptor subtypes (i.e. excitatory or inhibitory) have a major impact on the ultimate outcome to the individual. These synaptic effects and the influence of physiological effects that occur prior to drugs reaching the brain will be explored further in the next section of this chapter.

#### 7.1.5 Supplemental Resources

Learn more about psychiatric drugs that are being researched to treat mental health disorders. In this inspiring TED talk, neurobiologist David Anderson explains how modern psychiatric drugs treat the chemistry of the whole brain and why a more nuanced view of how the brain functions could lead to targeted psychiatric drugs that work better and avoid side effects.

#### 7.1.6 Attribution

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- Mitchell, J.M., Bogenschutz, M., Lilienstein, A. *et al.* (2021) MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med* 27, 1025–1033. <https://doi.org/10.1038/s41591-021-01336-3>

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## 7.2: Mechanisms of Psychoactive Drug Action

This page is a draft and under active development. Please forward any questions, comments, and/or feedback to the [ASCCC OERI \(oeri@asccc.org\)](mailto:ASCCC_OERI@asccc.org).

### Learning Objectives

1. Describe the key elements of pharmacokinetics and their relationship to drug action.
2. Compare and contrast the various drug administration methods in terms of potency, latency of action, and abuse potential.
3. Describe the key elements of pharmacodynamics, particularly drug effects on steps of synaptic transmission and major neural circuitry
4. Differentiate the major structures of the mesolimbic, "reward" pathway and the role of dopamine in its function.

### 7.2.1 Overview

Do drugs affect the body or does the body affect drugs? This may seem like either a very easy or a very odd question. Of course, the answer is drugs affect the body, right? For example, you take a certain drug and then your heart rate changes or you feel energized to move around a lot. In terms of psychoactive drugs, the brain, which is part of the body, is definitely affected by drugs. As we will see, neurotransmitters can become more active and the receptors that these neurotransmitters bind to may trigger either increased or decreased communication with other neurons, glands, or muscles. These examples should make it clear that drugs definitely affect the body. However, even before these effects on the body occur, the *body* is able to affect incoming drugs in profound ways. Thus, the answer to the earlier question is that the body affects drugs and drugs affect the body.

This section will review the basics on how both of these processes occur with a general review of the concepts of **pharmacokinetics** (how the body affects drugs) and **pharmacodynamics** (how drugs affect the body, or more specifically the brain). In covering these topics we will address various physiological processes, such as drug metabolism and elimination and the influence of drug administration methods on a drug's impact. In addition, we will go into the specifics of how drugs interact with the process of synaptic communication and then zoom out to see how they alter the activity of major circuits and structures of the brain, such as the so-called, "reward pathway."

### 7.2.2 Pharmacokinetics: What Is It – Why Is It Important?

**Pharmacokinetics** refers to how the body processes drugs as they enter the body. While this section may sound more like pharmacology, it is important to realize how important pharmacokinetics can be when considering the ultimate effects of psychoactive drugs. As mentioned previously, psychoactive drugs exert their effects on behavior by altering neuronal communication in the brain, and the majority of drugs reach the brain by traveling in the blood.

The acronym **ADME** is often used to specify the processes of:

- **A - Administration and Absorption** (how the drug gets into the blood),
- **D - Distribution** (how the drug gets to the organ of interest – in this case, the brain),
- **M - Metabolism** (how the drug is broken down so it no longer exerts its psychoactive effects), and
- **E - Elimination** (how the drug leaves the body).

We will focus on some of these processes to show their importance in determining the effects of psychoactive drugs.

#### 7.2.2.1 Drug Administration and Absorption



Figure 7.2.1: A drug delivered by IV reaches the brain more quickly than if the drug is taken orally. While rapid delivery has advantages, there are also risks involved with IV administration. (CC BY-SA 3.0; Calleamanecer via Wikimedia Commons)

Before a drug can be absorbed by the body it needs to be administered in some way (i.e., the drug has to get into the body). There are many ways to take drugs, and these routes of drug administration can have a significant impact on how quickly that drug reaches brain.

The most common route of administration is **oral administration**, which begins in the mouth and continues in the digestive system. This route is relatively **slow** and – perhaps surprisingly – often the most variable and complex route of administration. Drugs enter the stomach and then get absorbed by the blood supply and capillaries that line the small intestine. The rate of absorption can be affected by a variety of factors including the quantity and the type of food in the stomach (e.g., fats vs. proteins). This is why the medicine label for some drugs (like antibiotics) may specifically state foods that you should or should not consume within an hour of taking the drug because they can affect the rate of absorption.

Two of the most **rapid** routes of administration include **inhalation** (i.e., smoking or gaseous anesthesia) and **intravenous (IV)** in which the drug is injected directly into the vein and hence the blood supply. Both of these routes of administration can get the drug to brain in less than 10 seconds. IV administration also has the distinction of being the most dangerous because if there is an adverse drug reaction, there is very little time to administer any antidote, as in the case of an IV heroin overdose.

Key Elements of Drug Routes of Administration (Keys)

| Route of Administration | Typical Methods Used  | Speed of Absorption in Blood | Advantages / Disadvantages                                                                                                           |
|-------------------------|-----------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Oral (PO)               | Pill, Liquid, Edibles | <b>SLOWEST</b>               | Convenient, Gradual onset, Relatively safe / Variable blood levels due to individual differences in absorption and metabolism        |
| Subcutaneous            | Injection into skin   | ↓                            | Gradual onset, Avoids 1st pass metabolism / Only small volumes can be given, Possible localized irritation, tissue damage, infection |

| Route of Administration | Typical Methods Used                   | Speed of Absorption in Blood                                                       | Advantages / Disadvantages                                                                                                                                                                  |
|-------------------------|----------------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Intramuscular (IM)      | Injection into muscle                  |   | Steady absorption rates, Avoids 1st pass metabolism, Extended release possible / Only small volumes can be given, Possible localized irritation, tissue damage, infection                   |
| Rectal                  | Rectal Suppository                     |  | Useful in those with digestive issues or unconscious, Mostly avoids 1st pass metabolism, Relatively high blood levels / Invasive, Unpredictable absorption rates                            |
| Sublingual              | Under tongue                           |  | Direct & fast absorption, Avoids 1st pass metabolism, Quick termination possible                                                                                                            |
| Inhalation              | Smoke, Vape, Huff, Inhaler, Intranasal |  | Rapid absorption, Useful for emergency applications or localized effect (i.e. asthma), Reaches brain quickly / Variable dose & absorption, Relatively high abuse potential w/ certain drugs |
| Intravenous             | Injected into vein                     | <b>FASTEST</b>                                                                     | Very rapid absorption (~instantly), Avoids 1st pass metabolism, Useful for emergency applications, Accurate dosing / High abuse potential and risk for overdose with certain drugs          |

Why might knowing how quickly a drug gets to the brain be important? If we are considering therapeutic drugs, such as those used to treat anxiety, depression, or psychotic disorders, the time it takes to begin to relieve symptoms and how long this lasts can be critical information. For example, if treating an acute panic attack you would want a drug to act fast, whereas, if you want to prevent non-specific anxiety from occurring on a daily basis, you may use a different drug that acts more gradually but sticks around longer.

When considering potential drugs of abuse, administration and absorption rates are important for other reasons. Although there are multiple non-pharmacological risk factors for drug craving and substance use disorders, the pharmacokinetics of a drug can play a significant role. For example, if a drug activates the reward circuits in the brain and reaches these areas quickly, the drug may have a relatively high risk for abuse and psychological dependence. Psychostimulants like amphetamine or cocaine are examples of drugs that have high risk for abuse in part because they are agonists at dopamine neurons involved in reward and because these drugs exist in forms that can be either smoked or injected intravenously. Some argue that cigarette smoking is one of the hardest addictions to quit, and although part of the reason for this may be that smoking gets the nicotine into the brain very quickly (and indirectly acts on dopamine neurons), it is a more complicated story.

For drugs that reach the brain very quickly, not only is the drug potentially very addictive, but so are the cues associated with the drug (see Rohsenow, Niaura, Childress, Abrams, and Monti, 1990). A learned connection between drug use and the environmental elements that accompany it can complicate quitting by triggering symptoms of withdrawal and/or cravings. For an IV opioid user, this could be the sight of a container in which the drug and syringes are typically stored or other aspects of their typical drug-taking environment. For a cigarette smoker, it could be the smell of another person's smoke or even something as typical as finishing

dinner or waking up in the morning (if that is when the smoker usually has a cigarette). For both the opioid user and the cigarette smoker, the cues associated with the drug may actually cause craving that is alleviated by (you guessed it) – lighting a cigarette or injecting the opioid (i.e., relapse). This is one of the reasons individuals that enroll in drug treatment programs, especially out-of-town programs, are at significant risk of relapse if they later find themselves in proximity to old "environments", including friends and situations associated with drug use. But this is much *more* difficult for a cigarette smoker. How can someone avoid eating? Or avoid waking up in the morning, etc. These examples help you begin to understand how important the route of administration can be for psychoactive drugs.

#### 7.2.2.2 Drug Metabolism

**Metabolism** involves the breakdown of psychoactive drugs, and this occurs primarily in the liver. The liver produces **enzymes** (proteins that speed up a chemical reaction), and these enzymes help catalyze a chemical reaction that breaks down psychoactive drugs. Enzymes exist in "families," and many psychoactive drugs are broken down by the same family of enzymes, the Cytochrome P450 super family. Usually, there is not a unique enzyme for each drug; rather, certain enzymes can break down a wide variety of drugs. **Tolerance** to the effects of many drugs can occur with repeated exposure; that is, the drug produces less of an effect over time, so more of the drug is needed to get the same effect. This is particularly true for sedative drugs like alcohol or opiate-based painkillers (e.g., fentanyl, codeine). *Metabolic tolerance* is one kind of tolerance and it takes place primarily in the liver. Some drugs, such as alcohol cause **enzyme induction** – an increase in the enzymes produced by the liver. For example, chronic drinking results in alcohol being broken down more quickly, so the alcoholic needs to drink more to get the same effect – of course, until so much alcohol is consumed that it damages the liver (i.e. fatty liver or cirrhosis).

There are a variety of other ways that enzyme action can be altered by both physiological and environmental aspects of drug taking. For example, just the expectation of drug taking or the cues from the environment where drug taking regularly occurs can trigger either enzyme induction or inhibition and, thus altering the ultimate physical and/or psychological effects of the drug. These differences in response can be particularly dangerous if they involve an unexpected increase in life-threatening side effects, such as the respiratory depression seen in response to opioids.

After "surviving" the processes of absorption and initial metabolism but before being eliminated, drugs are distributed throughout the body until they reach their target. In the case of psychoactive drugs, the main target is the brain. At this point, the process shifts to *pharmacodynamics* where the roles reverse and drugs are now able to affect the body.

#### 7.2.3 Pharmacodynamics

If you have a headache or muscle pain, you might take a drug like ibuprofen (Advil, Motrin) or acetaminophen (Tylenol). Part of how these drugs work is to block the production of chemicals that cause the inflammation that is responsible for the pain. Thus, their target is the location of action is where the inflammation or pain is occurring. For psychoactive drugs, including those which treat pain the target of action for their effects is the brain or nervous system. The pharmacodynamics of their effects can be divided into two general categories: Their influence on specific steps of communication at the level of the synapse and the more holistic effect on the activity of certain circuits or major structures of the nervous system.

Just about all psychoactive drugs have their initial effects on one or more of the **steps of synaptic communication: neurotransmitter synthesis, storage, release, binding, reuptake, and breakdown** (See Figure 6.2.2). Remember, drugs can act as either agonists or antagonists of a neurotransmitter's typical effects. The drug L-dopa, for example acts as an agonist to increase the synthesis of dopamine and treat the dopamine dysfunction present in Parkinson's disease. Other agonist drugs like amphetamine and some other stimulants can increase the amount of dopamine activity by enhancing the release step. And yet others, such as cocaine can increase the synaptic activity of dopamine by blocking its reuptake. All these drugs are dopamine agonists (increase dopamine synaptic activity), but they can have very different psychological and behavioral effects due to the difference in the synaptic step targeted.

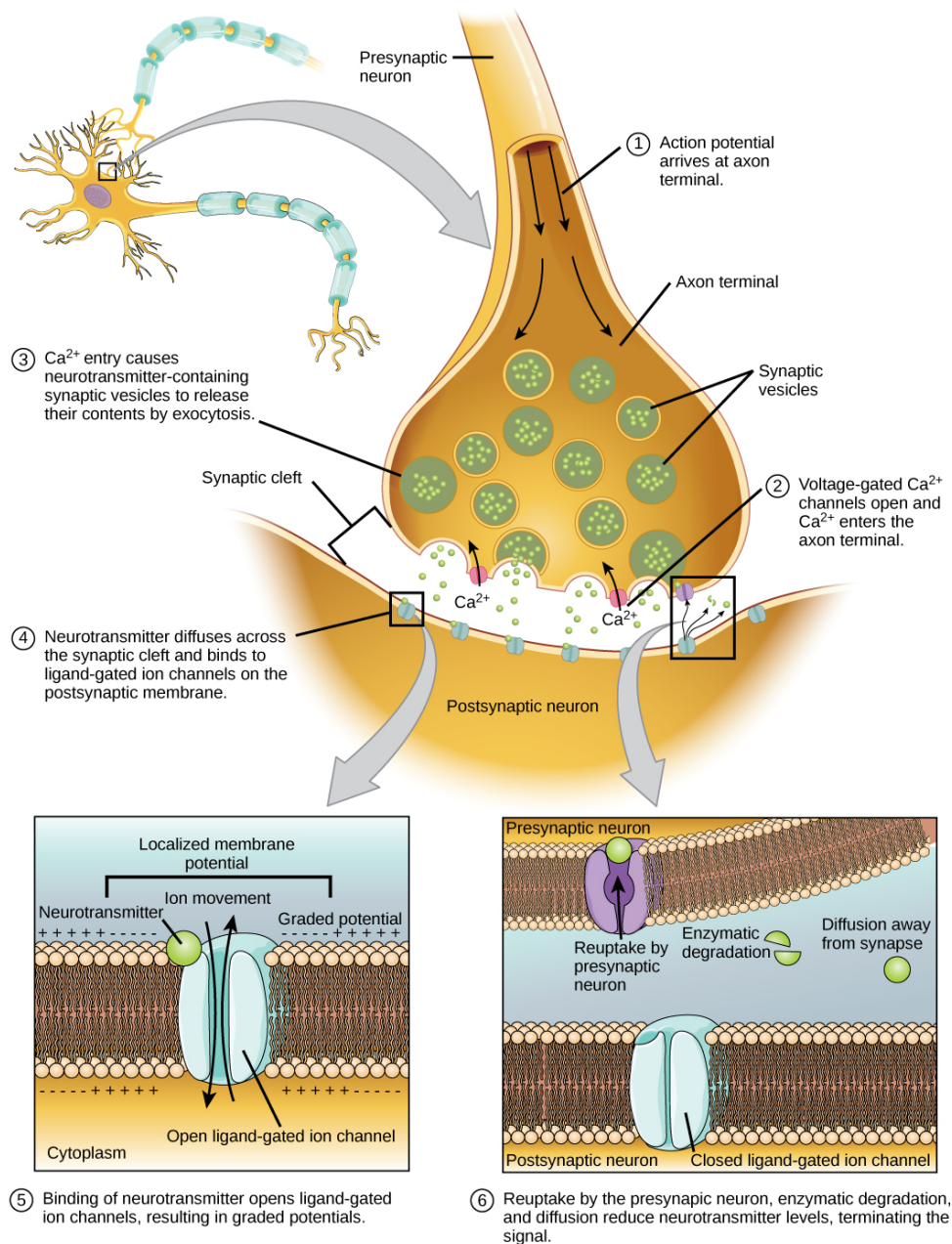


Figure 7.2.2: Steps in Synaptic Transmission starting with the arrival of the action potential and culminating in transmitter release into the synapse. Details of neurotransmitter binding and termination mechanisms in the synapse are included in insets. Psychoactive drugs can affect one or more of these steps, depending on the drug. (CC BY 4.0 by OpenStax)

Knowing these initial actions of drugs at the level of the synapse is important in order to understand how they ultimately affect our thinking, feeling, and behavior. However, the thousands or even millions of synaptic changes that occur every split second due to

drug action first need to be integrated in order to have noticeable effects. This integration is reflected in alterations of the activity of key structures and circuits of the nervous system.

