A flock of Canada geese use auditory and visual cues to maintain a V-formation in flight. How are these animals able to respond so quickly to environmental cues? All animals possess **neurons**, cells that form a complex network capable of transmitting and receiving signals. This neural network forms the **nervous system**. The nervous system coordinates the movement and internal physiology of an organism, as well as its decision-making and behavior.

In all but the simplest animals, neurons are bundled into **nerves** that facilitate signal transmission. More complex animals have a **central nervous system (CNS)** that includes the brain and nerve cords. Vertebrates also have a **peripheral nervous system (PNS)** that transmits signals between the body and the CNS.

Cells of the Nervous System

Structure of the neuron.

Figure 1 shows the general structure of a neuron. The organelles and nucleus of a neuron are contained in a large central structure called the **cell body**, or soma. Most nerve cells also have multiple dendrites in addition to the cell body. **Dendrites** are short, branched extensions that receive signals from other neurons. Each neuron also has a single **axon**, a long extension that transmits signals to other cells. The point of attachment of the axon to the cell body is called the **axon hillock**. The other end of the axon is usually branched, and each branch ends in a synaptic terminal. The synaptic terminal forms a **synapse**, or junction, with another cell. In most neurons, electrical impulses are initiated at the axon hillock and travel down the axon to the synapses. When the signal is passed from one neuron to another, the neuron transmitting the signal is called the presynaptic neuron, and the neuron receiving the signal is called the postsynaptic neuron. The signal is passed across the synapse by chemical **neurotransmitters**.

In invertebrates, the axon diameter influences the speed of signal transduction: wider axons are able to send signals more rapidly than narrow axons. Vertebrate axons are all relatively narrow, but many are insulated by a **myelin sheath** that greatly improves signal transduction. The presence of myelin sheath enables vertebrate axons to transmit signals faster than considerably wider invertebrate axons. The myelin sheath is formed by specific types of glial cells that wrap themselves around the axon many times, forming a multilayered lipid membrane insulator. The myelin sheath insulates the axon and restricts the signal to unmyelinated segments called **nodes of Ranvier**. These nodes are essential for maintaining the signal along the length of the myelinated axon.

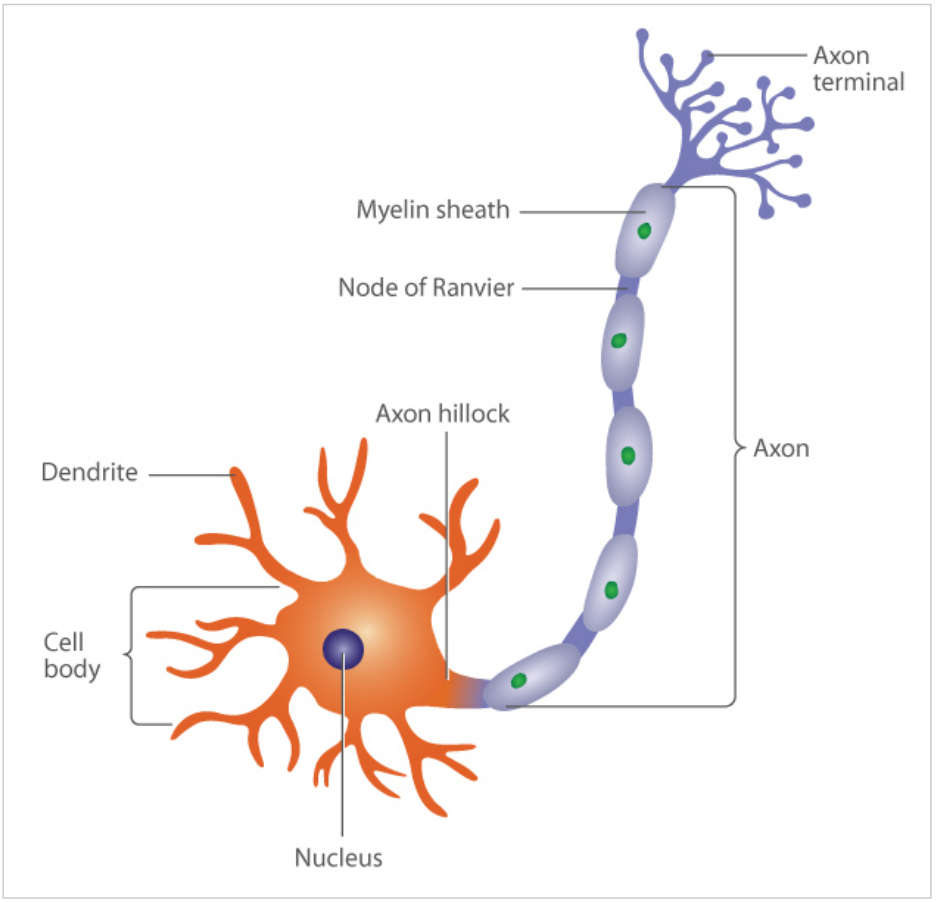


Figure 1: Structure of the neuron.
The cell body of the neuron contains the nucleus and most cellular organelles. Short, branched dendrites receive signals, and a long axon transmits signals.
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Most animals have specialized types of neurons used to detect relevant external stimuli. **Sensory neurons** detect information about the external environment. The stimuli that may be detected by sensory neurons include sight, sound, touch, smell, taste, and temperature. Many sensory neurons also detect internal stimuli such as blood pressure. Information from sensory neurons is transmitted to processing centers in the brain and spinal cord, where it is translated into an appropriate response. A simple example of this is represented by the motor reflex arc. The structure of the neurons involved in this pathway are shown in Figure 2. A sensory neuron stimulates an **interneuron** located in the spinal cord. This interneuron takes in the information from the sensory neuron and then transmits the signal to **motor neurons** that project onto the appropriate muscle to stimulate the proper motor response.

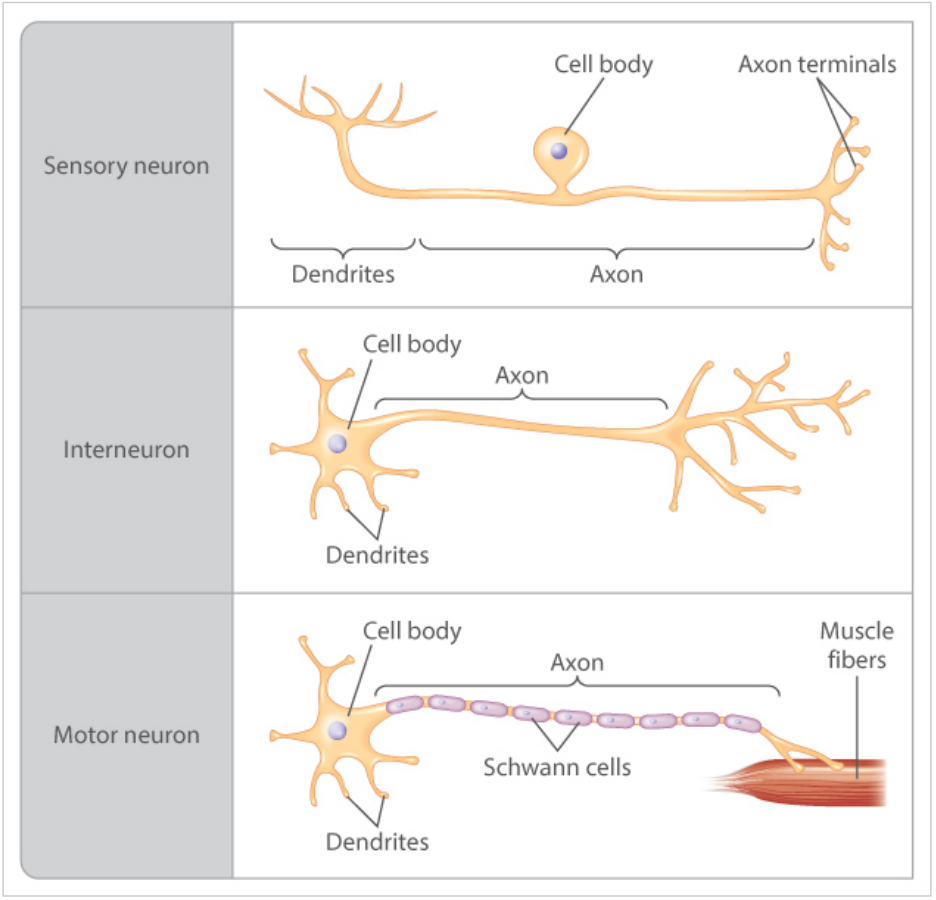


Figure 2: Structure of neurons involved in the reflex arc.
The different morphologies of sensory neurons, interneurons, and motor neurons reflect their respective roles in the reflex arc. In the sensory neurons that respond to touch, the cell body is located along the axon near the middle of the neuron. Interneurons relay signals between neurons and have a wide variety of sizes and branching patterns. In motor neurons, the axon extends from the neuron cell body and terminates at the neuromuscular junction of a muscle fiber. Often, motor neuron axons are also myelinated to facilitate rapid transmission of electrical signals.
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Test Yourself

How might sensory neurons, interneurons, and motor neurons be involved in allowing an animal to escape from a predator?

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Figure 3: Signal transduction between neurons.
A signal travels from the axon of one neuron to the dendritic spine of the next.

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Support cells of the nervous system.

Vertebrate neurons require support from other cells to function properly. **Glial cells**, or glia, provide nourishment and protection to neurons and regulate their surrounding environment. They also play essential roles in neurodevelopment and in mediating the immune response in the brain. Two types of glia form the myelin sheath. **Oligodendrocytes** form the myelin sheath in the central nervous system, and **Schwann cells** form the myelin sheath in the peripheral nervous system. Astrocytes are another type of glial cell and are abundant in the brain and spinal cord. For a long time, researchers have known that astrocytes play a role in nourishing neurons and maintaining a stable environment. However, recent evidence indicates that astrocytes may also be involved in relaying important physiological information directly to neurons through signal transduction.

Signal transduction by nerve cells.

Nerve cells maintain a difference in electrical charge across their plasma membrane called a **membrane potential** that is generated by the differential distribution of charged ions. The **resting potential** of a nerve cell refers to membrane potential that exists when the cell is at rest and not actively sending information. If sufficient stimuli from other neurons are received, the membrane potential becomes depolarized to a certain threshold level and an **action potential** is generated. An action potential is a massive depolarization of the membrane that spreads spontaneously across the membrane. The action potential is usually generated at the axon hillock and travels down the axon to the synaptic terminals. When the action potential reaches the synaptic terminals, vesicles containing chemicals known as **neurotransmitters** fuse with the plasma membrane, releasing their contents into the synapse. The neurotransmitters travel across the synapse and bind to the receptors on the postsynaptic neuron (Figure 4). Binding of neurotransmitters to receptors triggers a response in the postsynaptic neuron that may result directly in an action, such as the contraction of a muscle, or may be passed on to other nerve cells.

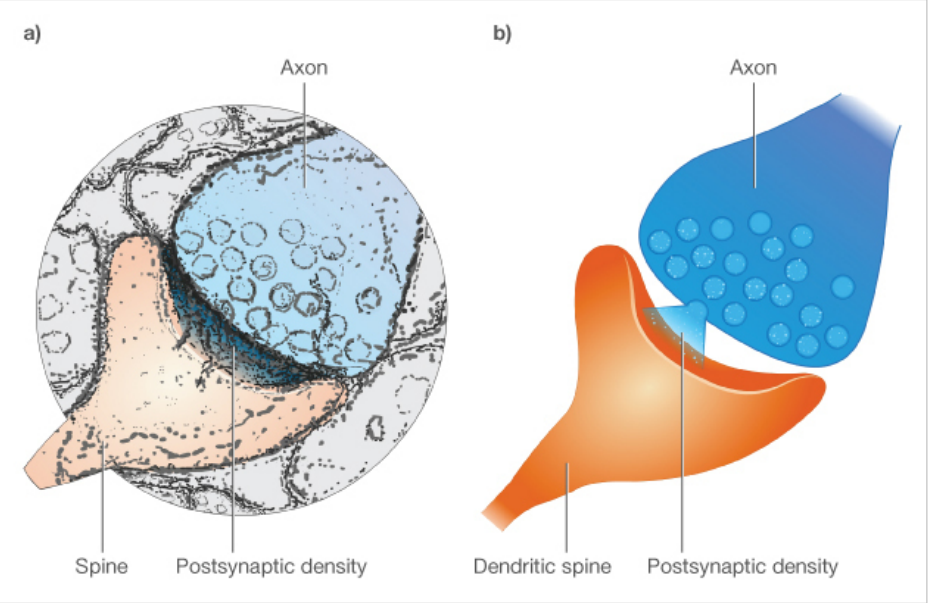


Figure 4: Signal transduction across the synapse.
Illustrations (a) and (b) both show a synapse, the space between the axon of a presynaptic neuron and the dendritic spine of a postsynaptic neuron. When an action potential reaches the synaptic terminal, it triggers the fusion of vesicles with the plasma membrane. The vesicles release neurotransmitters that travel across the synapse to the postsynaptic neuron and bind to specific receptors located on the dendritic spine that can either activate or inhibit the downstream neuron.
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Test Yourself

What type of chemicals do vesicles in the synaptic terminal of the axon contain, and what is the function of these chemicals?

Submit

Neurons can be classified as either excitatory or inhibitory. Excitatory neurons release neurotransmitters that excite, or depolarize, the membrane potential of the recipient neurons. Inhibitory neurons release neurotransmitters that inhibit, or hyperpolarize, the membrane potential of the recipient neurons. In this way, inhibitory neurons can effectively "shut off" other neurons for a brief period of time and are absolutely essential for the proper management of neuronal signaling networks in the brain. Modern techniques enable scientists to determine the direction signals move in the mouse brain and to determine which signals are stimulatory and which are inhibitory (Figure 5).

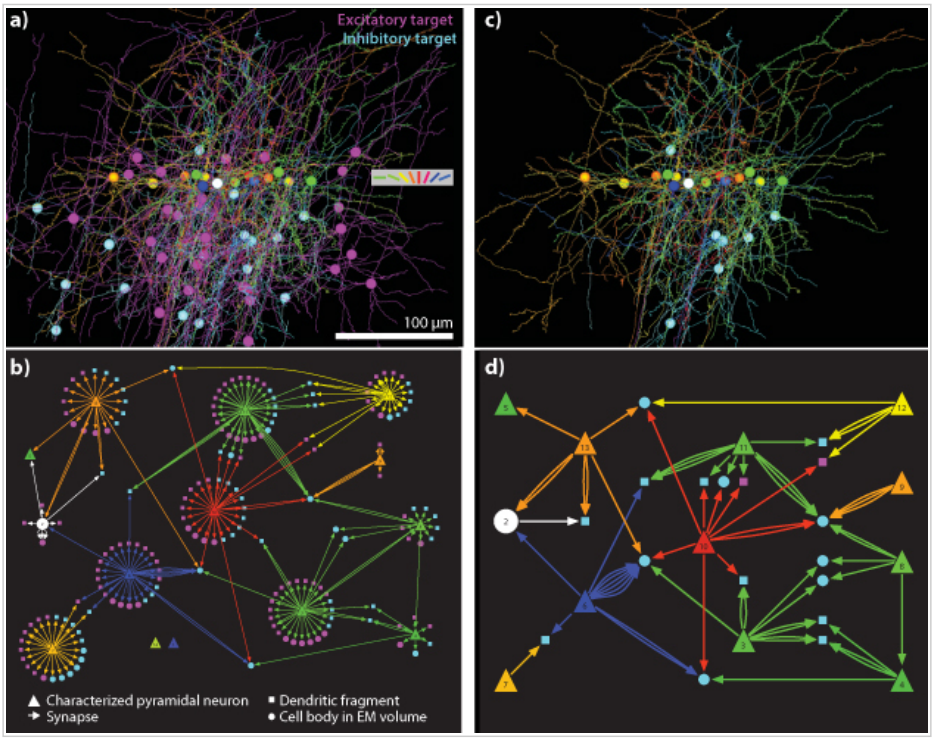


Figure 5: Interactions among neurons in the mouse brain.
In panels (a) and (c), dots indicate cell bodies, and lines indicate axons and dendrites. In panel (a), neurons receiving excitatory signals are indicated in magenta, and neurons receiving inhibitory signals are indicated in cyan. In panel (b), the direction of signal transduction for various neurons is shown. Panels (c) and (d) only show neurons for which scientists have determined a function. Note that the color of dots in panels (a) and (c) match the color of circles and triangles in panels (b) and (d).
© 2011 Nature Publishing Group Bock, D. *et al.* Network anatomy and *in vivo* physiology of visual cortical neurons. *Nature* 471, 177–182 (2011) doi:10.1038/nature09802. Used with permission.

Nervous systems of different animals.

The simplest nervous system, found in cnidarians such as hydra and jellyfish, consists of an evenly distributed web of nerve cells called a **nerve net** (Figure 6). None of the nerve cells are specialized, and the nerve net regulates the contraction and expansion of the gastrovascular cavity during digestion. Echinoderms (such as the sea star) have bundles of neurons, called nerves, which facilitate signal transduction. **Cephalization**, or the clustering of neurons in the anterior part of the body, occurs in flatworms (such as planarians) to form a primitive brain.



Figure 6: Jellyfish nerve net.
This cnidarian has a nerve net that spreads throughout its umbrella-shaped body.
Gregory Ochocki/Science Source.

The nematode has a very simple nervous system composed of very few cells. For example, the adult hermaphrodite nematode *Caenorhabditis elegans* has exactly 302 neurons. Arthropods have a more complex nervous system with a brain and a ventral nerve cord that runs down the center of the body and contains clusters of neurons called ganglia (singular ganglion). The complexity of a nervous system often depends on the lifestyle of an organism. For example, among mollusks, sessile species tend to have simple nervous systems, whereas predatory species such as octopi and squid have much more complex nervous systems that enable them to hunt. Vertebrates have the most complex nervous system of all animals, with a central nervous system containing a brain and spinal cord, as well as a peripheral nervous system.

IN THIS MODULE

Cells of the Nervous System
Summary
Test Your Knowledge

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Stem Cells
Stem cells are powerful tools in biology and medicine. What can scientists do with these cells and their incredible potential?

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Read what the NIH says about how stem cells may be used to rebuild the nervous system

The Nerves in Our Body
See if you can correctly match the body part to the nerve

Test Your Knowledge

1. Which neuron structure receives signals directly from other neurons?

- axon terminal
- cell body
- dendrite
- axon hillock
- Schwann cell

2. What is a major role of glial cells in the nervous system?

- Glial cells sense changes in the condition of an animal's body.
- Glial cells provide nourishment to neurons.
- Glial cells generate neurons that would replace defective cells.
- Glial cells sense pain and transmit pain information to the CNS.
- None of the answers are correct.