### 7.2.4 Drug effects on Neural Structures and Circuits

Every distinct brain area or neural circuit can be affected in some way by the action of psychoactive drugs due to the integration process discussed above. For example, drugs that increase endorphin activity (i.e. Opioids) in certain areas of the brain can trigger changes in a major pain-inhibition pathway. Circuits involved with attention are affected by drugs that enhance norepinephrine systems and can be effective treatments for ADHD. Still other drugs, such as anti-anxiety medications (i.e. Xanax, Valium) are GABA agonists and can enhance the action of GABA throughout the brain, including the amygdala, which plays a significant role in fear and anxiety responses.

#### 7.2.4.1 Mesolimbic "Reward" Circuitry

One of the most interesting and significant circuits that has been studied for its role in drug taking and substance use disorder is the "reward circuit" or "pleasure pathway" of the brain. This circuitry is technically called the mesolimbic circuitry and contains major dopamine pathways in addition to other transmitters which play a role in the positive feelings associated with both natural and drug rewards (See Figure 6.2.3).

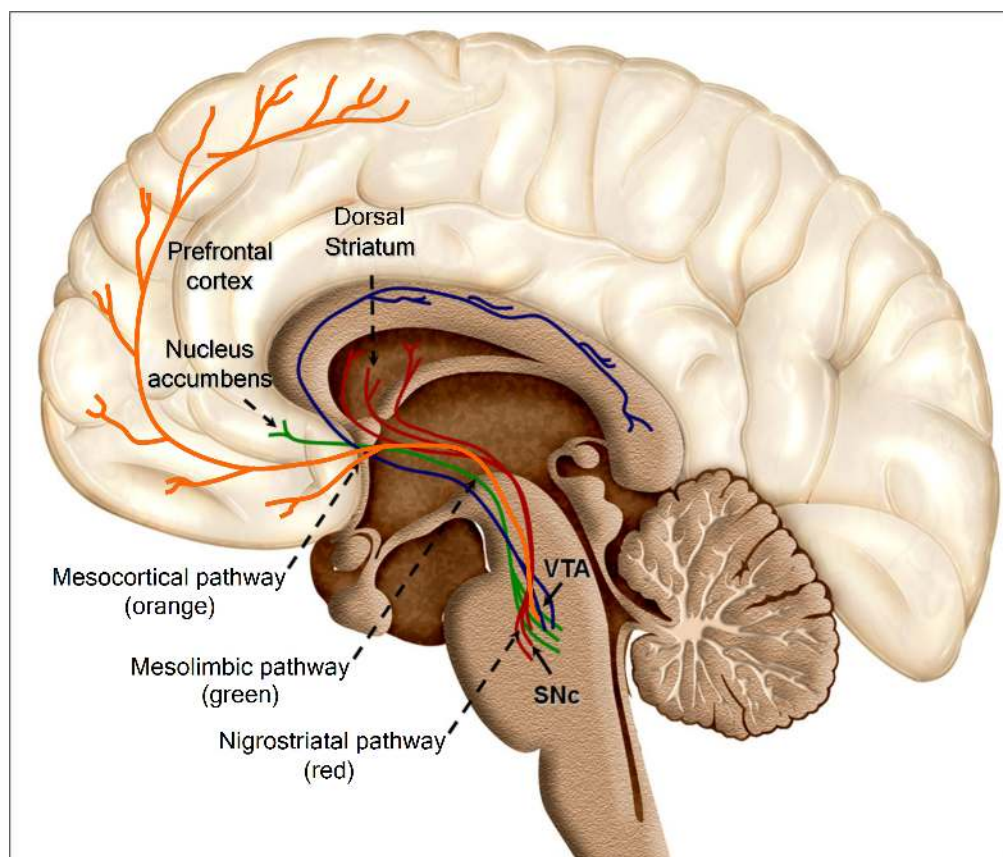


Figure 7.2.3: Mesolimbic, "Reward" Circuit and other Dopamine Pathways. These include pathways from both the Substantia Nigra (SNc) and Ventral Tegmental Area (VTA) to forebrain targets such as the Nucleus Accumbens and Prefrontal Cortex. From: Oscar Arias-Carrión1, Maria Stamelou, Eric Murillo-Rodríguez, Manuel Menéndez-González and Ernst Pöppel. Substantially modified by Seppi333, CC BY 2.0, via [Wikimedia Commons](https://commons.wikimedia.org/wiki/File:Mesolimbic_circuitry.png)

**The nucleus accumbens** definitely plays a central role in the **reward circuit**. Its operation is based chiefly on two essential neurotransmitters: dopamine, which promotes desire, and serotonin, whose effects include satiety and inhibition. Many animal studies have shown that many psychoactive drugs and natural rewards increase the production of dopamine in the nucleus accumbens, while reducing that of serotonin.

But the nucleus accumbens does not work in isolation. It maintains close relations with other areas involved in pleasure and reward. One area in particular is the **ventral tegmental area (VTA)**. Located in the midbrain, at the top of the brainstem, the VTA is one of the most primitive parts of the brain. Neurons of the VTA synthesize dopamine and then send it via their axons primarily to the

nucleus accumbens. The VTA is also influenced by endorphins whose receptors are targeted by opiate drugs such as heroin and morphine.

Another structure involved in pleasure mechanisms is the **prefrontal cortex**, whose role in planning and motivating action is well established. The prefrontal cortex is a significant relay in the reward circuit and also is modulated by dopamine.

**The locus coeruleus**, an alarm area of the brain and packed with norepinephrine, is another brain structure that plays an important role in drug abuse. When stimulated by a lack of the drug in question, the locus coeruleus drives the user to do anything necessary to obtain more drug.

Three other structures in the limbic system also play an active part in the pleasure circuit and, consequently, in drug dependency. The first is the **amygdala**, which can provide affective or mood information in response to drugs or environmental stimuli.

The second is the **hippocampus**, which preserves the agreeable memories associated with drug taking or other non-drug behaviors and, by association, all of the details of the environment in which these behaviors occur. The memory of these details may trigger positive feelings and, in the case of drugs reawaken the desire to take the drug again contributing to the possibility of relapse.

The third structure, the most anterior portion of the **insular cortex**, or insula, is regarded as part of the limbic system that is thought to play a role in the active pleasure-seeking associated both with food and with psychoactive substances. It has been proposed that this part of the cortex tells us about the bodily states associated with our emotional experiences and then relates these feeling states to cognitive processes such as decision-making (Damasio et al., 2013).

### 7.2.5 Summary

Psychoactive drugs clearly undergo quite a journey through the body and, ultimately the brain prior to causing changes in how we think, feel, perceive the world, and behave. The pharmacokinetic steps of administration, distribution, metabolism, and elimination have a major impact on the timing and amount of drug action prior to their arrival at their targets in the nervous system. Upon arrival, pharmacodynamic actions primarily at the synapse contribute to the diverse and dynamic action of drugs on neural communication and subsequent psychological and behavioral changes. Psychoactive drugs have the potential to affect structures in all parts of the nervous system as long as the appropriate receptors are there to receive the. The structures of the Mesolimbic Reward Circuitry play a particularly critical role in the action of many psychoactive drugs, both therapeutic and recreational.

### 7.2.6 Attributions

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### 7.2.7 References

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## CHAPTER OVERVIEW

### 8: Stimulants and Alcohol

[8.1: Stimulants](#)

[8.2: Alcohol](#)

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## 8.1: Stimulants

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A **stimulant** is any drug that increases the activity of the central nervous system. For this reason, they are also known as CNS stimulants or “uppers” due to their stimulating effects. Before examining any specific drugs, we will first go over some properties that are common across all stimulants.

### 8.1.1. Stimulant Overview

As mentioned, stimulants tend to increase CNS activity. A common method for doing so involves enhancing the effects of the sympathetic nervous system. Recall that this is the division of the autonomic nervous system that is responsible for our “fight-or-flight” response. When our sympathetic nervous system is activated, we enter a state of heightened arousal. Our bodies prepare for action by increasing our heart rate, dilating pupils, constricting blood vessels, increasing blood flow to the skeletal muscles, and causing various other physiological changes.

Stimulants target the pathways of the catecholamines norepinephrine and dopamine in the CNS and the sympathetic nervous system. Many stimulants, including the ones in this chapter, possess direct or indirect agonist activity at adrenergic receptors. These drugs are called **sympathomimetic drugs** because they evoke physiological changes that mimic the activation of the sympathetic nervous system.

Most stimulants cause euphoria and agitation while increasing energy, alertness, confidence, and sexual desire. Many stimulants have therapeutic uses, although the pleasurable effects and addictive properties of the drugs mean that they are also used frequently for recreational purposes.

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## 8.2. COCAINE

**Cocaine**, often informally referred to as *coke*, is one of the most well-known illicit drugs. Aside from its common depictions in media, it is also the second-most used illicit drug in the U.S. behind marijuana (National Survey of Drug Use and Health, 2019). In the following section, we will explore its role in culture and medicine and outline the exact mechanisms through which it causes its stimulatory effects.

### 8.2.1. Drug History and Overview

Cocaine is a psychoactive substance extracted from the leaves of the coca plant, *Erythroxylum coca*, which grows on the eastern slopes of the Andes Mountains. Coca leaves have been chewed as a mild stimulant for thousands of years in South America. They were also chewed for medicinal purposes and as a remedy to the stress of living at high altitudes. The use of coca spread to other parts of the world with the help of Spanish conquistadors, who found its ability to make workers eat less and work longer appealing.

Chemists began to try to isolate the alkaloid responsible for these effects from the plant in the 1800s. In 1860, graduate student Albert Niemann isolated the alkaloid and named it cocaine, after the coca plant. Interest in the drug’s potential medicinal uses quickly followed. Ophthalmologist Karl Koller demonstrated its properties as a local anesthetic, while Sigmund Freud advocated for its use as a stimulant and pain reliever.

The use of cocaine was popularized throughout the late 1800s. In Europe and America, it was readily available and advertised for its therapeutic effects. The original recipe for Coca-Cola included coca leaves, hence the name. Cocaine was purchased as an over-the-counter drug up until 1916. Not long afterward, it became regulated under the Harrison Narcotics Act. By then, reports of addiction and dependence had become more common, and governments moved to regulate cocaine use.

Cocaine remains a favored anesthetic in otolaryngology because of its local anesthetic and vasoconstricting properties. For other medical and dental uses, cocaine has mostly been replaced by safer local anesthetics such as lidocaine (Xylocaine®) and procaine (Novocain®), which derive their *-caine* suffixes from cocaine. Clinical use of cocaine is tightly regulated as it is classified as a Schedule II controlled substance (*i.e.*, a drug accepted for medical use with a high potential for abuse).

### 8.2.2. Administration and Pharmacokinetics

Cocaine, like many stimulants, comes in multiple forms. The salt form, **cocaine hydrochloride** (HCl), appears as a white powder that is typically snorted intranasally or dissolved and injected directly into a vein. Cocaine can be taken orally, but its effects are heavily reduced as stomach acid tends to leave it inactive, so oral administration is uncommon. It can also be used topically as a local anesthetic.

Removing the HCl from cocaine salt converts it to **cocaine freebase** or **crack**, which can be conveniently smoked. Technically, cocaine salt can be smoked as well, but this method is not popular because the resulting fumes are much more unpleasant. Cocaine freebase can be made by heating the HCl salt with volatile chemicals such as ammonia or by mixing it with baking soda in water and drying the crystals to produce the freebase cocaine. The name *crack* comes from the popping or crackling sound when it is heated and smoked. See the image below to compare the physical appearance of cocaine HCl (left) with that of crack cocaine (right):



Figure 8.2. Cocaine Hydrochloride and Cocaine Freebase (Crack)

Source: [Drug Enforcement Administration \(2014\)](#) United States government works (works prepared by officers and employees of the U.S. Government as part of their official duties) are not protected by copyright in the U.S. (17 U.S.C. § 105) and may be used without obtaining permission from DEA.