3. Which of the following organisms would likely have the least intricate nervous system?

- flatworms
- jellyfish
- bivalves
- insects
- All of these organisms have equally complex nervous systems.

4. In which of the following should the rate of action potential conduction be the fastest?

- an invertebrate neuron of narrow diameter
- an invertebrate neuron of wide diameter
- an unmyelinated vertebrate neuron
- a myelinated vertebrate neuron
- All the neurons described would have the same rate of action potential conduction.

5. Which of the following is an example of a glial cell that develops in the CNS?

- Schwann cells
- astrocyte
- motor neurons
- sensory neurons
- None of the answers are correct.

6. Which of the following statements is true about sensory neurons and motor neurons?

- Sensory neurons take in information and send it to the CNS, whereas motor neurons receive information from the CNS and transmit it to muscle.
- Sensory neurons send messages to the motor neurons.
- Motor neurons send faster signals than sensory neurons.
- Motor neurons receive information from the PNS.
- None of the answers are correct.

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Membrane Potential

All cells have a **membrane potential**, or an uneven distribution of ions and charge across the plasma membrane that contains potential energy. The normal potential for an inactive neuron is called the **resting potential**. Various stimuli can cause the membrane potential to change, resulting in a **graded potential**. Graded potentials can either increase or decrease the membrane potential. Small graded potentials usually have no effect. If the graded potential is large enough to pass a threshold value, a positive feedback loop is initiated and a complete depolarization of the membrane, called an **action potential**, occurs. The action potential travels down the axon to the synapse like a wave, triggering a downstream response. In the rest of this section we will explore how resting potentials, graded potentials, and action potential are generated.

Resting neuron membrane potential.

The sodium/potassium pump (Na^+/K^+ pump) uses energy derived from ATP hydrolysis to pump three Na^+ out of the cell and two K^+ in. Because more positively charged ions move out than in, a net charge develops across the membrane, positive on the outside and negative on the inside, resulting in an electrical potential. A chemical potential results from the uneven distribution of Na^+ and K^+ ions across the membrane. Together, the electrical and chemical potentials form an **electrochemical potential** (Figure 1).

In addition to the Na^+/K^+ pump, **ion channels** are present in the neuron plasma membrane. Ion channels allow the passive movement of ions through the plasma membrane. Each ion channel is selective for a particular type of ion. For example, neurons have ion channels selective for K^+ and others for Na^+.

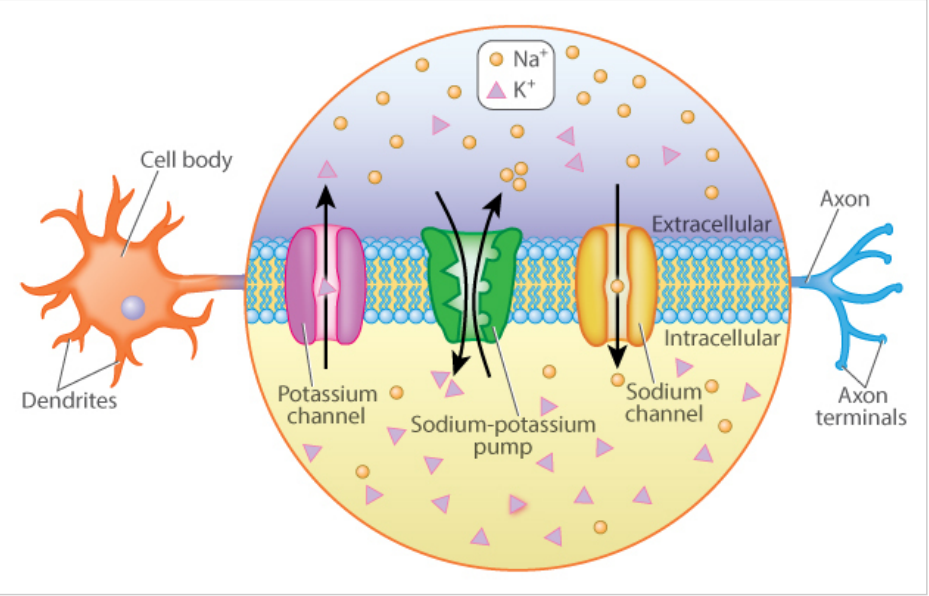


Figure 1: The Na^+/K^+ pump and Na^+ and K^+ ion channels.
The Na^+/K^+ pump moves three Na^+ ions out of the cell for every two K^+ ions it moves into the cell, resulting in an electrochemical potential. The K^+ ion channel allows passage of K^+ ions and the Na^+ ion channel allows passage of Na^+ ions.
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Some ion channels are **gated ion channels** that open or close in response

to a stimulus, whereas others are ungated. The K^+ channels in a neuron are ungated and always open. Na^+ channels are all gated, and most are closed in a resting neuron. Therefore, the plasma membrane of a resting neuron is highly permeable to K^+ but relatively impermeable to Na^+. Because more K^+ ions are inside the cell than outside, a net movement of K^+ ions out of the cell occurs. This outward movement of K^+ ions continues until the electrical potential across the membrane is sufficiently high to impede further ion movement. There is a net negative charge inside the cell because chloride and other negatively charged ions cannot diffuse freely across the membrane. An equilibrium between the K^+ and charge gradients is reached, resulting in a relatively constant resting potential between -60 and -80 mV (millivolts).

The study of the electrical properties of cells is called **electrophysiology**. Membrane voltage is measured using a pair of microelectrodes (Figure 2). One electrode is inserted through the plasma membrane into the cytoplasm and the other is placed into the extracellular fluid. A voltmeter measures the potential difference between the two environments. Membrane potential was first measured in 1939 by Alan Lloyd Hodgkin and Andrew Huxley, two English physiologists who conducted experiments using the largest known neurons from a squid (*Loligo pealei*). Hodgkin and Huxley shared the 1963 Nobel Prize in Physiology or Medicine for their work. Modern electrophysiology equipment allows scientists to measure membrane potential in the much smaller neurons present in mammals.

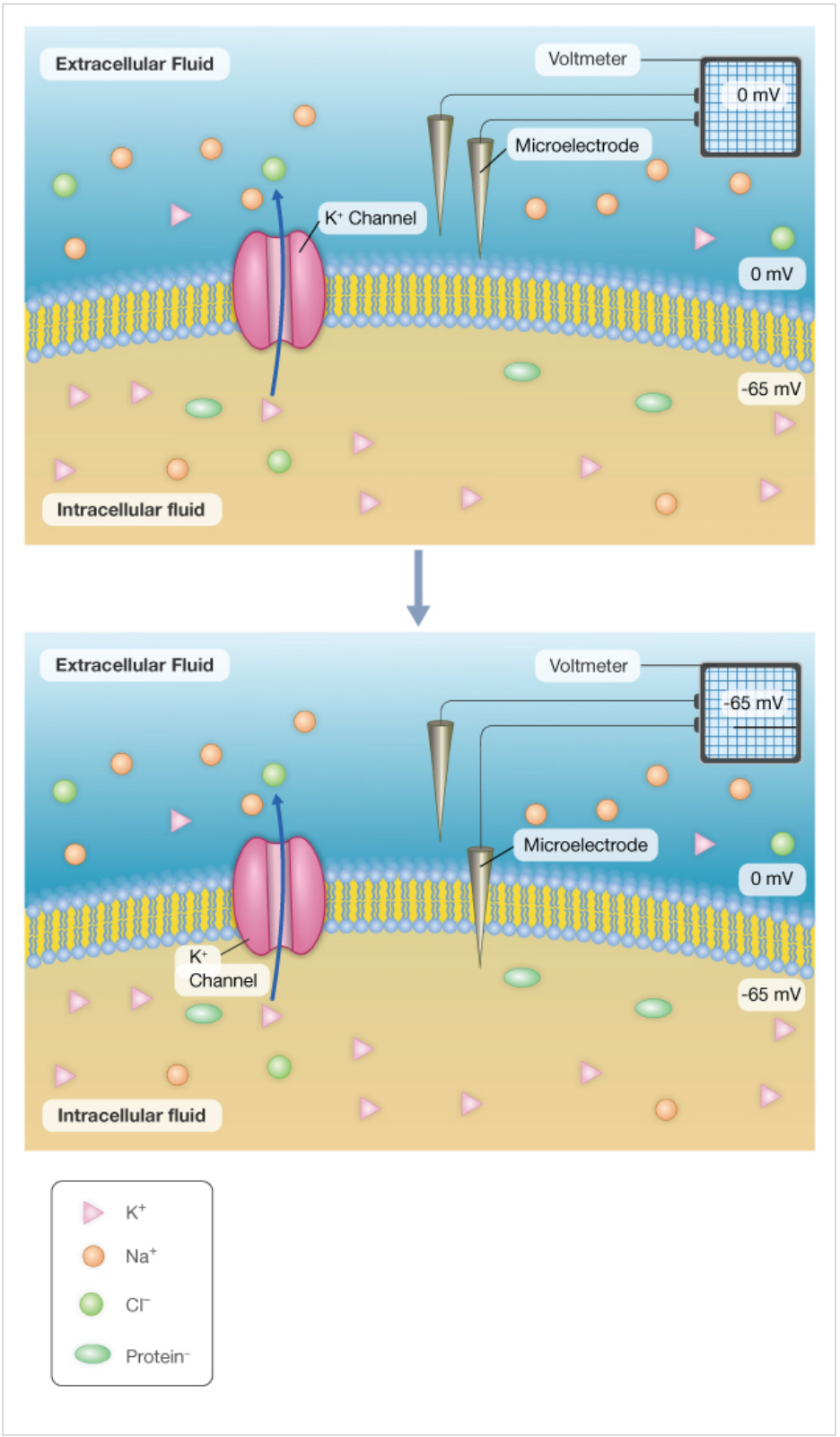


Figure 2: Measuring membrane potential.
Microelectrodes are used to measure membrane potential across a cell membrane. A microscope is used to place the microelectrode in the cell. *Top*: When both microelectrodes are in the extracellular environment, there is no electrical potential between them and the voltage measured is zero. *Bottom*: When one microelectrode is inserted through the plasma membrane to the cell interior, an electrical potential of -65 mV is measured.
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Test Yourself

Why can K^+ ions move across the cell membrane of a resting neuron more easily than Na^+ ions?

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Generation of graded potentials

Gated ion channels are classified into two types depending on how they are activated. **Ligand-gated** ion channels open or close in response to the binding of a specific ligand, such as a neurotransmitter. **Voltage-gated ion channels** open or close in response to a change in membrane potential. Both voltage-gated and ligand-gated ion channels exist in a neuron.

The relative permeability of Na^+ and K^+ depends on whether gated ion channels are open or closed. A resting neuron, in which most gated channels are closed, has net negative charge on the inside of the cell of about -60 to -80 mV. If a stimulus causes gated K^+ channels to open, the increased efflux of K^+ ions out of the cell results in **hyperpolarization**, or a more negative membrane potential (Figure 3, yellow line). If a stimulus causes gated Na^+ channels to open, influx of Na^+ into the cell occurs and results in **depolarization**, or a less negative membrane potential (Figure 3, blue line). A shift in membrane potential due to hyperpolarization or depolarization is called a graded potential. The magnitude of a **graded potential** depends on the strength of a stimulus.

Depolarization has a stimulatory effect. However, a neuron does not become activated unless depolarization is of sufficient magnitude to cross a **threshold potential**. In mammalian neurons, the threshold potential is about -55 mV. Once the threshold potential is reached, an action potential is rapidly generated (Figure 3, red line). Activation of a neuron is an all-or-nothing event and unlike graded potentials, the magnitude of the action potential is always the same. Because a threshold potential must be reached before activation occurs, a neuron cannot become activated by a minor stimulus or random fluctuations in membrane potential.

Hyperpolarization often occurs after the generation of an action potential and has an inhibitory effect on subsequent neuron activation, ensuring that a neuron is not reactivated too quickly (Figure 3, tail end of red line).

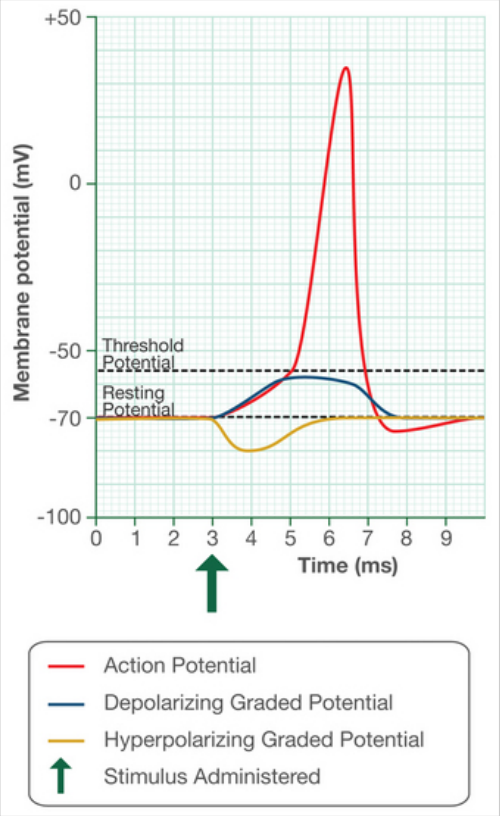


Figure 3: Graded potentials and action potentials.
Gated ion channels may open or close in response to a stimulus. If K^+ channels open, hyperpolarization occurs. If Na^+ channels open, depolarization occurs. If depolarization passes a threshold potential, an action potential is generated. After the action potential is terminated, the membrane becomes briefly hyperpolarized.
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Generation of action potentials

An **action potential** is generated when voltage gated channels open, as shown in figure 4. In step 1, the neuron is at a resting state and both gated K^+ and Na^+ ion channels are closed, resulting in a resting potential of -60 to -70 mV. In step 2, a stimulatory signal causes voltage gated Na^+ channels to open. Na^+ enters the cell and the membrane slightly depolarizes. In step 3, the threshold potential of -55 mV is reached, and most of the remaining gated Na^+ channels open. The massive influx of Na^+ reverses the normal polarity of the membrane for a brief instant. In step 4, voltage-gated K^+ channels, which are activated more slowly than Na^+ channels, begin to open so that K^+ can flow out of the cell. Na^+ channels are inactivated for a period of time called the **refractory period**, during which the Na^+ channel cannot be activated by changes in voltage. Note that the conformational change that causes Na^+ channel inactivation is different than the conformational change that closes the channel. In step 5, The K^+ channels begin to close. However a brief hyperpolarization of the membrane occurs until more K^+ channels can be closed. Na^+ channels revert from the inactive to the closed state. The Na^+/K^+ pump restores the membrane to the resting potential.

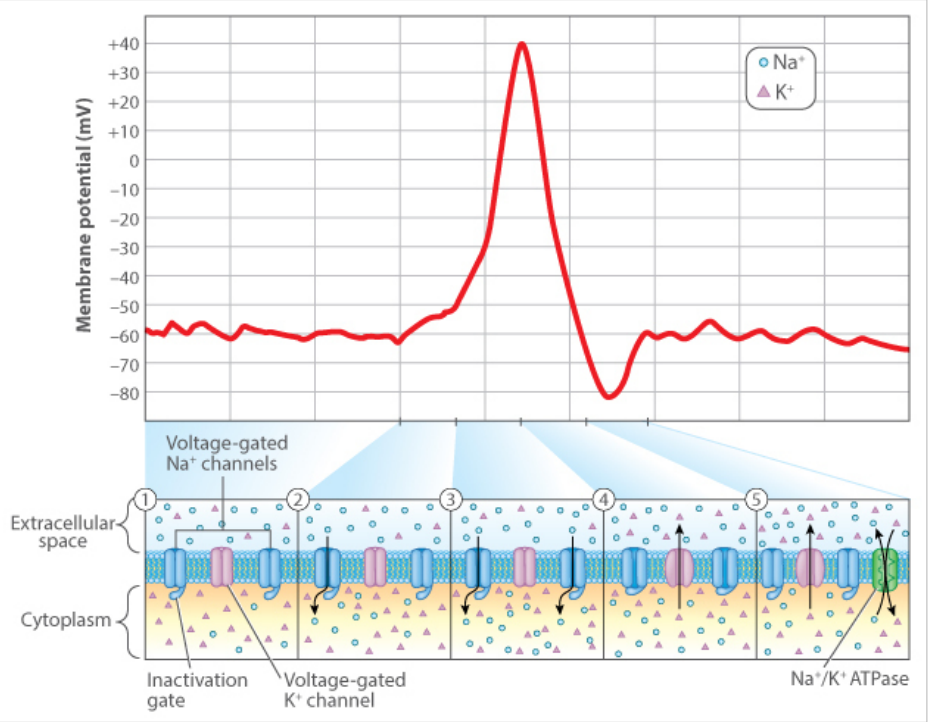


Figure 4: Generation of the action potential.
(1) Voltage-gated Na^+ and K^+ channels are closed and the membrane potential is at the resting potential of about -60 mV. (2) A stimulus causes voltage-gated Na^+ channels to open and Na^+ enters the cell, causing the membrane to depolarize. (3) At the threshold potential, all the voltage-gated Na^+ channels open and the membrane rapidly depolarizes. (4) The voltage-gated Na^+ channels become inactivated and voltage-gated K^+ channels begin to open and K^+ flows out of the cell so that the membrane can begin to repolarize. During this refractory period, voltage-gated Na^+ channels are unresponsive to changes in membrane potential to prevent further depolarization.(5) The voltage-gated K^+ channels begin to close and the Na^+/K^+ pump restores the resting membrane potential. The Na^+ channels revert from an inactive to a closed state.
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Test Yourself

Repolarization is driven primarily by K^+ outflow through voltage-gated K^+ channels. If a drug was administered that prevented voltage-gated K^+ channels from opening, how would the shape of the action potential change?

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- **Membrane Potential**
- Propagation of the Action Potential
- Summary
- Test Your Knowledge

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Propagation of the Action Potential

An action potential is typically generated at the **axon hillock**, which connects the cell body to the axon. An action potential depolarizes the membrane because of a rapid influx of Na^+ through voltage gated sodium channels. This causes adjacent voltage gated sodium channels to open and depolarize the adjacent membrane (Figure 5). Because the gated Na^+ channels are inactivated during the refractory period, channels that were just activated cannot be immediately reactivated. As a result, the action potential moves in one direction down the axon to the synapse.