Cocaine freebase has a higher bioavailability and onset of action compared to its salt form. It also produces a more intense effect due to its increased lipid solubility and more rapid entry into the brain. As a result, smoking cocaine freebase provides a stronger and more immediate rush that is more addictive than using cocaine salt. (This should make sense to you, as in the last chapter, we discussed how the size and immediacy of a reinforcer can increase its reinforcing effect.) The *Manual of Adolescent Substance Abuse Treatment* calls crack the most addictive form of cocaine (Estroff, 2008). Take a look at the following chart comparing various pharmacokinetic properties of cocaine hydrochloride and cocaine freebase:

Table 8.1. Comparison of Cocaine Hydrochloride and Cocaine Freebase (Crack)

|                           | COCAINE<br>HYDROCHLORIDE                          | COCAINE FREEBASE (CRACK)                      |
|---------------------------|---------------------------------------------------|-----------------------------------------------|
| Source                    | Isolated from leaves of the coca plant            | Conversion from cocaine HCl using baking soda |
| Routes of Administration  | Topical, injection, oral, insufflation (snorting) | Inhalation (smoking)                          |
| Bioavailability           | 70-75% (snorting)                                 | 90% (smoking)                                 |
| Onset of Action           | 10-30 sec (snorting)                              | 1-2 sec (smoking)                             |
| Time to Peak Brain Levels | 10 min (snorting)                                 | 8 sec (smoking)                               |
| Duration of action        | 2 hours                                           | 5-15 min                                      |

As you can see, the absorption rate depends on the route of administration. Once the drug is in the bloodstream, it is actively hydrolyzed by enzymes and has a relatively short half-life of approximately 1 hour because it is metabolized by esterase enzymes

in the blood. Cocaine is capable of crossing the blood-brain barrier, which is how it reaches its neuronal targets in the CNS.

When cocaine is taken with alcohol, the two drugs interact to produce a toxic metabolite called **cocaethylene** in the liver, which has a lower LD50 than cocaine. Cocaethylene is psychoactive and has a similar mechanism of action to cocaine, but it has a longer half-life. Cocaethylene enhances the euphoric effects of both cocaine and alcohol, making it a synergistic interaction. But it also increases the potential toxicities of both drugs.

### 8.2.3. Mechanisms of Action and Effects

Cocaine produces its effects by blocking transporter proteins responsible for the neuronal reuptake of monoamines. To refresh, these are the pumps that remove the excess transmitter from the synapse and return it to the presynaptic cell. Cocaine blocks NET and DAT, which are the transporter proteins for norepinephrine and dopamine, respectively. By blocking neuronal reuptake, cocaine causes an increase in the overall amount of transmitter present in the synapse to act on postsynaptic receptors. Cocaethylene, the byproduct of cocaine and alcohol inhibits not only NET and DAT but also the serotonin transporter (SERT) so that levels of all three biogenic amines are elevated.

The cocaine-induced surge in synaptic levels of norepinephrine results in increased activation of postsynaptic alpha-adrenergic receptors in the brain. This gives rise to *objective* central effects of cocaine, including increased wakefulness, increased respiration, and decreased appetite (upper panel of the figure below). A buildup in synaptic levels of dopamine causes increased activation of postsynaptic dopamine receptors. This will result in *subjective* central effects of cocaine, including a sense of well-being (euphoria), increased sense of energy, increased sense of confidence, and, at high doses, psychotic behavior (lower panel of the figure below). Another effect of increased dopamine is the activation of the brain's reward center which contributes to the development of physical dependence. Following the intense but short-lived stimulatory effects of cocaine, a “crash” ensues in which the subjective effects rapidly dissipate and are replaced with compensatory depression and physical exhaustion.

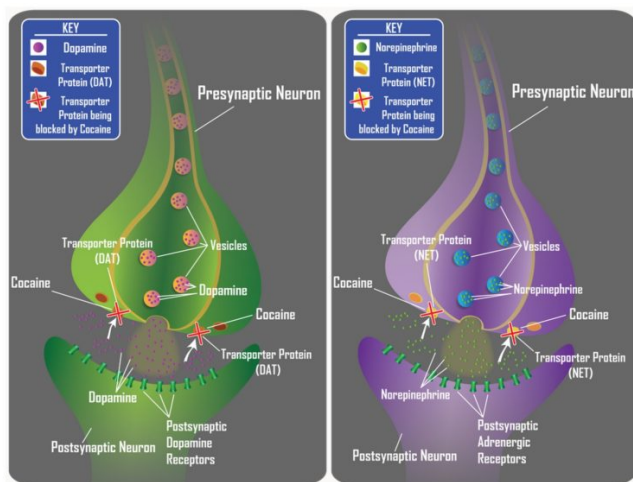


Figure 8.3. Mechanism of Action of Cocaine

Original drawing by Nathan Olivier

In addition to its actions in the brain, cocaine has profound physiological effects in the periphery. Inhibition of norepinephrine reuptake increases synaptic availability of the transmitter and activation of alpha-adrenergic receptors. This is responsible for the increased heart rate, vasoconstriction of blood vessels, dilation of the pupils, and other sympathomimetic effects. Excessive doses of cocaine are prone to producing cardiotoxicity, including acute myocardial infarction, heart failure, and/or cardiac arrhythmia.

Tolerance to the euphoric effects can develop over time due to downregulation (reduction in the number) of dopamine receptors. This causes the user to continually increase the dose of cocaine, which increases the risk of addiction. Cross-tolerance is also common between different stimulants that share similar mechanisms. According to researchers, tolerance to cocaine develops very rapidly over a period of days. Some scientists claim that tolerance begins after the first dose of cocaine.

Since cocaine is a psychostimulant, withdrawal signs will proceed in the opposite direction and feature depression, lethargy, dysphoria, sleep disturbance, and increased appetite. The primary withdrawal signs are drug craving, mental depression, and

suicidality, which can persist for 1-2 weeks following the last use of the drug. Withdrawal signs are intensified if the polysubstance use combines abuse of cocaine with other addictive drugs.

At high doses of cocaine, people may experience psychosis and hallucinations. A common hallucination involves feeling like bugs are crawling under the skin (formication). Overdose may cause abnormally high blood pressure, excessive heart rate, or other cardiopulmonary symptoms, which may sometimes be fatal. The psychosis is consistent with the Dopamine Hypothesis of Schizophrenia, which will be discussed later in Unit 4.

Cocaine is used recreationally as a party drug most often due to the increase in energy and euphoria that it provides. Because of this, its use often correlates with that of other party drugs such as MDMA (*ecstasy*) and amphetamines or other drugs such as heroin. The presence of alcohol in such environments can be particularly dangerous due to the synergistic interaction between the two mentioned earlier.

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### 8.3. AMPHETAMINE

**Amphetamine** is another major stimulant that sees therapeutic and recreational use. Its chemical structure is the basis for **substituted amphetamines**, which are drugs that have similar structures to amphetamine and include cathinone and MDMA. The most notable of these is **methamphetamine** (often called *meth* or “speed”). It is an even more potent psychostimulant than amphetamine itself. We will focus on amphetamine and methamphetamine in this section, but keep in mind that some other drugs like methylphenidate and cathinone can produce similar effects.

#### 8.3.1. Drug History and Overview

Amphetamine was first synthesized in 1927 by chemist G. A. Alles, who was searching for a substitute for ephedrine to treat asthma and allergies. Ephedrine is a psychoactive ingredient found in numerous species of *Ephedra* plants, most notably *má huáng* in Asia, where it has been used in Chinese medicine for thousands of years.

Amphetamine was initially marketed under the name Benzedrine® as a treatment for narcolepsy, obesity, mild depression, and various other medical conditions. Amphetamines were soon seen as being capable of enhancing cognition, which led to their widespread use in academics in the late 1930s. It was also given to World War II bomber pilots and sentries as energy pills to increase wakefulness and reduce fatigue and appetite. The potential for addiction was largely ignored until after the war when addiction rates soared and governments around the world started to regulate amphetamines more strictly.

Currently, amphetamine is classified as a Schedule II controlled substance, the same as cocaine. The accepted medical use for amphetamine that keeps it out of Schedule I is its use in treating attention deficit hyperactivity disorder (ADHD). This was one of the earliest therapeutic applications discovered for amphetamine, and it has remained one of the primary options in treating ADHD to this day. That said, the exact formulation used to treat ADHD has changed since the 1930s.

Methamphetamine is also an approved medication for ADHD and treatment-resistant obesity. However, there are safer alternatives with less toxicity and a lower potential for developing physical dependence. Because of this, there is only one legal prescription form of methamphetamine (Desoxyn®) that cannot be refilled. As such, the most common use of methamphetamine is illicit for recreational purposes. Its limited accepted medical uses is still enough for methamphetamine to be classified as a Schedule II drug. That said, its prescription and use are tracked much more intently than amphetamine.

One consequence of the abuse potential of methamphetamine is the limitations placed on the distribution of pseudoephedrine, a substance found in the same plants as ephedrine. It is an active ingredient in certain decongestants (e.g., Sudafed®), but, because of its chemical structure, it can be used to illegally manufacture methamphetamine. Consequently, decongestants containing pseudoephedrine that used to be sold as over-the-counter medicines are now more tightly regulated, with requirements for photo ID and limits on purchase quantity. Illicit production of methamphetamine overseas also involves conversion of pseudoephedrine or a precursor to pseudoephedrine.

#### 8.3.2. Administration and Pharmacokinetics

For therapeutic use, amphetamine is typically given orally, which allows for consistent blood concentrations over time. Amphetamine can also be administered via injection, inhalation, or intranasally, which results in more rapid absorption. The rate of

absorption is also dependent on the ionization of the drug. Amphetamine is a weak base that is commonly ionized in the acidic environment of the stomach, which contributes to the slow rate of oral absorption.

Once amphetamine reaches the bloodstream, it is readily distributed throughout the body and can easily cross the blood-brain barrier. Some amphetamine (about 20%) is bound to plasma proteins. Amphetamine and methamphetamine have much longer half-lives than cocaine. The half-life is typically around 10-12 hours and changes depending on the pH level and mixture of enantiomers. In addition, the effects last longer. The high from smoking cocaine tends to last 20 to 30 minutes, while the high from methamphetamine can last from 8 to 24 hours. Ultimately, amphetamine and methamphetamine are both metabolized by enzymes in the liver.

Part of the reason for the increased potency and effects of methamphetamine is due to the fact that one of its active metabolites is amphetamine itself. Thus, to eliminate methamphetamine from the system, it must first be metabolized into amphetamine, which in turn must be metabolized as well. The amphetamine produced as a metabolite helps to prolong the effects of methamphetamine.

### 8.3.3. Mechanisms of Action and Effects

Similar to cocaine, amphetamine increases synaptic levels of monoamines such as norepinephrine, dopamine, and serotonin. Amphetamine has a similar chemical structure to monoamines, so instead of blocking transport proteins, amphetamine molecules are actually mistakenly taken into the axon terminal by the reuptake mechanism.

Once inside the nerve terminal, amphetamine increases the release of monoamines while also forcing the transporter proteins to work in reverse. Instead of pumping neurotransmitters out of the synapse, more and more neurotransmitters are pushed into the synapse. The figure below shows amphetamine-induced release of norepinephrine in the left panel and dopamine in the right panel. In addition, amphetamines have been found to also inhibit monoamine oxidase, the enzyme responsible for breaking down monoamine transmitters that have been taken back up by the presynaptic cell. But this is a secondary effect that has been reported, but the main mechanism of action is induction of neuronal release of transmitter.

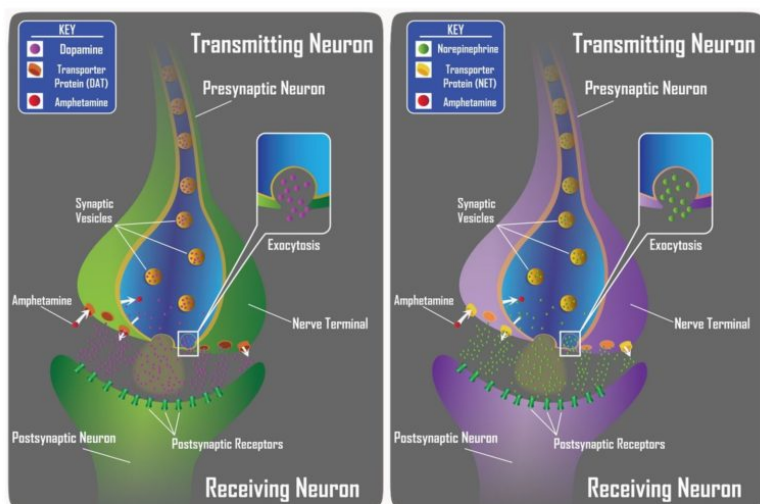


Figure 8.6. Amphetamine-Induced Neuronal Release of Norepinephrine and Dopamine

Original drawing by Nathan Olivier

The neurotransmitters released by amphetamine activate the same alpha-adrenergic and dopaminergic receptors that cocaine does, leading to similar stimulating effects and euphoria. Methamphetamine has a similar mechanism of action but has a stronger effect on the dopamine transporter, which accounts for its greater addictive properties.

Because of its spectrum of pharmacological effects, amphetamines can be misused for a variety of different purposes. Common reasons include weight loss, pleasure-seeking, increased focus, enhanced cognition, or enhanced sports performance. Amphetamines are among performance-enhancing drugs (PED) that are banned by the Olympics and other international and other professional sports.

The tolerance and withdrawal symptoms are also very similar to those of cocaine since they target similar receptors. High doses can result in some of the cardiopulmonary symptoms seen with cocaine intoxication, but changes in mental state such as anxiety, paranoia, and hallucinations are more common with amphetamine and methamphetamine. Physical effects of amphetamine overdose include hypertensive emergency, tachycardia, and cerebrovascular accident (stroke).

The tolerance and withdrawal symptoms are also very similar to those of cocaine since they target similar receptors. High doses can result in some of the cardiopulmonary symptoms seen with cocaine intoxication, but changes in mental state such as anxiety, paranoia, and hallucinations are more common with amphetamine and methamphetamine. Physical effects of amphetamine overdose include hypertensive emergency, tachycardia, and cerebrovascular accident (stroke).



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## 8.2: Alcohol

**Alcohol** (or more specifically, ethanol) is a drug that has a long history and is extensively used throughout the world. Before exploring the pharmacology of alcohol, we will start by learning more about its use, prevalence, legislation, chemical composition, and measurement.

### 11.1.1. History and Legislation

It is estimated that humans have been consuming alcohol for around 9000 years. Wine and beer existed in ancient Egyptian and Sumerian civilizations, with records dating as far back as 3200 B.C. Ancient Greeks used wine in religious ceremonies around 800 B.C., and Roman culture involved heavy drinking that persisted until the fall of Rome in 476 A.D. Distilled liquor first appeared around 1250 A.D., eventually followed by brandy, gin, and rum.