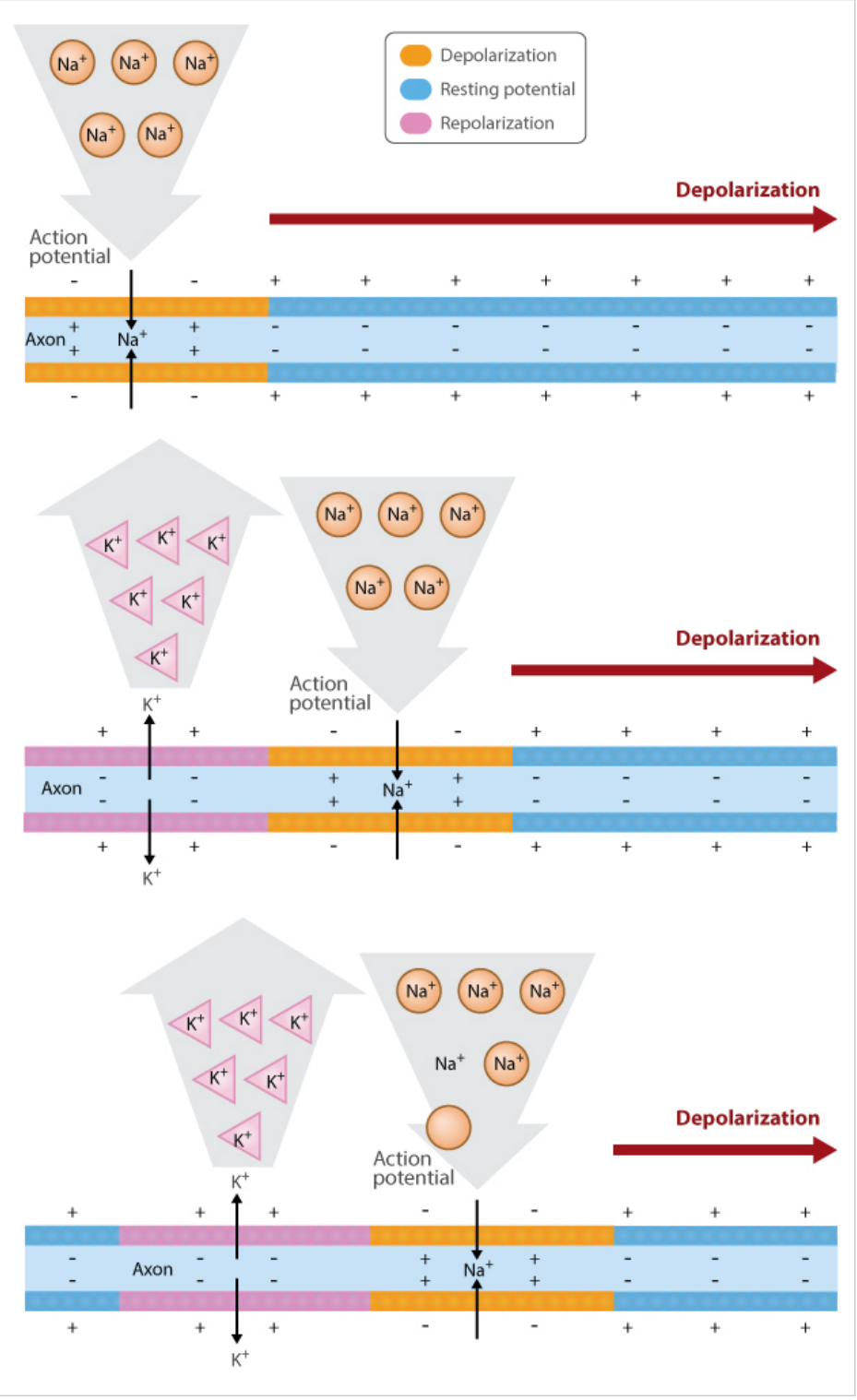


Figure 5: Conduction of an action potential down an axon.
Top: The action potential, which is usually generated at the axon hillock (left side of illustration), causes the membrane to depolarize. *Middle*: This depolarization causes voltage gated Na^+ channels in adjacent portions of the membrane to open. Because voltage gated Na^+ channels that were just activated are in a refractory period, they cannot be reactivated immediately, and the action potential moves in one direction down the axon. *Bottom*: As the action potential moves down the axon, the resting potential is restored in the membrane behind the action potential.
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The speed of an action potential varies.

In invertebrates, the speed of transmission depends on the diameter of the axon. In narrow axons, an action potential may travel no more than a few centimeters per second whereas in giant squid axons, which are 1 mm in diameter, the action potential travels at 30 meters per second.

Vertebrates have an insulating layer called a myelin sheath that wraps around the axon. Between myelinated regions are naked regions called **nodes of Ranvier**, named after the French pathologist Louis-Antoine Ranvier who discovered them, where the exchange of ions with the extracellular fluid occurs. The action potential leaps from one node of Ranvier to the next, resulting in a type of conduction called **saltatory conduction** (saltatory is derived from the Latin *saltare*, to leap) (Figure 6). Saltatory conduction reduces the number of gated ion channels that must open and greatly increases the speed at which an action potential can be transmitted. Thus, a myelinated human axon 20 μm in diameter can transmit a signal 40 times faster than an unmyelinated squid axon 1 mm in diameter. Multiple sclerosis is a disease that causes loss of myelination, which impairs muscle function by slowing neural impulse conduction.

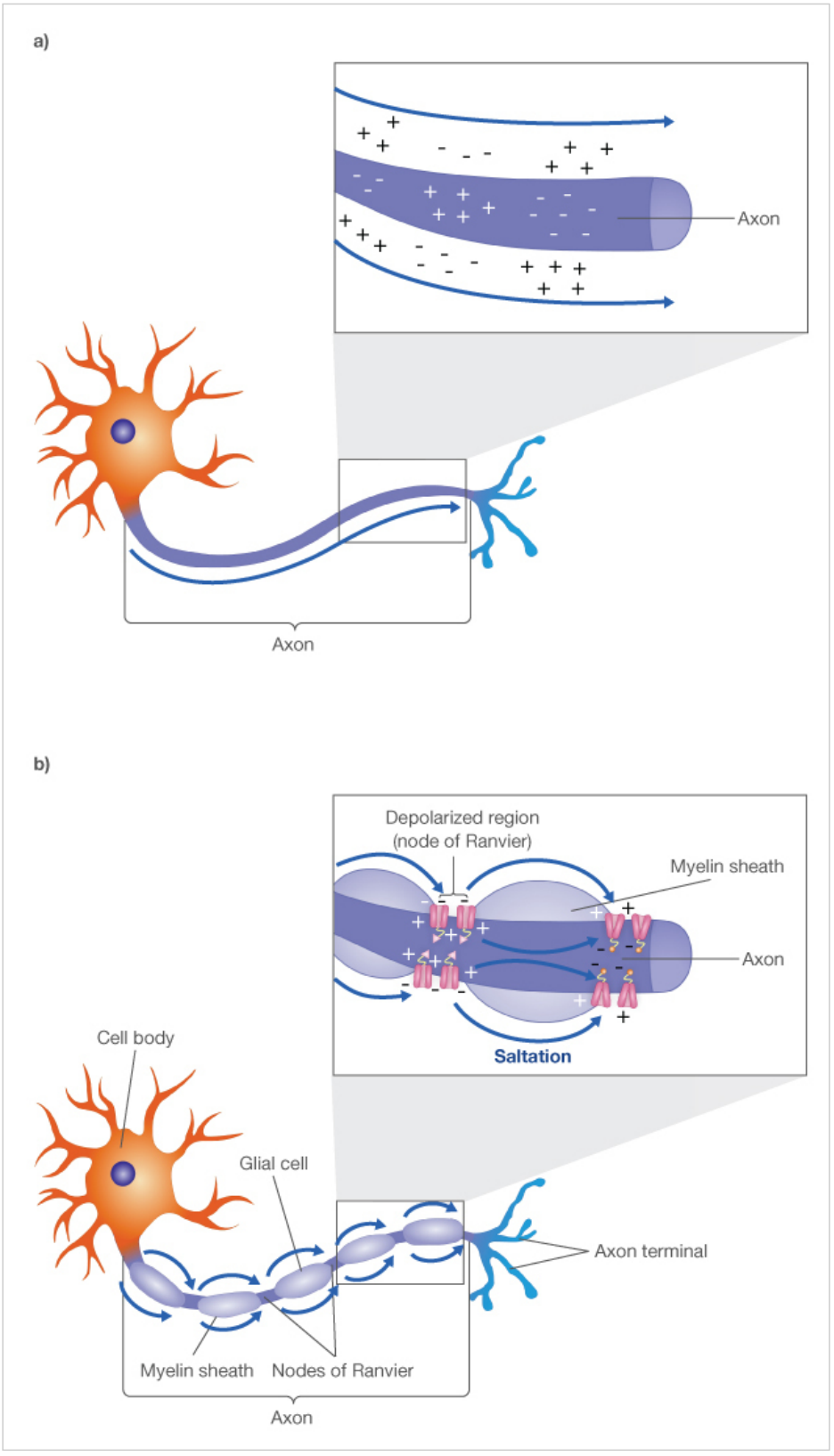


Figure 6: Saltatory conduction.
In unmyelinated axons (a), the action potential travels continuously down the axon. In myelinated axons (b), the action potential leaps from one node of Ranvier to the next, a type of conduction known as saltatory conduction.