Alcohol is created by the fermentation of sugars from a variety of sources, such as grapes (wine), grains (beer), honey (mead), and sugarcane (rum). Methods of production spread throughout the world and contributed to its popularity. Alcoholic beverages were seen as more nutritious than water. Its consumption was also tied to social interaction, religious ceremonies, and celebrations, which increased its cultural importance.

Opposition to alcohol use has existed for as long as the recorded history of alcohol. In the United States, Dr. Benjamin Rush was a signer of the Declaration of Independence and was recognized by the American Psychiatric Association as the “Father of American Psychiatry”. He recognized alcoholism as a disease and was an early temperance leader. The movement to prohibit alcohol started to pick up steam in the 1800s. After the Civil War, traction for the movement increased, fueled largely by the Women’s Christian Temperance Union. The National Prohibition Act, also known as the Volstead Act, was passed in 1920 and added to the Constitution as the 18th Amendment. It banned the sale and distribution but not the consumption of alcohol across the U.S.

During the Prohibition era, consumption of alcohol was driven underground to speakeasies. At the same time, widespread smuggling of alcohol, known as bootlegging, arose to meet demand sparking an increase in organized crime. Support for prohibition steadily dropped, and 13 years later, it was repealed by the 21st Amendment in 1933. Although this marked the end of national prohibition, some counties and towns remained “dry” and continued to prohibit the sale of alcohol to this day. Individual states were assigned responsibility for regulating alcohol and setting their own legal drinking ages. The National Minimum Drinking Age Act, passed in 1984, ensured that sale was prohibited to anyone under the age of 21. Any state that did not comply with this legislation lost 10% of its federal highway funding. This was reinforced by the National Highway System Designation Act of 1995, which required that states adopt a “zero-tolerance law” to prohibit under-21 driving if the operator had at least a blood alcohol level of 0.02%.

### 11.1.2. Prevalence of Alcohol Use

Alcohol is one of the most commonly used drugs. According to the 2020 National Survey on Drug Use and Health (NSDUH), over half of Americans aged 12 or older reported that they drank in the past month. This widespread use of alcohol also contributes to risky behaviors. **Binge drinking** involves drinking large amounts of alcohol in a short time span (usually 4–5 drinks in about 2 hours) and carries a higher risk than normal drinking. Roughly 23% of people 18 and older reported binge drinking in the past month (SAMHSA, 2021).

Driving while intoxicated (DWI), also known as driving under the influence (DUI), is another common consequence of alcohol use. Vehicle collisions involving alcohol-impaired driving accounted for 29% of all driving fatalities in the U.S. in 2019. Similar to smoking, alcohol consumption also imparts considerable health risks to the user. Alcohol is the third-most preventable cause of death in the U.S, after smoking and poor diet (Mokdad et al., 2004).

Underage drinking is also common. According to the 2020 NSDUH, nearly 40% of people ages 12-20 reported drinking alcohol. Although young people drink less often than adults, they also engage in riskier behaviors. More than 90% of all alcoholic drinks consumed by young people involved binge drinking. Statistics show that at least 60% of undergraduate students acknowledge past-month consumption of alcohol.

### 11.1.3. Ethanol Properties and Concentrations

A common shorthand for determining alcohol consumption is a **standard drink** or an alcoholic drink equivalent. A standard drink contains about 0.6 fluid ounces or about 14 grams of pure ethanol. This amount of alcohol would be contained within a 12-oz can of beer (around 5% ethanol), a 5-oz glass of wine (around 12% ethanol), or a 1.5-oz shot of distilled spirits (upwards of 40% ethanol). Three standard drinks of any of these alcoholic beverages will usually put you over the legal limit for driving, though there is individual variability and even a single drink in some individuals can cause significant impairment.

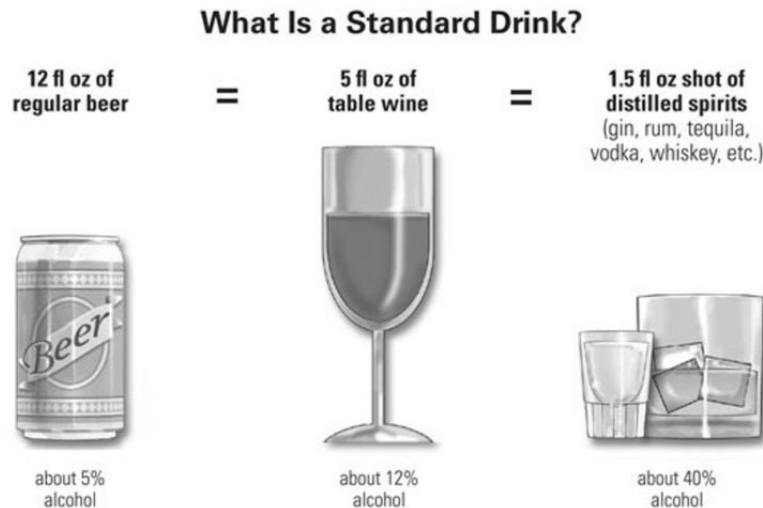


**Figure 11.3. What Is a Standard Drink?**

Source: NIAAA (n.d.)

## 11.2. ABSORPTION AND DISTRIBUTION

The pharmacokinetics of ethanol starts with its absorption and distribution. These topics are important to more than just neuroscience and health professional students. Understanding how alcohol is absorbed is necessary for responsible drinking. Laws that are written to punish drunk driving reference the concentration of ethanol in the blood.

### 11.2.1. Absorption of Ethanol

Ethanol is extremely soluble in both water and fat, making it readily absorbed through tissue. Ethanol is typically ingested orally through alcoholic drinks. These can also be administered rectally, although the practice is uncommon and not advised. Alcohol enemas results in faster absorption and higher blood concentrations because it bypasses the stomach. Another practice called vodka eyeballing involves introducing vodka into the eye sockets. Contrary to popular belief, eyeballing vodka does not induce rapid intoxication and runs the risk of corneal abrasions and scarring.

When taken orally, only 20-25% is absorbed by the stomach, while 75-80% is absorbed through the small intestine. The oral bioavailability of ethanol is poor for two reasons. First, there are alcohol-metabolizing enzymes found in the stomach wall. Second, any ethanol that is absorbed from the digestive tract enters the hepatic portal vein which goes straight to the liver. This will be explained further in the section on Metabolism of Ethanol.

The presence of food in the stomach delays transit from the stomach to the small intestine. This results in stomach enzymes having a longer time period to oxidize ethanol before it can enter the small intestine. Consequently, food reduces peak blood concentration. This is the reason why eating food while drinking is advised. Refer to the graph below to see the effect of food on ethanol absorption:

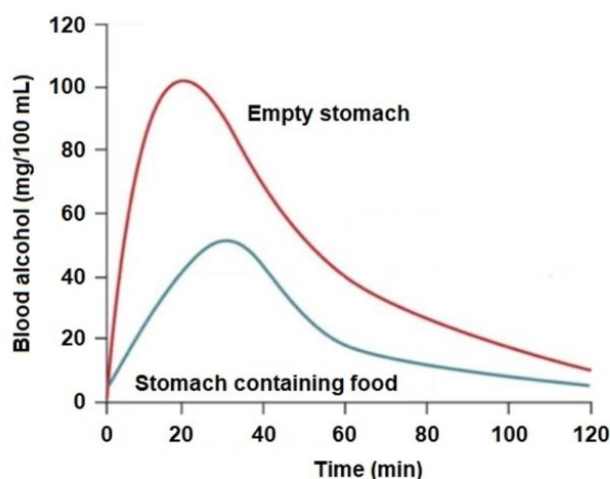


**Figure 11.4. Changes in Blood Alcohol Concentration in Presence and Absence of Food in the Stomach**

Original drawing by Raymond M. Quock

On an empty stomach, 50% of ethanol is absorbed in 15 minutes, with maximum blood levels being reached in 20 minutes. Most of the ethanol (80–90%) is absorbed within an hour or less of administration. The more food in the stomach, the less ethanol absorbed, although there is a gender difference. There is a gender difference in the activity of stomach and liver enzymes so that a larger amount of ethanol will be absorbed by women than men.

### 11.2.3. Blood Alcohol Concentration

The concentration of ethanol in the body is measured as **blood alcohol concentration** (BAC), also called blood alcohol content or **blood alcohol level** (BAL). BAC is defined as the number of grams of ethanol per 100 mL of blood. For example, a BAC of 0.05 is equivalent to 0.05 grams of ethanol per 100 mL of blood.

The legal limit for BAC while driving is 0.08, *except* in Utah where it is 0.05. For drivers under 21 years of age, most states have penalties for BAC above 0.02, although some states have stricter laws. BAC can be estimated by breathalyzer tests, which measure the amount of ethanol expelled through respiration. Although this is not identical to actual blood alcohol concentration, it is reasonably close in most circumstances and can be used as a basis for arrest.

Below is a table of the effects of alcohol at different BACs. As you can see, although the legal limit is 0.08, impairment occurs at lower concentrations. Take a moment to study the contents of the table before moving on.

[Blood Alcohol Concentration \[5:27\]](#)

**Table 11.3. BAC-Dependent Physical and Behavioral Effects of Ethanol**

| BAC   | PHYSICAL AND BEHAVIORAL EFFECTS                                                                             |
|-------|-------------------------------------------------------------------------------------------------------------|
| >0.40 | Respiratory depression, circulatory collapse, coma, death                                                   |
| 0.30  | Stupor, confusion, inability to stay awake                                                                  |
| 0.20  | Depressed sensory and motor capacity, difficulty keeping eyes open, extremely slurred speech, double vision |
| 0.15  | Impaired balance, movement, judgment, and perception; blurred vision                                        |
| 0.10  | Slowed reaction time, impaired motor function, slurred speech                                               |
| 0.05  | Lowered alertness, euphoria                                                                                 |
| 0.03  | Relaxation, happiness, mild motor impairment                                                                |

## 11.3. METABOLISM AND EXCRETION

### 11.3.1. Metabolism of Ethanol

Most of the ethanol ingested (around 90–95%) is metabolized by the body. The remainder is excreted as is in urine, feces, and other secretions. Some of the non-metabolized ethanol escapes via the lungs, which is why breathalyzers can measure BAC indirectly.

Ethanol is eliminated by zero-order kinetics. All the drugs we have covered so far followed first-order kinetics and have half-lives. Ethanol does not have a half-life because a fixed amount of it is metabolized per unit of time (note the relatively flat and parallel slopes of the graphs below). Therefore, drinking more alcohol does not speed up metabolism—with a few notable exceptions that we will get to later in this section. Typically, it takes about an hour for the body to clear itself of one standard drink of alcohol (*i.e.*, 12-oz beer, 5-oz wine, or 1.5-oz distilled spirits).

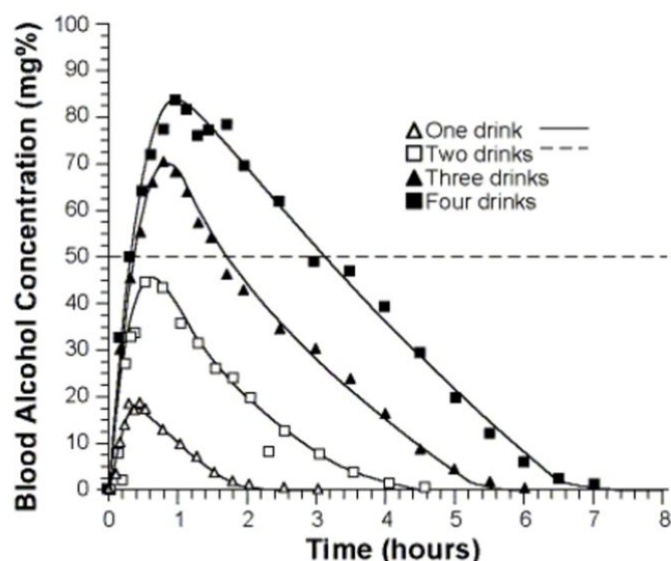


**Figure 11.5. Elimination of Ethanol Following Consumption of Different Amounts of Ethanol**

Source: Wilkinson (1977)

#### 11.4.1. Receptors and CNS Effects

Ethanol is considered a “dirty drug,” an informal term meaning that it affects many different receptors in the body and can produce a wide range of effects. The primary depressant mechanism of ethanol occurs at the GABAA chloride channel receptor complex. The exact site that ethanol binds to is unknown, as is its exact effect on chloride ion channels, but it enhances the effects of GABA and causes hyperpolarization.

The effects of ethanol are biphasic. At low doses, consumption of alcohol can elicit relaxation, giddiness, and euphoria. This is known as a *buzz* and is what makes initial drinking feel good. As BAC rises, depressant effects start to kick in. Motor coordination is impaired, speech becomes slurred, and sensory input is diminished. At high doses, ethanol can induce stupor, sleep, respiratory depression, coma, and death. (For a full list of effects at different BACs, check the table under the BAC subsection 11.2.3 above.)

#### 11.4.2. Ethanol Dependence

Chronic ethanol use results in both tolerance and dependence. Tolerance develops in multiple ways. Standard pharmacodynamic tolerance occurs, which involves changes in target receptor regulation (neuroadaptation). Long-term exposure to ethanol causes the receptors to downregulate and become less responsive.

Pharmacokinetic tolerance also develops with heavy drinking. Recall that when ADH is saturated, the MEOS kicks in and CYP2E1 starts oxidizing excess ethanol. Unlike ADH, CYP2E1 and other cytochrome P450 enzymes can be induced, which results in faster metabolism of ethanol. This only occurs when ADH is saturated, so this type of tolerance only affects binge drinkers and other heavy users.

Finally, becoming familiar with the effects of inebriation leads to behavioral tolerance. This is a conditioned response to the drug that allows the user to compensate for its behavioral effects. People with behavioral tolerance can appear sober even after drinking a significant amount of alcohol and may have better control over their speech, movement, appearance, and emotional state compared to inexperienced drinkers.

Like other drugs, ethanol causes reward and reinforcement by altering dopamine transmission in the reward system. Normally, dopaminergic neurons in the VTA are under tonic inhibition by GABA interneurons. This means that ambient GABA activity somewhat inhibits these neurons from firing and releasing dopamine in the nucleus accumbens.