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Test Your Knowledge

1. The action of which of the following maintains the normal resting potential of a neuron?

- voltage-gated chloride channel
- sodium/potassium pumps
- voltage-gated potassium channel
- voltage-gated sodium channel
- voltage-gated calcium channel

2. Select the best answer to correctly complete the sentence: During the process of repolarization, ___ ions flood into the ___.

- potassium, sodium-potassium pump
- sodium, interior of the cell
- potassium, extracellular space
- sodium, extracellular space
- potassium, interior of the cell

3. Which statement accurately describes the concentration of potassium ions in a resting neuron?

- The concentration of potassium ions in the cell is low because open voltage-gated potassium ion channels are open.
- The concentration of potassium ions is high because voltage-gated potassium ion channels are open.
- The concentration of potassium ions is lower in the interior of the cell than in the extracellular medium.
- The concentration of potassium ions is the same in the extracellular medium as in the cell interior.
- The concentration of potassium ions is greater in the interior of the cell than in the extracellular medium.

4. If the membrane potential of a neuron reaches its threshold potential, which event is most likely to occur next?

- opening of all voltage-gated potassium channels
- generation of an action potential
- hyperpolarization
- inhibition of the sodium/potassium pump
- repolarization

5. The membrane potential in a cell changes from -70 mV to -60 mV. What change has taken place within the cell?

- hyperpolarization
- depolarization
- repolarization
- an action potential
- None of these answers are correct.

6. What happens at the peak of an action potential?

- All sodium and potassium ion channels are closed.
- Many sodium ion channels begin to close and many potassium ion channels begin to open.
- Both sodium ion channels and potassium ion channels begin to close.
- All sodium and potassium ion channels are open.
- Sodium ion channels begin to open and potassium channels begin to close.

7. Why does the presence of a myelin sheath increase the speed at which a nerve impulse travels?

- Myelin conducts electrical impulses more easily than bare axons, increasing the speed of transmission.
- Myelin decreases the diameter of the axon.
- Myelin increases the speed of transmission by allowing the nerve impulse to jump from a node of Ranvier to the myelin sheath.
- Myelin increases the diameter of the axon.
- Myelin insulates the axons, allowing nerve impulses to jump from one node of Ranvier to another.

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IN THIS MODULE

- Membrane Potential
- Propagation of the Action Potential
- Summary
- **Test Your Knowledge**

WHY DOES THIS TOPIC MATTER?



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PRIMARY LITERATURE

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Neurons Interface with Other Cells at Synapses

An action potential is generated at the axon hillock and travels down the axon to the synapse. At the synapse, the signal is transmitted to another cell. There are two types of synapses, electrical synapses and chemical synapses.

In electrical synapses, ions and other molecules, including chemical messengers, flow from one cell to another through gap junction channels. Electrical synapses can transmit signals much more quickly than chemical synapses and can be found throughout the brain and spinal cord. They are typically used in those neuronal circuits in which a rapid response is especially important for survival. For example, gap junctions are often found in the spinal cords of vertebrates at synapses that connect afferent sensory neurons to efferent motor neurons. They facilitate the rapid transmission of signals that stimulate motor systems which allow an animal to escape from a predator. Gap junctions may also interconnect axons from different neurons such that when a threshold potential is reached, all of the interconnected neurons fire in a synchronous manner. Movement of signals through electrical synapses in this example is bidirectional, meaning that the signal can travel in either direction through the gap junction.

A more common type of synapse is called a **chemical synapse**. In chemical synapses, a space called the **synaptic cleft** separates the presynaptic neuron from the postsynaptic neuron. The synaptic cleft is typically less than 50 nm across. Chemicals called **neurotransmitters** are stored in vesicles at the synaptic terminals. In response to an action potential, these vesicles fuse with the plasma membrane, and the neurotransmitters are released into the synaptic cleft. Transmission of signal is always unidirectional. The properties of chemical and electrical synapses are summarized in Table 1.

Characteristic	Electrical	Chemical
Speed of transmission	<0.1 ms	1- >10 ms
Connection	Gap junction channel	extracellular fluid
Direction of flow	Bidirectional	Unidirectional

Table 1: Properties of electrical synapses and chemical synapses.

Test Yourself

How does an electrical synapse differ from a chemical synapse?

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IN THIS MODULE

- **Neurons Interface with Other Cells at Synapses**
- The Chemical Synapse
- Postsynaptic Potential Generation
- Types of Neurotransmitters
- Summary

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The Chemical Synapse

Neurotransmitter receptors can be classified into two different types: ionotropic receptors and metabotropic receptors. **Ionotropic receptors**, which are associated with an ion channel, directly regulate the movement of ions through the channel. Binding of a neurotransmitter to an ionotropic receptor causes the channel to open or close and affects the flow of ions accordingly. For this reason, ionotropic receptors are also referred to as "ligand-gated ion channels."

Signal transmission at synapses with ionotropic receptors.

Events that occur at a synapse in which the postsynaptic cell has ionotropic receptors are shown in Figure 1. When an action potential in the presynaptic cell arrives at the synapse, it depolarizes the membrane. As a result, voltage-gated calcium (Ca^{2+}) channels open, and calcium enters the presynaptic cell. Ca^{2+} causes synaptic vesicles containing neurotransmitter to fuse with the plasma membrane, releasing neurotransmitter into the synaptic cleft. The neurotransmitter travels across the cleft and binds the ionotropic receptor and opens the channel. To terminate the signal, released neurotransmitter may be actively transported back into the presynaptic neuron or metabolized by hydrolytic enzymes in the postsynaptic cleft or in nearby glial cells. The neurotransmitter molecules may also simply diffuse away.

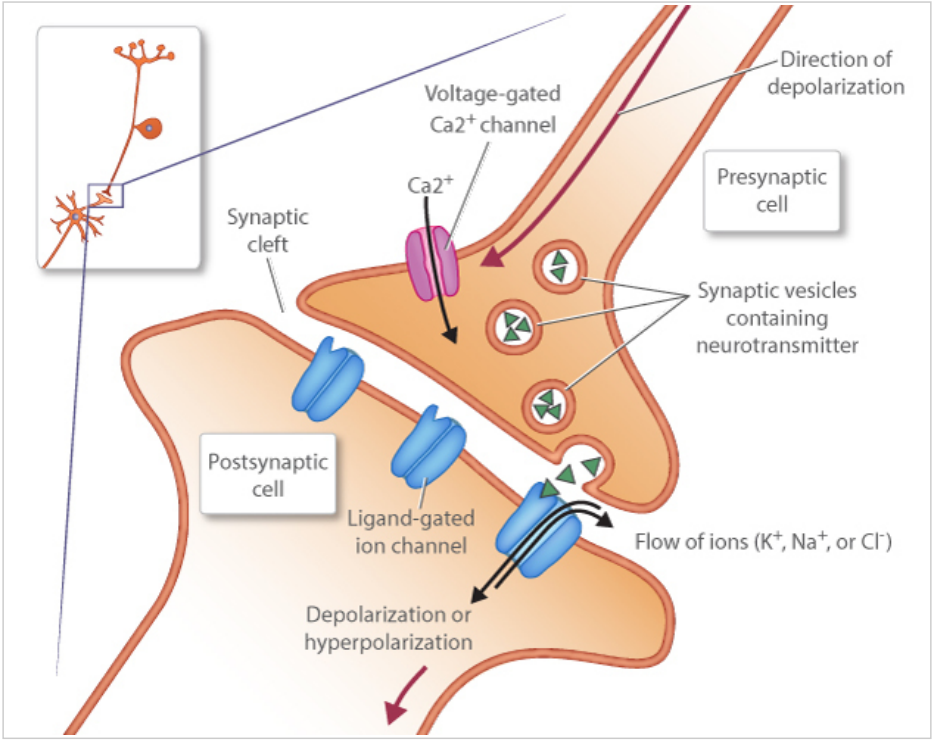


Figure 1: Transmission of a message at a chemical synapse.
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The selectivity of ligand-gated ion channels in the postsynaptic neuron varies. The channels present at some synapses are selective for sodium (Na^+) and potassium (K^+) ions, while the channels present at other synapses are selective for potassium and chloride (Cl^-) ions. When Na^+/K^+-selective ion channels open, Na^+ rushes into the cell and depolarizes the postsynaptic membrane in a graded manner. If depolarization of the membrane reaches a certain threshold level, an action potential is produced. For this reason, the graded depolarization of a membrane is called an excitatory postsynaptic

potential (EPSP). However, when K^+/Cl^- ion channels open, K^+ leaves the cell and Cl^- enters. This results in a graded hyperpolarization of the membrane. A hyperpolarized membrane will inhibit the generation of an action potential and therefore is called an inhibitory postsynaptic potential (IPSP).

Signal transmission at synapses with metabotropic receptors.
Binding of neurotransmitter to metabotropic receptors activates a signal transduction pathway that indirectly regulates the opening or closing of ion channels. A well-characterized pathway is the cyclic AMP (cAMP) pathway, which is mediated by G proteins. Binding of neurotransmitter to the receptor activates a G protein, which in turn activates adenylyl cyclase. Adenylyl cyclase is an enzyme that converts ATP into cAMP. cAMP activates protein kinase A, which phosphorylates specific ion channels and causes them to open or close. The response at synapses containing metabotropic receptors is slower than at synapses containing ionotropic receptors but tends to last longer, from minutes to hours. This is because protein kinase A can remain activated for an extended period of time and phosphorylate multiple ion channels.