When ethanol is ingested,  $\beta$ -endorphin is released from an opioid nerve terminal.  $\beta$ -Endorphin, in turn, activates  $\mu$ -opioid ( $\mu$ -opioid) receptors on the GABA interneurons and inhibits the tonic release of GABA. This, in turn, depolarizes the dopaminergic neurons and increases dopamine release in the nucleus accumbens. This is the mechanisms that underlies the reward and reinforcing effects of ethanol. See the image below for the full process:

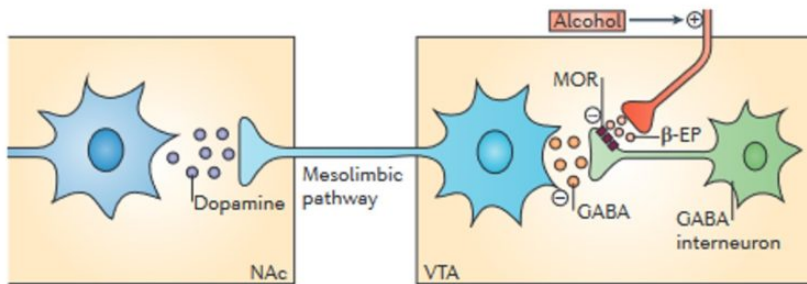


**Figure 11.10. Actions of Ethanol in the Reward Center**

Source: Heilig *et al.* (2011)

Ethanol withdrawal can be very dangerous and can last for days. Because chronic use decreases the number of GABAA receptors and increases NMDA receptors, CNS activity is significantly increased during withdrawal. Symptoms can include seizures, agitation, anxiety, increased heart rate and blood pressure, insomnia, nausea and vomiting, and paranoia. Again, we observe that signs of withdrawal proceed in the opposite direction from the effects of the drug. The intensity of the withdrawal is dependent on the duration and degree of physical dependence. During severe withdrawal, **delirium tremens** may occur, which involves shaking, confusion, and hallucinations and may lead to death. Delirium tremens usually occurs a few days after the onset of withdrawal and may last for two to three days.

Because ethanol withdrawal is so dangerous, treatment is usually intensive and requires hospitalization. Sedatives such as benzodiazepines are administered to mitigate withdrawal symptoms. Of those with severe symptoms, up to 15% may die from withdrawal.

#### 11.4.3. Effects on Other Systems

Ethanol has considerable effects on systems in the body outside of the CNS. The first and foremost is the liver. The majority of ethanol is metabolized in the liver, which leads to a buildup of acetaldehyde in the liver. As mentioned before, acetaldehyde is toxic and can cause damage to the liver. Consuming large amounts of alcohol regularly will lead to a gradual deterioration of liver functioning known as alcoholic liver disease.

Ingestion of ethanol also affects the gastrointestinal system in a variety of ways. Low doses of ethanol accelerate gastric emptying, while moderate consumption stimulates digestive juices and acid secretion. At high doses, ethanol damages the lining of the stomach and causes inflammation, while also reducing the digestive system's ability to absorb nutrients. This is the reason why physicians advise ulcer patients not to drink. Ethanol can impair the healing of the ulcer and may cause the ulcer to get worse.

The endocrine system, which is a series of glands that secrete hormones, is also altered by ethanol use. Ethanol increases blood sugar levels, which eventually results in the over-production of insulin and a subsequent decrease in blood sugar. If the patient is diabetic and receiving therapy with oral hypoglycemic drugs, ethanol is likely to complicate efforts to maintain normal blood glucose levels.

Ethanol interferes with the synthesis of Vitamin D, a hormone essential for absorption of calcium from the digestive tract. Without Vitamin D, the body's calcium pool is diminished, affecting bone growth and remodeling. This can result in decreased bone density (osteoporosis) and an increased likelihood of broken bones.

Ethanol inhibits the release of vasopressin from the posterior pituitary gland. Vasopressin normally promotes water retention by the kidney and regulates the production of urine. In the absence of vasopressin, water is not reabsorbed back into the body and is eliminated as urine. This results in polyuria or the production of abnormally large volumes of dilute urine.

Ethanol suppresses testosterone production in males by interfering with gonadotropin release from the pituitary gland. Reduced testosterone also reduces the sperm count and causes erectile dysfunction.

The effect of ethanol on women's health is also complicated. Ethanol can increase estrogen levels but can increase the risk of estrogen-dependent breast cancer in pre-menopause women. Ethanol also reduces progesterone levels which disrupts the normal menstrual cycle and causes low libido and hot flashes. In post-menopausal women, ethanol may reduce risks for coronary heart disease and osteoporosis.

Finally, excessive ethanol consumption may suppress the immune system. This manifests as a decrease in T cells, increased memory T cells, and higher rates of induced cell death. A weakened immune system causes increased susceptibility to bacterial infections such as pneumonia, tuberculosis, hepatitis, and septicemia.



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## CHAPTER OVERVIEW

### 9: Opioids and Cannabinoids

9.1: Opioids

9.2: Cannabinoids

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## 9.1: Opioids

The term **opiate** originally referred to alkaloids extracted from the opioid poppy, including morphine and codeine. With the emergence of semisynthetic and synthetic compounds that mimicked the effects of morphine, they became known as **opioids** because they resembled opiates. But today the terms opiate and opioid are used interchangeably as opioid has become a blanket term for all drugs with pharmacological properties similar to morphine.

Another common description of these drugs is narcotic (*narkoun* in Greek for “to make numb.”). The origin of the word was based on the ability of opioid drugs to cause sedation and sleep. However, the Federal government continues to use the term narcotic synonymous with illicit. For that reason, cocaine, which is not a narcotic, remains listed in Federal law as a narcotic.

### 12.1.1. Types of Opioids

Opioids can be classified into three different types. **Natural opioids** are opium alkaloids that have a phenanthrene nucleus found in the opium poppy plant (*Papaver somniferum*). They are also referred to as **opiates**. The three most important opiates are thebaine, morphine, and codeine. Thebaine is not used clinically but serves as a precursor to many semisynthetic opioids. Morphine and codeine are useful as clinical analgesics. Of the two, morphine is stronger and has greater effects. Because of this, morphine is the prototypical opioid and the benchmark against which other opioids are measured. Codeine is considered a weak analgesic drug and is used more for its antitussive property.

The drugs that are synthesized from natural opioids are called **semisynthetic opioids** and have similar chemical structures to opiates. Perhaps the most notable semisynthetic opioid is heroin, also called diacetylmorphine or diamorphine, the generic name in the United Kingdom. The names of most semisynthetic opioids will reflect which substance they are most chemically related to. The names hydromorphone (Dilaudid®) and oxymorphone (Opana®) are reminiscent of morphine, while hydrocodone (Vicodin®) and oxycodone (Percocet®, OxyContin®) are more similar to codeine.

Finally, **synthetic opioids** are synthesized independently within a lab instead of being based on naturally occurring opiates. These do not share the phenanthrene nucleus of opiates or semisynthetic opioids but can, nonetheless, couple to the opioid receptor and produce similar pharmacological effects. Synthetic opioids include methadone, fentanyl, meperidine, and tramadol. See the table below for a summary of the different types.

**Table 12.1. Types of Opioid Drugs**

|                    | NATURAL             | SEMISYNTHETIC                                                      | SYNTHETIC                                       |
|--------------------|---------------------|--------------------------------------------------------------------|-------------------------------------------------|
| Source             | Naturally occurring | Derived from natural opioids                                       | Synthesized independently                       |
| Chemical Structure | Typical             | Similar                                                            | Dissimilar                                      |
| Examples           | Morphine<br>Codeine | Hydromorphone<br>Oxymorphone<br>Hydrocodone<br>Oxycodone<br>Heroin | Methadone<br>Fentanyl<br>Meperidine<br>Tramadol |

### 12.1.2. History and Legislation

Opium has been used for thousands of years in medicines and religious rituals. The earliest evidence of human use dates back to 5000 B.C. in the Mediterranean area, although by ancient times, it had spread throughout Asia, Europe, and Africa. The first documented recreational use of opium occurred in China during the 15th century. Shortly after, there were reports of opium addiction. The production and trade of opium flourished. In the 1800s, in response to attempts by the Chinese government to reduce opium use and smuggling, Britain and France fought wars to ensure the continued trade and consumption of opium.

The main active component of opium, morphine, was isolated in the early 1800s by German pharmacist Friedrich Sertürner, who named it after Morpheus, the Greek god of dreams. It was marketed as a pain medication and treatment for opium addiction,

although it was soon discovered to have addictive properties itself. Morphine was also used regularly in surgical procedures following the invention of the hypodermic needle in the 1850s.

Heroin was developed in 1898 and marketed by Bayer the German pharmaceutical company as a cough suppressant and non-addictive alternative to morphine. It was not long until this “non-addictive” claim was found to be untrue. In response to rising rates of opium, morphine, and heroin use, the Harrison Narcotics Act of 1914 effectively banned their prescription and use. As a result, opioid use was stigmatized, and physicians generally avoided prescribing opioids to patients.

In recent decades, however, the U.S. has seen an opioid epidemic. The epidemic began in the 1990s when certain pharmaceutical companies made a major push to reduce the stigma around opioids and increase prescription rates. Through aggressive marketing and misinformation during this period, the safety of chronic opioid use was exaggerated, and many semisynthetic and synthetic opioids were developed and widely prescribed as painkillers, such as oxycodone (OxyContin®).

Due to the increase in opioid prescriptions, overdose deaths related to opioid use hit all-time highs, totaling 400,000 deaths in the U.S. from 1999 to 2017. Part of this is because people started by misusing opioid painkillers but moved on to more potent drugs when supply was restricted. Examine the graph below. You will notice that deaths related to prescription opioid use increased first, then heroin, then synthetic opioids like fentanyl.

### Three Waves of Opioid Overdose Deaths

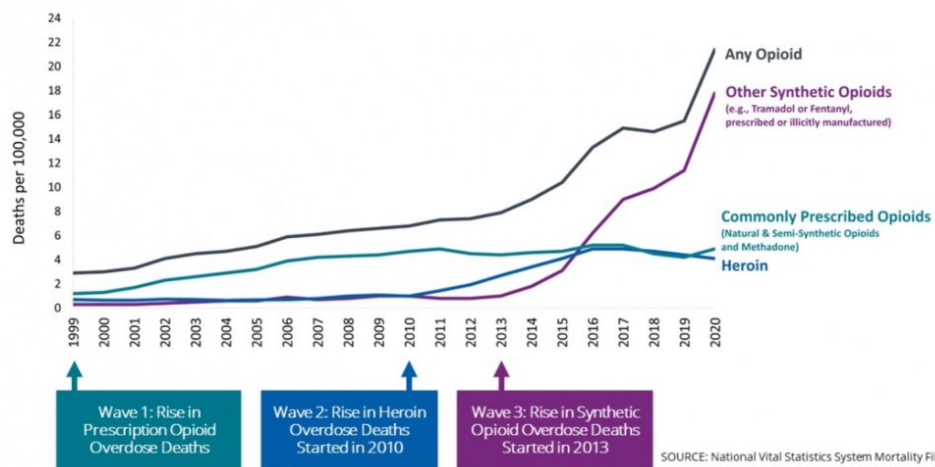


**Figure 12.1. Overdose Fatality Rates Involving Opioids, 2000-2017**

Source: Centers for Disease Control and Prevention (2018). United States government works (works prepared by officers and employees of the U.S. Government as part of their official duties) are not protected by copyright in the U.S. (17 U.S.C. § 105) and may be used without obtaining permission from DEA.)

Various opioids are placed under different schedules because some have greater potential for dependency and addiction. Most opioids are Schedule II because they have high abuse potential but also have accepted medical uses. These include morphine, codeine, oxycodone, fentanyl, and many other opioid pain relievers. Heroin is classified as a Schedule I drug with no accepted medical use. Some medicines containing codeine are classified in lower schedules, such as codeine-containing Tylenol® (Schedule III) or cough medicines (Schedule V).

#### 12.1.3. Opioid Receptors

Opioids are defined by their effects on **opioid receptors**. There are three main opioid receptor subtypes: the mu-opioid receptor, delta-opioid receptor, and kappa-opioid receptor. By taking the first letter of each Greek letter ( $\mu$ ,  $\delta$ , and  $\kappa$ ), it is also common to abbreviate them as either MOP, DOP, and KOP (with OP = opioid), or as MOR, DOR, and KOR (with OR = opioid receptor).

Different terminologies are used by different teachers and scientists. Researchers have discovered other receptors in the opioid receptor family, but for this class, we will focus on these three subtypes.

Each opioid peptide has a different affinity and efficacy for opioid receptor subtypes. Thankfully, the overall pattern is fairly straightforward. Endorphins tend to target mu-opioid receptors, enkephalins tend to target delta-opioid ones, and dynorphins tend to target kappa-opioid receptors. Although they are relatively selective for certain receptor subtypes, this does not mean they cannot activate other subtypes or even other non-opioid receptors. See the following table for comparison:

**Table 12.2. Endogenous Opioid Peptides and Opioid Receptor Subtypes**

| ENDOGENOUS OPIOID PEPTIDE | EXAMPLE        | RECEPTOR              |
|---------------------------|----------------|-----------------------|
|                           |                | SELECTIVITY           |
| Endorphins                | Beta-endorphin | mu-opioid receptor    |
| Enkephalins               | Met-enkephalin | delta-opioid receptor |
| Dynorphins                | Dynorphin A    | kappa-opioid receptor |

So, what is the difference between the opioid receptor subtypes? The effects commonly associated with opioids such as pain relief and euphoria are mediated primarily through the mu-receptor and, to a lesser extent, the delta-receptor. The kappa-receptor is interesting in that it contributes to increased pain sensitivity through dysphoria while also evoking spinal analgesia.

## 12.2. PHARMACOKINETICS

In this section, we will discuss the pharmacokinetics of opioids. Because morphine is the prototypical opioid, we will use its pharmacological properties as a baseline. When there are notable differences in how other opioids behave, we will highlight the differences and compare them.

### 12.2.1. Absorption and Distribution

Opioids can be administered in myriad ways. Although they are most often injected or taken orally, opioids can also be administered sublingually, subcutaneously, intranasally, rectally, epidurally, buccally, or inhaled. The route of administration is usually determined by the reason for use. Opioid pain medications like oxycodone often come in pill or tablet forms, which are convenient for outpatient settings but have low bioavailability because of the first-pass effect. For this reason, morphine is typically injected intravenously (i.v.) or intramuscularly (i.m.) in hospitals.

Illicit use of opioids also follows the same pattern. Because IV administration results in the fastest onset of symptoms, injection is often preferred. Another common method is to vaporize heroin or other opioids by heating them and inhaling the smoke, a process known as “chasing the dragon.”

In general, opioid administration causes a four-phase subjective effect. The first phase is the **rush** or rapid onset of euphoria that occurs seconds after injection. This is followed by the **high**, which causes a feeling of joy and ease. The third phase is called the **nod** and is characterized by feelings of calm and disinterest. During this phase, the user may feel no anxiety and engage in light sleep. The final phase is the **straight** phase, which is a period of normalcy (Agar, 1974).

- Rush = sensation of heroin entering system
- High = pleasurable state, chemically induced
- Nod = semi- or unconscious state induced by heroin
- Straight = not sick

Once absorbed, opioids are capable of crossing the blood-brain barrier. Because different opioids have different lipid solubilities, some are absorbed and cross the blood-brain barrier faster than others. A prime example is heroin, which has greater lipid

solubility than morphine, which is why it has a faster onset of action. Peak concentrations of morphine occur in about 20 minutes, while heroin can peak in 5 minutes.

The onset of action is a large contributor to which opioids have the highest potential for addiction. Certain synthetic opioids, such as fentanyl and its derivatives, have a rapid onset and a potency hundreds of times greater than morphine. Recall the opioid epidemic graph shown in the previous section. Prescription opioids, which are taken orally, tend to have a slower rate of absorption and longer onset of action. As users switched to heroin and fentanyl, the rush of euphoria increased as did the potency, creating a stronger dependence on the drug and increasing the risk of overdose.

### 12.2.2. Metabolism and Excretion

Metabolism of morphine and other opioids largely takes place in the liver. Morphine is metabolized by linking it with glucuronic acid to form a **glucuronide** conjugate. About 90% is converted to morphine-3-glucuronide (M3G), while the remaining 10% is converted to morphine-6-glucuronide (M6G). M3G is inactive, while M6G is active and produces a powerful analgesic effect. Glucuronides are easily eliminated through urine and feces. Morphine typically has a half-life of around 2 hours, although there can be individual differences in the rate of metabolism and excretion.

One particular opioid worth mentioning is methadone. One of the reasons why methadone is so effective as a treatment drug is because it has a much longer half-life than most opioids. In someone with opioid tolerance, the half-life is around 24 hours. In patients without tolerance, this increases to 55 hours (Grissinger, 2011). This means that methadone is active for longer and can be administered less frequently, usually in an oral daily dose.

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## 12.3. PHARMACODYNAMICS

In this last portion of the chapter, we will explore the various ways that opioids influence physiological functioning. Similar to the previous section, we will primarily be discussing the mechanism of action for morphine. Most opioids have similar effects as morphine, though there are some differences. Keep this in mind as you move forward.

### 12.3.1. Pain Relief

Morphine's main site of action is the mu-opioid receptor. Its affinity and efficacy are highest for this receptor subtype, although it is also an agonist at the delta- and  $\kappa$ -opioid receptors. Activation of the MOR is the primary cause of the analgesic effect of opioids.

To understand how opioids like morphine provide pain relief, it is necessary to first understand how pain works. **Nociception** is the sensation of pain stimuli and begins in **nociceptors**, which can be found throughout the body in the peripheral nervous system. Nociceptors convert potentially damaging mechanical, chemical, or thermal stimuli into electrical signals, a process known as **transduction**.

When the original pain stimulus is so intense that activation of the endogenous opioid system is insufficient to mitigate the pain, exogenous opioid drugs may be administered to the patient to control the pain. Exogenous opioids will similarly activate presynaptic and postsynaptic opioid receptors to moderate the pain signal.

Opioids are best suited for reducing chronic dull pain since they have a greater inhibitory effect on Type C fibers than the Type A $\delta$  fibers responsible for acute pain. They are less effective for neuropathic pain, which is caused by nerve damage. Despite this, at high enough doses, opioids will reduce almost any type of pain. Because they are highly effective but also addictive, opioids are usually used to treat moderate-to-severe pain.

### 12.3.2. Other Effects

Considering how opioid dependence has been firmly established as a potential danger of opioid use throughout this chapter, it should come as no surprise that opioids increase dopamine transmission in the reward system. The opioid receptors are inhibitory and will reduce the release of GABA from the interneuron. Freed from GABA inhibition, the VTA neuron releases dopamine to activate its receptors in the nucleus accumbens (NAc). The mechanism is very similar to how opioids act upon the reward center except that morphine directly activates the opioid receptors rather than releasing an endorphin. Activation of mu opioid receptors (MOR) on GABA interneurons in the ventral tegmental area (VTA) and decreases the tonic GABA inhibition of the dopamine neuron.

Opioids produce a myriad of effects on the body. Opioid receptors are widely distributed body and have effects on virtually every physiological and psychological function. If we examine the effects of oxycodone, a popular prescription painkiller, we find that its effects extend beyond control of pain.

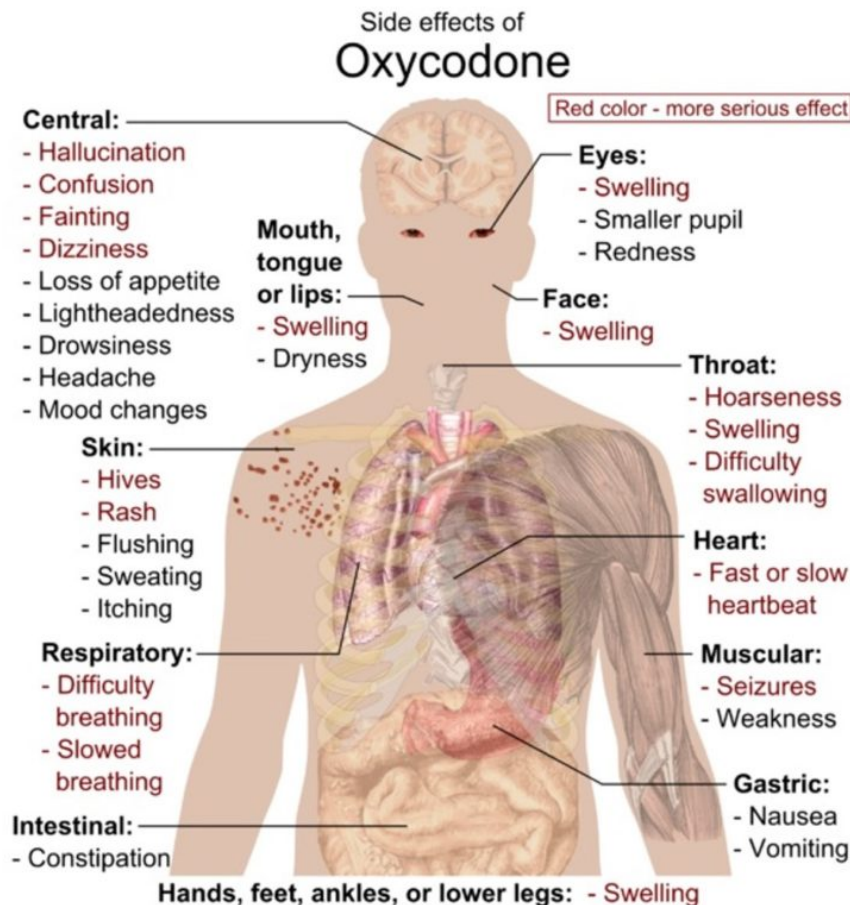


**Figure 12.6. Side Effects of Oxycodone**

Source: Häggström (2009)

Because opioid receptors are found throughout the nervous system, opioids cause other effects aside from pain relief. In the CNS, effects include sedation and euphoria. Opioids can interact with other CNS depressant drugs to produce a synergistic degree of depression.

Heroin was originally marketed as a cough suppressant. Indeed, opioids, especially codeine and hydrocodone, exhibit powerful antitussive (cough-preventing) properties, which is why they can be found in some cough syrups and cold medications. The cough reflex is managed by the cough center in the medulla and is triggered in response to irritation in the lungs and airways. Opioids reduce coughing by increasing the threshold for the cough reflex in the medulla. This antitussive effect of opioids is not mediated by opioid receptors. The popular antitussive drug dextromethorphan is the *dextro* enantiomer derived from a *levo* opioid drug; it has poor affinity for the mu-opioid receptor yet retains the antitussive property.

Opioids also have marked effects on respiration. Breathing is an involuntary action that is also stimulated by various chemical cues. First, there is a respiratory drive, in which chemoreceptors in the medulla oblongata are activated by the detection of large amounts of carbon dioxide in the blood. And second, there is also a hypoxic drive, in which chemoreceptors in the carotid artery and ascending aorta are activated by the detection of low amounts of oxygen in the blood. Morphine and other opioids specifically act on mu-opioid receptors in the respiratory center to reduce the responsiveness of the chemoreceptors to high levels of carbon dioxide, resulting in respiratory depression and, in severe cases, failure.

Another process in the medulla that is influenced by opioids is nausea and vomiting. Opioid activation of delta- and kappa-opioid receptors cause stimulation of the chemoreceptor trigger zone (CTZ) which, in turn, activates the emetic or vomiting center to induce nausea and vomiting. Opioids also activate mu-opioid receptors in the vomiting center to cause a delayed inhibition of activity and reduction in nausea and vomiting. In other words, initial doses of an opioid painkiller cause vomiting, but with repeated doses, nausea decreases. This is why people often feel nauseous after their surgical procedure where opioids are used to suppress pain. But they often feel less nauseous with subsequent doses. This is not the development of tolerance but is due to the time difference in the actions of opioids on the two medullary centers.

Another frequent side effect associated with opioid use is **constipation**. Normally, the smooth muscle in the intestines moves food through the tract through coordinated contraction and relaxation of the smooth muscle, known as **peristalsis**. Opioid receptors in the gastrointestinal tract are excitatory and can cause spontaneous contractions of the muscle. This reduces peristalsis and results in constipation (Fig. 12.7). It is important to know that even with chronic drug treatment, there is no development of tolerance to the constipating effect of opioids.

Opioids cause a variety of other effects. In the kidneys, opioids stimulate the secretion of vasopressin, which promotes the reabsorption of water from the kidneys and results in a decreased volume of urine known as **oliguria**. Note that this is the exact opposite effect from ethanol which reduces the reabsorption of water and increases the production of urine (polyuria).

Activation of opioid receptors in the oculomotor nerve also causes **pupillary constriction**, often so extreme that it is referred to as **pinpoint pupils**. This is another opioid drug effect to which there is no development of tolerance upon repeated drug use. This is an unavoidable sign to law enforcement officials of recent opioid use.

Opioids also inhibit gonadotropin release which results in **hypogonadism**, a condition characterized by decreased testicular size and erectile dysfunction in men, also infertility, missed periods, and hot flashes in women. Finally, exogenous opioids are also implicated in immunosuppression.

### 12.3.3. Tolerance and Overdose

As noted above, tolerance develops to the effects of morphine except for constipation and pupillary constriction. Not all effects develop tolerance at the same rate, however. Tolerance to pain relief and euphoria tends to develop at lower doses than respiratory depression (see image below). As users will typically escalate opioid use to achieve similar effects, long-term users will often begin to develop a tolerance for respiratory depression as well. This is unlike the pattern of tolerance to euphoria and respiratory depression during continuous use of CNS depressants such as barbiturates (Chapter 10).

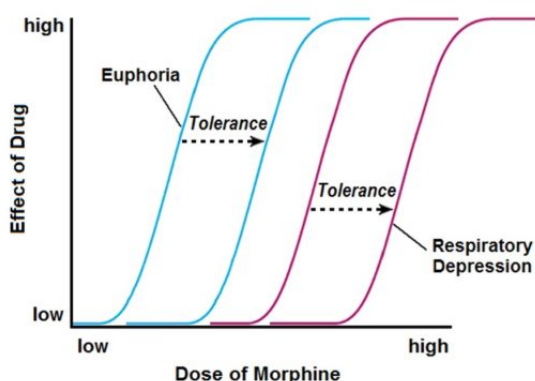


**Figure 12.9. Development of Tolerance to Morphine-Induced Drug Effects**

Original drawing by Raymond M. Quock

Because opioids share similar mechanisms of action, there is a high degree of cross-tolerance between different opioids. This is why during the opioid epidemic, users of prescription opioids could transition to more potent drugs such as heroin and fentanyl.

Although tolerance to respiratory depression can be built, it is highly context-dependent and involves a conditioned compensatory response. Recall from Chapter 7 that this is an automatic response that is learned through repeated drug use. Cues in the

environment such as location, time of day, or the presence of other people signal the body to prepare for the effects of the drug. This is why administering the same dose in a different setting can result in an accidental overdose.

Opioid overdose is severe and comes with many signs, most of which mimic the typical effects of the drug. Respiratory depression, pinpoint pupils, stomach and intestine spasms, drowsiness, disorientation, and loss of consciousness are all hallmark signs, as are dry mouth, low blood pressure, and bluish-colored nails and lips. When opioids are combined with other depressants, respiratory depression is intensified. Most deaths due to overdose are caused by respiratory failure.

To reverse opioid overdose, an opioid antagonist such as naloxone or naltrexone is administered. These drugs have a high affinity for opioid receptors and bind to them, displacing the opioid and reversing its effects. Opioid antagonists are commonly injected, although a naloxone nasal spray has been developed and approved by the FDA for emergency overdose treatment. Nasal sprays are easier to use and reduce the risk of emergency responders contracting blood-borne diseases.

Different opioids have different rates of overdose. An overdose on fentanyl, a potent synthetic opioid, can occur very quickly, which reduces the window for emergency treatment. This is part of the reason why fentanyl and fentanyl derivatives have been singled out as particularly dangerous drugs responsible for many deaths during the recent opioid epidemic, especially since their use has increased in the past few years.

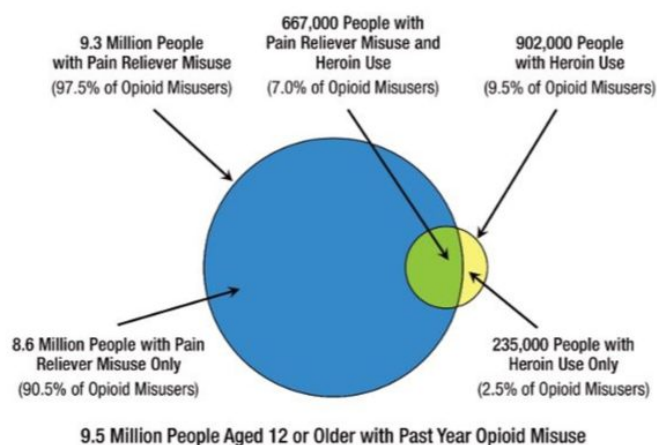


**Figure 12.10. Extent of Opioid Use Disorder with Prescription Pain Relievers and/or Heroin**

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## 9.2: Cannabinoids

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A **cannabinoid** is a biologically active compound found in cannabis. There are over 100 such substances that can be isolated from cannabis, only some of which are psychoactive. In this chapter, we will focus on two of the most common cannabinoids and compare the effects of cannabis containing them in different amounts.