IN THIS MODULE

- Neurons Interface with Other Cells at Synapses
- **The Chemical Synapse**
- Postsynaptic Potential Generation
- Types of Neurotransmitters
- Summary
- Test Your Knowledge

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Postsynaptic Potential Generation

Changes in the membrane potential of a neuron are called graded potentials. A postsynaptic neuron may have hundreds or even thousands of synapses, and the magnitude of the graded potential depends on how many EPSPs or IPSPs are generated. If more EPSPs are generated that push the membrane past the threshold level, the membrane becomes completely depolarized and generates an action potential. If more IPSPs are generated, the membrane becomes hyperpolarized and less prone to being able to generate an action potential. If EPSPs and IPSPs of equal magnitude occur simultaneously, the membrane potential will remain at roughly its resting potential, and the two signals will effectively cancel one another out (Figure 2).

If more than one EPSP arrives at a single synapse simultaneously, the depolarization has an additive effect, a process known as temporal summation. Likewise, multiple EPSPs arriving simultaneously at different synapses have an additive effect, a process known as spatial summation. If summation results in a graded membrane depolarization sufficiently large enough to cross the threshold potential, an action potential is generated, and the neuron fires.

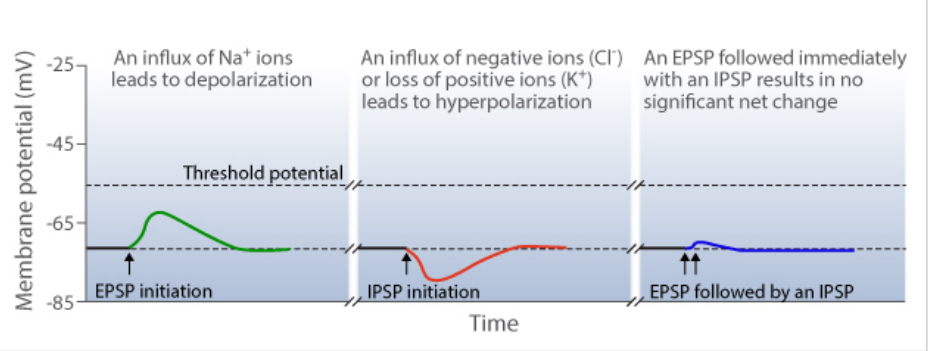


Figure 2: Summation of EPSP and IPSP at a postsynaptic neuron. An excitatory postsynaptic potential (EPSP) causes depolarization of the postsynaptic cell. An inhibitory postsynaptic potential (IPSP) causes hyperpolarization of the postsynaptic cell. An excitatory postsynaptic potential (EPSP) and an inhibitory postsynaptic potential (IPSP) of similar magnitudes cancel each other out.

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Test Yourself

Describe how an action potential is generated in the postsynaptic neuron.

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Types of Neurotransmitters

Over 100 neurotransmitters have been identified, which are divided into five groups based on chemical structure: acetylcholine, amino acids, biogenic amines, neuropeptides, and gases (Table 2). The effect of a neurotransmitter depends on the type of receptor it binds on the postsynaptic cell. Many neurotransmitters bind different types of receptors, and in some cases, a neurotransmitter may excite one cell and inhibit another, depending on the type of receptor that is present.

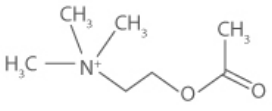
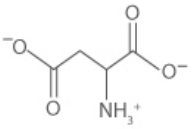
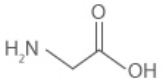
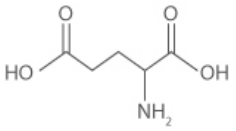
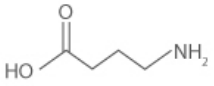
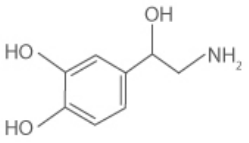
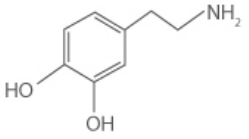
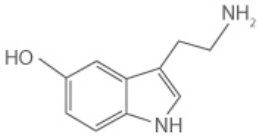
Category	Example	Chemical Structure
Acetylcholine	Acetylcholine	
Small amino acids	Aspartate	
	Glycine	
	Glutamate	
	GABA	
Monoamines	Norepinephrine	
	Dopamine	
	Serotonin	
Neuropeptides	Substance P	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met
	Endorphins	Ex) Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu
	Enkephalins	Ex) Tyr-Gly-Gly-Phe-Leu
Inorganic gases	Nitric oxide	N=O
	Carbon monoxide	C≡O

Table 2: Major neurotransmitters.
In the neuropeptide chemical structures, three-letter abbreviations for amino acids are shown. The endorphin shown is β endorphin, and the encephalin shown is Leu-enkephalin.
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The first category of neurotransmitter listed in Table 2 consists of a single compound, acetylcholine, often abbreviated as ACh. Acetylcholine was the first neurotransmitter to be discovered. For their discovery of it, English pharmacologist Henry Hallett Dale and German pharmacologist Otto Loewi shared the 1936 Nobel Prize in Physiology or Medicine. Acetylcholine acts as a neurotransmitter in both the peripheral and central nervous systems,

and can either stimulate or inhibit downstream neurons depending on the receptor that is expressed in those neurons. In the PNS, acetylcholine stimulates muscle contractions by binding to ligand-gated ion channels located on muscle tissue. In cardiac tissue ACh has an inhibitory effect and can lower heart rate. Acetylcholine also stimulates metabotropic receptors in the autonomic ganglia. The nerve gas sarin inhibits acetylcholinesterase, the enzyme that breaks down acetylcholine. As a result, acetylcholine builds up and paralysis occurs due to overstimulation. ACh is also an important neurotransmitter in the brain, and misregulation of acetylcholine signaling may contribute to the decline in memory that is observed in the development of Alzheimer's disease.

Like ACh, amino acid neurotransmitters are present in both the CNS and PNS. Amino acid neurotransmitters, which are the second category of neurotransmitters listed in Table 2, include glutamate, GABA (γ-aminobutyric acid), and glycine. Glutamate, the most common neurotransmitter in the CNS, has a stimulatory effect and is important in formation of long-term memory. GABA is an inhibitory neurotransmitter that increases membrane permeability to Cl^- with the effect of hyperpolarizing the membrane (Figure 3). Glycine is an inhibitory neurotransmitter that is found in parts of the CNS outside the brain.

The third category of neurotransmitters listed in Table 2 is monoamines, which are also called biogenic amines and are synthesized from amino acids. Examples include norepinephrine, dopamine, and serotonin. Norepinephrine has a stimulatory effect on the autonomous division of the PNS. Dopamine and serotonin act in the brain and affect sleep, mood, and learning. A substantial amount of research has linked the misregulation of serotonin with a variety of neuropsychiatric disorders, including depression. A class of antidepressant drugs known as serotonin reuptake inhibitors (SSRIs) work by blocking the transporter that recycles serotonin from the synaptic cleft, thus increasing levels of the mood-regulating neurotransmitter in the brain.

The fourth category of neurotransmitters listed in Table 2 is neuropeptides, many of which act on metabotropic receptors. The neuropeptide substance P is involved in the transmission of pain sensations from the peripheral to the central nervous system. Endorphins, another type of neuropeptide, reduce pain sensation.

The final category of neurotransmitters is neurotransmitters that are gases. These gas neurotransmitters are not stored in presynaptic vesicles and do not function like other neurotransmitters in the classical sense. They are synthesized as they are needed and are permeable to cell membranes. They function at the synapse and diffuse through the lipid bilayers to modulate important regulatory molecules within the target neuron. The neurotransmitter nitric oxide is released during sexual arousal in men and works by stimulating vasodilation.

Future perspectives.

Individuals with Down's syndrome have three copies of chromosome 21, and as a result, they have three copies of over 200 hundred genes instead of the usual two (chromosome 21 is the smallest human chromosome). This leads to an imbalance in the number of protein products made. Recent evidence suggests one consequence of this imbalance is that firing of neurons is inhibited more often than they should be, which inhibits learning and memory formation.

Researchers in the Garner lab at Stanford University developed a strain of mouse that has three copies of many of the genes that are triplicated in Down's syndrome. These mice exhibit deficits in learning and memory similar to what is observed in humans with Down's syndrome. And, as in humans,

the stimulation versus inhibition of neurons is out of balance in these mice.

Given that Down's syndrome is associated with excessive neuronal inhibition, the Garner group hypothesized that by blocking the inhibitory GABA neurotransmitter they may be able to reverse some of the symptoms associated with Down's syndrome. One of the receptors GABA binds to is a ligand-gated ion channel called the GABA-A receptor. Researchers in the Garner lab administered a GABA-A receptor antagonist, pentylenetetrazole (PTZ), to the Down's-like mice; PTZ inhibits the effect of GABA by binding to and blocking the GABA-A receptor. After several weeks of treatment with PTZ, the Down's-like mice had their memory and learning restored to near normal, and the improvement lasted several weeks after treatment was terminated. The Garner group hopes to conduct clinical trials to determine if PTZ or another GABA antagonist could be used to reverse learning and memory deficits in humans with Down's syndrome.