### 13.1.1. The Cannabis Plant

All cannabinoids originate from the resin produced by the *Cannabis* genus of plants, which is often differentiated into three variations. The following table is a comparison of the three most common species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*.

**Table 13.1. Three Primary Varieties of Cannabis Plants**

|                     | CANNABIS SATIVA                                                                                                                                                                                                                            | CANNABIS INDICA                                                                                                                                                                                                                         | CANNABIS RUDERALIS                                                                                                                                                                                                                         |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Outstanding feature | Stimulating effect                                                                                                                                                                                                                         | Relaxing effect                                                                                                                                                                                                                         | Autoflowering                                                                                                                                                                                                                              |
| Origin              | Africa, SE Asia, Central America                                                                                                                                                                                                           | Middle East                                                                                                                                                                                                                             | Eastern Europe                                                                                                                                                                                                                             |
| Physical appearance | <p>Tall, lanky plant up to 12 feet high with thin, pointed leaves</p>   | <p>Short (2-4 feet high) bushy plant with broad chunky leaves</p>   | <p>Small (1-2 feet high) shaggy bush with light green leaves</p>   |
| THC and CBD content | High ratio of THC to CBD                                                                                                                                                                                                                   | Combination of THC and CBD                                                                                                                                                                                                              | Low levels of CBD with even less THC                                                                                                                                                                                                       |
| Notable effects     | Head-high effects best used in the daytime: decreased anxiety and stress, energizing, increased creativity and focus, increased sociability                                                                                                | Body-high effects best for use at nighttime: sedative, relaxing, pain relief, decreased nausea and vomiting, improved sleep, increased appetite                                                                                         | Not enough of either THC or CBD to produce mental or physical effects                                                                                                                                                                      |

Source: Craft Sense (2018)

Although these variations are often presented as distinct species, in reality, there is a large amount of overlap. Most strains of cannabis are hybrids that have undergone crossbreeding to enhance particular properties (i.e., to produce a stronger high, or to be easier to grow indoors). For example, *Cannabis ruderalis* is notable for being autoflowering, meaning that it will flower according to age rather than light stimulus and takes a shorter time before harvesting. *Cannabis sativa* and *Cannabis indica* are photoperiod flowering, dependent on the light cycle, and take a longer time before harvesting. Despite its low THC content, *Cannabis ruderalis* is frequently crossbred with other strains to transfer the autoflowering trait and increase the yield in the hybrid. As a

result, it is often more useful to distinguish between different strains by examining the type and concentration of cannabinoids each contains.

The most notable cannabinoid is **delta-9-tetrahydrocannabinol**, also referred to as **Δ9-THC** or simply **THC**. (Despite there being other tetrahydrocannabinols, when referring to THC in this chapter, we will be specifically talking about Δ9-THC). This is the main psychoactive component found in cannabis and is typically sought after for recreational use.

Another well-known cannabinoid is **cannabidiol** or **CBD**. Unlike THC, CBD is non-psychoactive. Although it can still interact with the nervous system, it does not produce psychoactive effects. Its presence may counteract some of the effects of THC (more on that later). Because of this, CBD is sought more often for therapeutic purposes.

As THC is the main psychoactive cannabinoid, another way of classifying cannabis strains is by THC content. Cannabis with low THC content (less than 0.3%) is also called **hemp** or industrial hemp. It has little THC and is non-psychoactive. It can be harvested for its fiber, seeds, and CBD but is never used recreationally. Hemp fibers have many industrial uses such as the manufacturer of clothing, textiles, and rope. Hemp can also be processed into foods, birdseed, and even biofuel. Legally, if the THC content is higher than 0.3%, it is then called **marijuana**. Because it is psychoactive, marijuana is only legal in some states and is used primarily for its psychoactive effects. See the table below for a comparison of the two.

**Table 13.2. Comparison of Industrial Hemp and Marijuana**

| Hemp                                                  | Marijuana                                          |
|-------------------------------------------------------|----------------------------------------------------|
| Less than 0.3% THC                                    | More than 0.3% THC                                 |
| Non-psychoactive                                      | Psychoactive                                       |
| Federally legal                                       | Only legal in some states                          |
| CBD > THC                                             | THC > CBD                                          |
| Available online and in many places                   | Available at licensed dispensaries in legal states |
| Used in clothing, textiles, foods, birdseed, and more | Used for recreational and therapeutic purposes     |

The THC content of marijuana is not fixed and has increased in recent decades. In the 1970s, the average THC content was 1–4%, but this has risen to 10–15% in recent years, with some strains containing as high as 30% THC content. This increase in potency is caused by hybridization and also changes in growing methods that selectively breed strains with a higher THC content that produce more resin.

One final thing worth noting is that it is possible to artificially manufacture substances that produce similar effects as cannabinoids. These compounds are known as **synthetic cannabinoids** and can have significantly different effects compared to cannabis. To distinguish the two types, cannabinoids extracted from plants are called **phytocannabinoids** (from *phuton* in Greek for “plant”). Synthetic cannabinoids will be covered in a later chapter on new drugs of abuse.

### 13.1.2. History and Legislation

The history of cannabis is much like the history of opium poppies and coca leaves. The earliest written record of cannabis use occurred in 2700 B.C. when Chinese emperor Shen Nung included it in a book of medicinal herbs. Cannabis originated in central Asia and India, but its cultivation and use spread throughout the world. In 200 B.C., cannabis was used in ancient Greece as a remedy for earaches, edema, and inflammation. From 800–1500 A.D., cannabis was used as medicine in the Arabian Peninsula, where it was also used as hashish for its mood-changing properties.

The history of cannabis in the U.S. dates back to the 17th century, where it was grown in the colonies for hemp products. British colonies were required by law to grow hemp for producing cordage, sails, and cloth for the Royal Navy and mercantile marine.

Marijuana saw its popular use as a remedy in the 1800s and early 1900s and was an ingredient in many medicines and tinctures at the time. Marijuana was also commonly smoked for recreational purposes at the time.

The legal status of marijuana changed in 1937 with the passage of the Marihuana Tax Act. The new law required registration and a tax levy on the importation and commercial use of marijuana. This effectively outlawed the non-medical or recreational use of marijuana. It also legitimized the term *marijuana* to refer to cannabis products, as it was previously only a slang term for cannabis. Because of the tax imposed by the act, medical use of marijuana also declined.

In 1970, the Controlled Substances Act classified marijuana as a Schedule I drug with no accepted medical use, meaning it was illegal to prescribe it for medical treatment. The initial placement of the drug in Schedule I was intended to be provisional because of the lack of studies on its safety. But in 1972, the Nixon administration refused to reschedule marijuana despite the report of a national commission recommending its decriminalization.

The Schedule I status of marijuana has been repeatedly challenged in subsequent decades. To this date, it is still federally classified as an illegal drug. Despite this, some exceptions have been carved out over the years, and state legislatures have passed laws legalizing its use. California was the first state to legalize medical cannabis in 1996, while Washington and Colorado were the first to legalize recreational use in 2012. Since then, 37 states and the District of Columbia have legalized medical marijuana. Canada also legalized marijuana in 2018.

Up until 2018, there was no distinction between industrial hemp and hemp grown for marijuana. The Hemp Farming Act passed by the U.S. Congress formally differentiated between hemp and marijuana using the THC content threshold of 0.3% mentioned above, effectively legalizing certain cannabinoids at the federal level for the first time. Hemp with greater than 0.3% THC was defined as marijuana, and hemp with less than 0.3% THC was considered industrial and categorized as an agricultural commodity.

### 13.1.3. The Endocannabinoid System

Similar to opioids, the effects of cannabis were well-established long before we knew how and why cannabis was capable of interacting with the brain. The eventual discovery of an endogenous system of cannabinoid receptors and ligands referred to as the **endocannabinoid system**, did much to further our understanding of how cannabis achieves its effects.

Two types of **cannabinoid receptors** have been identified: the cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2). Both are G-protein coupled receptors. CB1 receptors are found throughout the CNS and peripheral tissues while CB2 receptors are largely located outside of the nervous system on immune cells. The pharmacological effects of cannabinoids are mainly determined by their affinity and efficacy for CB1 receptors, although there are likely to be additional types of cannabinoid receptors not yet identified that account for other effects of cannabinoids.

Endogenous ligands for these receptors are called **endocannabinoids** as opposed to the exogenous phytocannabinoids found in plants. The first endocannabinoid discovered was named N-arachidonyl ethanolamine (AEA) or anandamide after the Sanskrit word *Ananda*, meaning joy or bliss. The other primary endocannabinoid is 2-arachidonoylglycerol (2-AG). Anandamide is an agonist of the CB1 receptor, while 2-AG is an agonist of the CB2 receptor, although the two have similar chemical structures and can interact with both receptor types. There are an additional one hundred cannabinoid-related substances found in the cannabis plant, but these have not been studied as intensively as anandamide and 2-AG.

Anandamide and 2-AG are not synthesized and stored in synaptic vesicles. Rather, both are made on-demand and released almost immediately into the synaptic space. They tend to have short half-lives and are quickly metabolized by enzymes. Anandamide is metabolized by fatty acid hydrolase (FAAH) into arachidonic acid, while 2-AG is metabolized by monoacylglycerol lipase (MAG-L) into fatty acids and glycerol.

Endocannabinoids act as **retrograde neurotransmitters** at many synapses. Instead of being released by the presynaptic neuron, endocannabinoids are released by the postsynaptic neuron, whereupon they travel across the synapse in the opposite direction from most transmitters and bind to CB receptors on the presynaptic neuron (see image below). This reduces neurotransmitter release, causing an inhibitory effect.

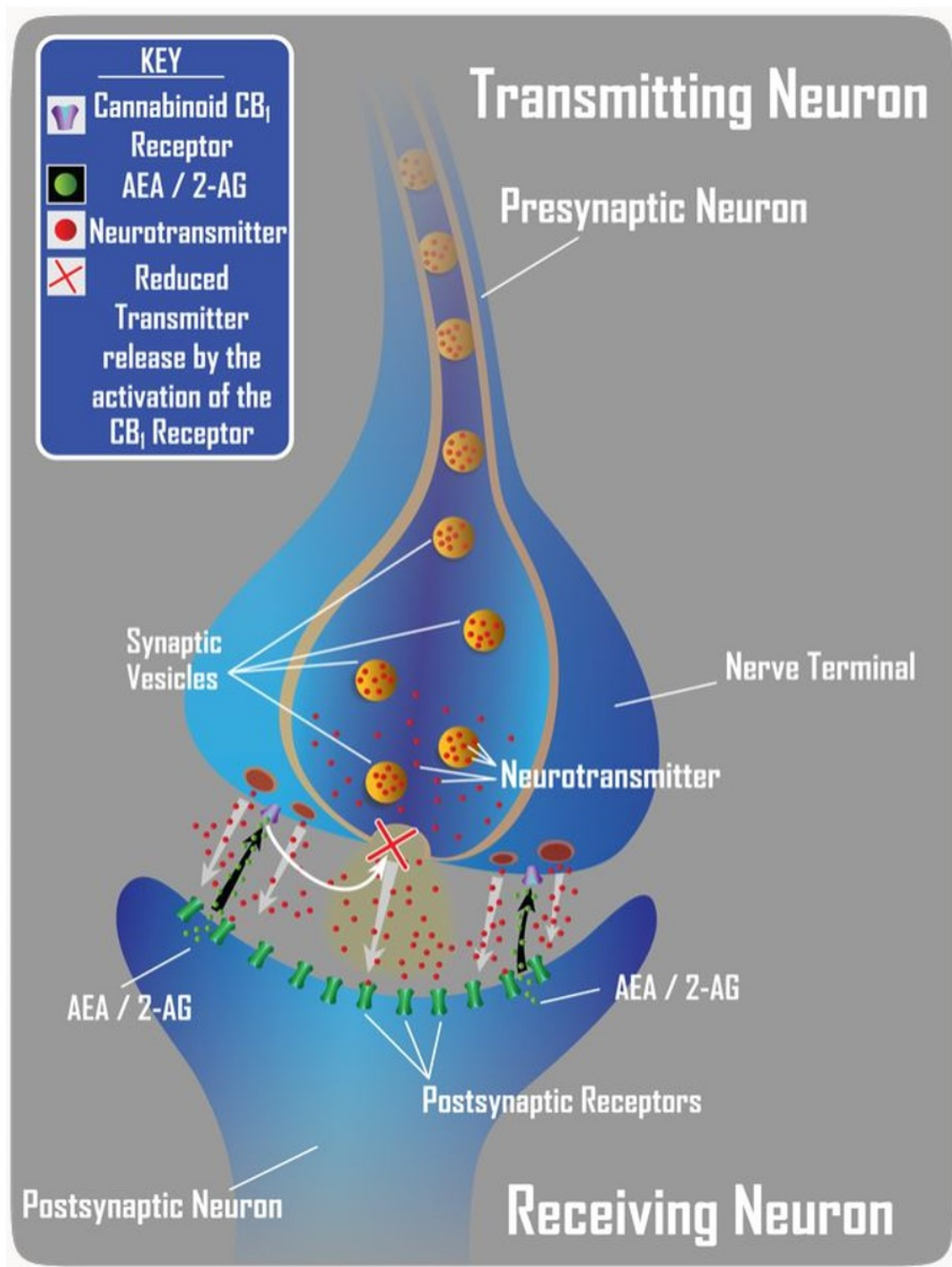


**Figure 13.1. Retrograde Signaling by Endocannabinoids**

Original drawing by Nathan Olivier

An example of the role of retrograde transmission in the modulation of a physiological function is in nociception and antinociception. In the example above, excessive neurotransmission across a Substance P or glutamate synapse in the pain pathway is responsible for the perception of intense pain. When overly stimulated, the postsynaptic neuron produces and releases

endocannabinoid (anandamide or 2-AG) which travels from the postsynaptic neuron back to the presynaptic neurons. Activation of cannabinoid CB1 receptors reduces the amount of primary transmitter released into the synapse. This reduces the intensity of the pain signal and may underlie the analgesic effect of cannabinoids. Endocannabinoids can also produce excitatory effects such as stimulation of appetite. This likely occurs through endocannabinoids reducing the inhibitory effects of GABA neurons.

As such, the endocannabinoid system is an important method of neuromodulation. Although our understanding of the endocannabinoid system is still evolving, preliminary research suggests that the system is involved in many functions, such as regulating appetite, sleep, mood, and pain. Scientists believe that the main role of the endocannabinoid system is the maintenance of homeostasis. The endocannabinoid system also seems to play an important role in forgetting by suppressing long-term potentiation in the hippocampus.

## 13.2. PHARMACOLOGY

As mentioned in the previous section, cannabinoids are many biologically active substances found in cannabis. Because there are numerous cannabinoids with varying properties, in this section, we will zero in on THC and CBD in particular. When talking about the psychoactive effects of cannabis or marijuana, remember that this is due to THC, its psychoactive component, and not due to CBD, which is non-psychoactive.

### 13.2.1. Administration and Pharmacokinetics

Cannabis is most often inhaled or ingested. Cannabis can be rolled into a cigarette or joint, or it can be smoked with the aid of hookahs or bongs. Second-hand exposure to the smoke can result in a contact high. Oral administration occurs when eating hash oil or preparations that contain cannabis, such as brownies.

When smoked, about 50% of the THC content is absorbed, with the remainder being released into the environment. Once absorbed into the bloodstream by the lungs, peak concentrations of THC are achieved within minutes, with maximal effects occurring within half an hour. The duration of the effects usually lasts for 1–3 hours depending on the amount administered.

In comparison, oral ingestion results in a higher rate of absorption of THC (about 90–95%), but due to first-pass metabolism in the liver, its bioavailability drops to around 6–20%. In addition, the effects are much more delayed compared to smoking. The onset of action occurs after 30–90 minutes, while peak effects may not occur until 2–3 hours after administration. Duration is prolonged, with effects lasting for at least 4 hours. Compare the two routes below:

**Table 13.3. Different Pharmacokinetics of Cannabis Following Inhalation or Ingestion**

| FEATURE                 | INHALATION | INGESTION  |
|-------------------------|------------|------------|
| <b>Absorption</b>       | 50% THC    | 90–95% THC |
| <b>Bioavailability</b>  | 10–35% THC | 6–20% THC  |
| <b>Onset of Effects</b> | < 10 min   | 30–90 min  |
| <b>Maximal Effect</b>   | 15–30 min  | 2–3 hr     |
| <b>Duration</b>         | 1–3 hr     | 4+ hr      |

Because it is lipid-soluble, THC can cross the blood-brain barrier and is readily distributed throughout body tissue. Metabolism of THC occurs primarily in the liver through cytochrome P450 enzymes, in particular CYP2C9, which converts  $\Delta^9$ -THC into 11-OH-

$\Delta^9$ -THC (often referred to simply as 11-hydroxy-THC). An active metabolite itself, 11-hydroxy-THC has similar effects to THC and is, in turn, metabolized into glucuronide conjugates and other inactive metabolites before being excreted.

THC tends to have a half-life of around 20–50 hours, although it can be detected for days or up to a month after administration. This is in part because it can accumulate in fat cells and is gradually re-released into the bloodstream over time. Most of the drug (more than 65%) is excreted in the feces, with about 20% excreted through the urine.

### 13.2.2. Mechanism of Action and Effects

The effects of cannabinoids are largely mediated by the CB1 receptor. THC is a partial agonist with a high affinity for the CB1 receptor, similar to the endocannabinoid anandamide. Some synthetic cannabinoids have a much higher affinity for the CB1 receptor compared to anandamide and THC. As mentioned previously, there may be additional cannabinoid receptors responsible for some of the effects of THC that are being investigated or yet to be discovered.

CBD is unique in that it may counteract the effects of THC. This is because CBD is a negative allosteric modulator of the CB1 receptor. In other words, when CBD binds to the CB1 receptor, it changes the conformation of the receptor site so that THC cannot bind to it as easily. At the same time, CBD also interacts with the receptors for other neurotransmitters, such as serotonin, and may enhance the effects of THC in some cases.

Because the endocannabinoid system is found throughout the CNS and peripheral tissues, administration of THC produces a variety of effects. Perhaps the most well-known physiological effect is an increase in appetite, also known as the munchies. THC also increases heart rate and blood pressure, reduces motor activity, and relaxes the airways. It also dilates the blood vessels in the conjunctiva, the membrane that covers the front surface of the eye. The presence of bloodshot eyes is a clear sign of cannabis use. THC can also cause drowsiness, dizziness, dry mouth and throat, and reduce restful sleep by suppressing REM sleep.

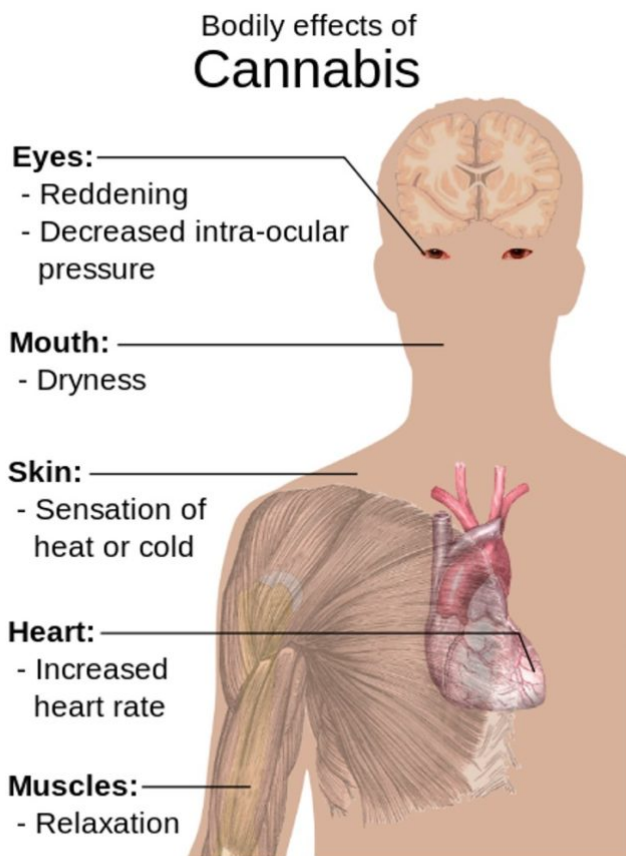


**Figure 13.2. Physiological Effects of Marijuana**

Source: [Häggström \(2009\). Public domain](#)

Cannabis also has effects on the endocrine system and the release of sex hormones. In men, the release of testosterone is decreased, which can result in erectile dysfunction and reduced sperm count and motility. In women, a decrease in progesterone can result in reduced sexual pleasure, disruption of menstrual cycles, reduced fertility, and an increased risk of premature birth.

The subjective effects of marijuana are dose-dependent and generally follow three stages. The **buzz** occurs at low doses and is characterized by feelings of dizziness, light-headedness, and tingling sensations. This is usually followed by the **high**, which may entail euphoria, exhilaration, and disinhibition. In first-time users or at very high doses, this may also result in anxiety, paranoia, and panic attacks. The effects on mood may be influenced by the setting, with pleasant settings causing positive effects and unpleasant settings causing negative effects. Finally, the **stoned** phase involves relaxation and altered perception. Users often report enhanced senses and the feeling that time passes more slowly.

Marijuana also interferes with judgment and short-term memory, which can increase risky behaviors and make it difficult to retain information. High doses of marijuana can cause paranoia and psychosis. Marijuana causes dose-dependent impairment of psychomotor activity, which results in decreased alertness, concentration, coordination, and reaction time. At low doses, there is relatively little effect, but the impairment increases with larger doses. In addition, combining marijuana with alcohol produces an additive effect, which can cause severe impairment and increase the risk of a car accident.

The impact of smoking marijuana is similar to the impact of smoking cigarettes. Smoking joints can cause inflammation in the lungs and can lead to chronic obstructive pulmonary disease (COPD), emphysema, and chronic bronchitis. Marijuana cigarettes reportedly contain more tar than tobacco cigarettes, and cannabis tar contains greater amounts of carcinogens. However, the risk of lung cancer is less than cigarettes. Marijuana smokers are at greater risk of pulmonary complications because they tend to inhale deeply and hold the smoke in their lungs longer. Secondhand smoke from marijuana can produce a contact high as well as serious breathing issues, especially in children exposed to marijuana smoke in an enclosed environment,

### 13.2.3. Tolerance, Withdrawal, and Long-Term Effects

Regular use of cannabis can cause tolerance to the behavioral and subjective effects of cannabis. If used frequently, withdrawal can occur upon stopping. Compared to other drugs we have examined, cannabis withdrawal is usually mild and rarely life-threatening. Symptoms include craving, irritability, anxiety, lack of appetite, sleep disturbance, and depression. Some users may also experience physical symptoms such as tremors, sweating, headache, stomach pain, and fever. Withdrawal tends to last for up to two weeks, with peak symptoms occurring 2–6 days after the cessation.

Activation of CB1 receptors causes an increase in dopamine release in the nucleus accumbens, although the exact mechanism through which this occurs is poorly understood at the time. This increase in dopamine is responsible for some of the euphoric effects of cannabis. Although dependence is possible, it is not common, and some researchers believe that dependence is psychological, rather than physiological. Tolerance and dependence are more likely to develop with frequent use of strains that are high in THC content.

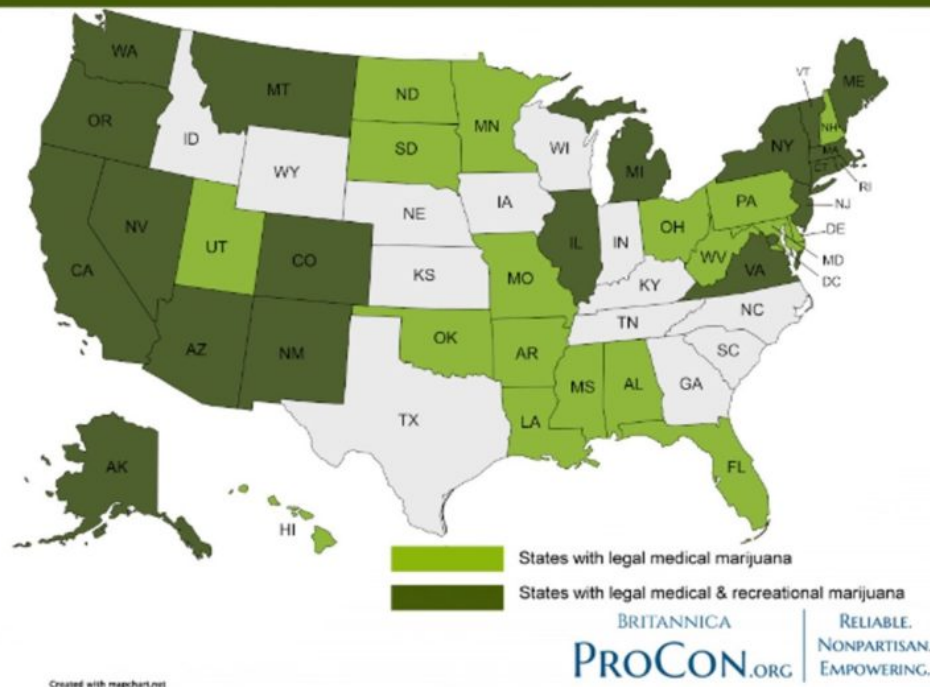
Although dependence and addiction are uncommon, they do occur. The *DSM-V* describes cannabis use disorder as a type of substance use disorder and lists 11 criteria to evaluate its severity. Similar to other substance use disorders, cannabis use disorder is characterized by cravings, preoccupation with obtaining cannabis, compulsive use despite negative consequences, and relapse after stopping use.

Frequent or heavy use of cannabis can cause many negative long-term effects, especially if the use begins in adolescence. Addiction occurs in 9% of overall users. This number increases to 17% in those who began in adolescence and 25–50% of those who use cannabis daily. Early use is also associated with changes to brain development and cognitive impairment, as well as diminished life satisfaction and educational achievement.

Chronic smoking of cannabis also increases the risks of certain respiratory diseases, such as emphysema and bronchitis. But cannabis use is not as strongly associated with lung cancer because some compounds in marijuana may suppress tumor growth. Smoking cannabis can also increase cardiovascular problems if there is a preexisting heart condition.

### 13.2.4. Medical Marijuana and Cannabinoid Medications

In 1996, California was the first state to approve medical marijuana as a voter initiative. In 2012, voters in Colorado and Washington states approved ballot initiatives to legalize recreational marijuana. By May 2022, 38 states and the District of Columbia were the first states have legally recognized the medical and recreational use of marijuana. The landscape of cannabis continues to change.



Source: ProCon.org (2022)

Charlotte's Web was a hybrid containing 17% CBD and only 0.3% THC but was never an officially approved medical treatment for seizures. In 2018, the FDA approved Epidiolex®, an extract mixture of 99% CBD and less than 0.1% THC, for treatment of Dravet

syndrome and another severe form of epilepsy, Lennox-Gastaut syndrome. This was the first FDA-approved drug containing a substance derived from marijuana. Epidiolex® was classified by the DEA as a Schedule V controlled substance.

Other cannabinoid medications have been released. Dronabinol (Marinol®) was a synthetic THC approved in 1985 by the FDA as an appetite stimulant and antiemetic (anti-vomiting) drug. Another cannabinoid, nabilone (Cesamet®), was approved by the FDA in 2006 to treat neuropathic pain, nausea, and vomiting. It is also a synthetic cannabinoid that mimics THC. DEA has classified nabilone and dronabinol as Schedule II and III controlled substances, respectively. Finally, in the early 2010s, several European nations approved nabiximols (Sativex®), an oral spray with approximately equal amounts of THC and CBD, for use in treating pains related to neuropathy, cancer, and multiple sclerosis. Nabiximols have not yet been approved by the FDA for use in the U.S. but have been studied in several Phase 3 clinical trials for the treatment of cancer pain.

As mentioned earlier, the FDA approved Epidiolex® (cannabidiol) as a treatment for dravet syndrome and Lennox-Gastaut syndrome, two rare and severe epileptic conditions. This was the first time the FDA had approved a purified drug substance derived from marijuana

With the passage of the Hemp Farming Act of 2018, CBD was legalized if it was derived from industrial hemp but remained classified as a Schedule I controlled substance if it was derived from marijuana hemp.

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