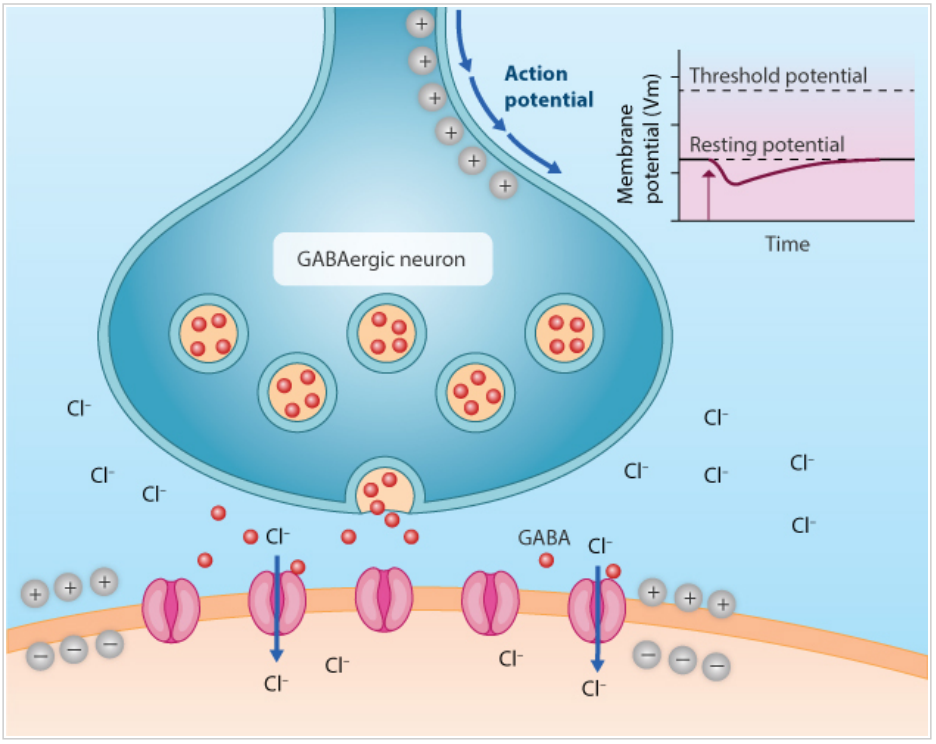


Figure 3: GABA is an inhibitory neurotransmitter.
When GABA binds to the GABA-A receptor, chlorine ions enter and hyperpolarize the cell.
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IN THIS MODULE

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- Postsynaptic Potential Generation
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Test Your Knowledge

1. Which ligand binds to a ligand-gated ion channel on a postsynaptic neuron?

- a neurotransmitter
- a calcium ion
- a potassium ion
- a sodium ion
- any type of inorganic ion

2. A neurotransmitter that directly opens or closes an ion channel works on what type of receptor?

- metabotropic
- second messenger
- ionotropic
- G protein
- acetylcholine

3. Which of the following is NOT a feature of an electrical synapse?

- use of neurotransmitters to carry information
- fast transmission
- neurons are connected by a gap junction
- bidirectional flow of information
- there is a short distance between neurons

4. Which two neurotransmitters are associated with inhibitory responses?

- glycine and glutamate
- glycine and GABA
- GABA and glutamate
- glutamate and acetylcholine
- None of the answers are correct.

5. How does the arrival of an action potential at the synaptic terminal lead to the release of neurotransmitters?

- through the movement of calcium ions into the presynaptic cell interior
- through the bundling of neurotransmitters into synaptic vesicles
- by increasing the concentration of potassium ions into the cell interior
- through the movement of sodium ions into the cell interior
- None of these answers are correct.

6. Following the flow of calcium ions into the cell interior via voltage-gated calcium ion channels, how do neurotransmitters from a presynaptic neuron reach the synaptic cleft?

- They are released into the cleft when the neurotransmitter vesicle fuses with the plasma membrane of the presynaptic neuron.
- They pass through voltage-gated sodium ion channels in the membrane of the presynaptic neuron.
- They are carried from the axon hillock by an action potential.
- They pass through voltage-gated calcium channels in the membrane of the

presynaptic neuron.

- They diffuse through gap junction channels in the membrane of the presynaptic neuron.

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The Two Divisions of the Vertebrate Nervous System

The nervous system has three basic functions: sensory input, central processing, and motor output. In vertebrates, these functions are carried out by two main subdivisions — the central nervous system and the peripheral nervous system (Figure 1). The **central nervous system (CNS)** includes the brain and spinal cord. All other nerves are in the **peripheral nervous system (PNS)**. The PNS acquires information about the internal and external environments and relays this information to the CNS. After processing the information, the CNS instructs the PNS to send specific motor commands to skeletal muscle, cardiac muscle, smooth muscle, and glands.

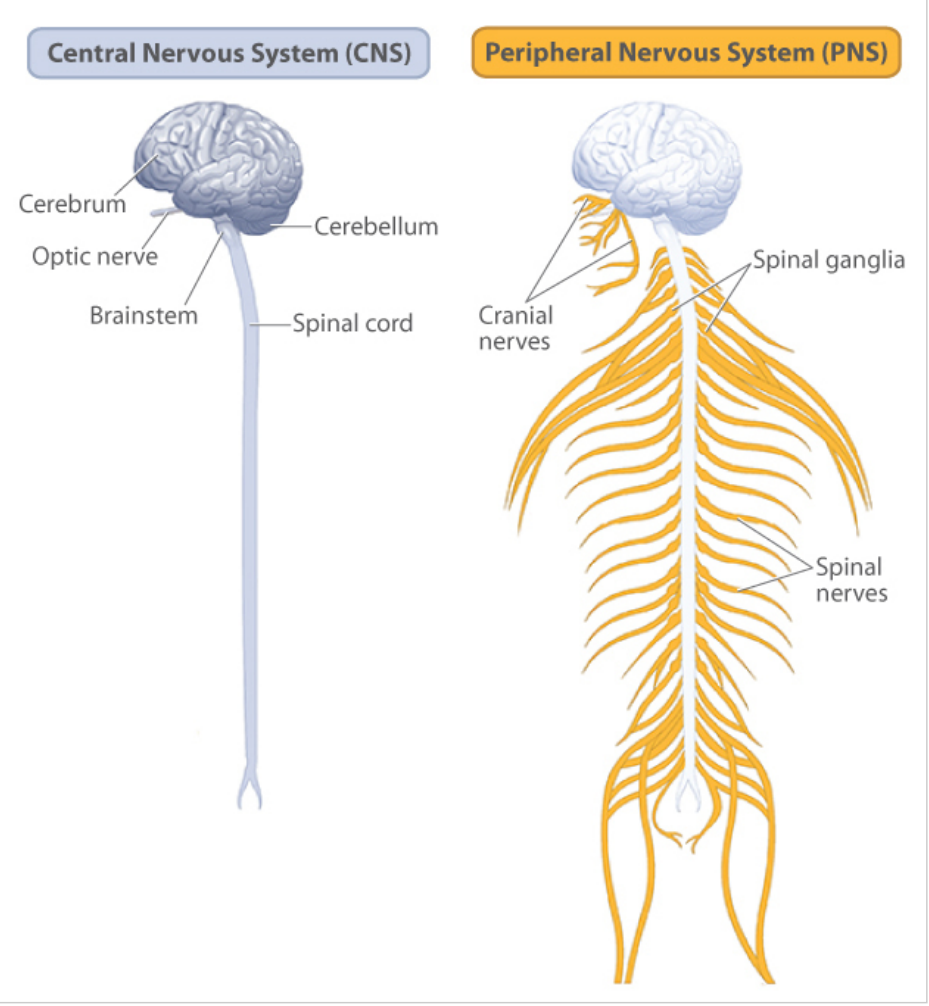


Figure 1: Vertebrate nervous system.
The CNS of vertebrate animals, shown in gray, consists of the the brain and spinal cord. All other nerves, shown in yellow, are part of the peripheral nervous system.
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The central nervous system.

The **central nervous system (CNS)** consists of the brain and the spinal cord, both protected by bone. The brain, which resides inside the cranium, acquires sensory information from the body. The brain is also able to store information from previous sensory experiences. Based on new and learned sensory information, the brain generates motor outputs. The spinal cord, encased in the bony vertebral column, transmits information between the

body and the brain and is also able to process sensory input and generate motor output, called reflexes, without help from the brain.

Two different types of tissue are found in the brain and spinal cord: white matter and gray matter (Figure 2). **White matter** consists mainly of axons wrapped in myelin sheath. The myelin sheath gives the white matter its white appearance. **Gray matter** is composed of neuronal cell bodies, unmyelinated axons, and dendrites. In the brain, white matter is surrounded by gray matter. In the spinal cord, gray matter is on the inside and is surrounded by white matter.

The gray matter of the spinal cord has dorsal and ventral horns that form an H shape. The dorsal horns face the back of the body and the ventral horns face the front. Each dorsal horn connects to a dorsal root ganglion. The dorsal root ganglia contain cell bodies from sensory neurons and transmit information from these neurons to the CNS. Nerves that carry information from the PNS to the CNS are called afferent nerves. Each ventral horn is attached to a ventral nerve root. The ventral nerve root is an efferent root, meaning it carries motor nerve signals from the CNS to the PNS.

Test Yourself

Which type of spinal nerves are "afferent" and which type are "efferent"?

Submit

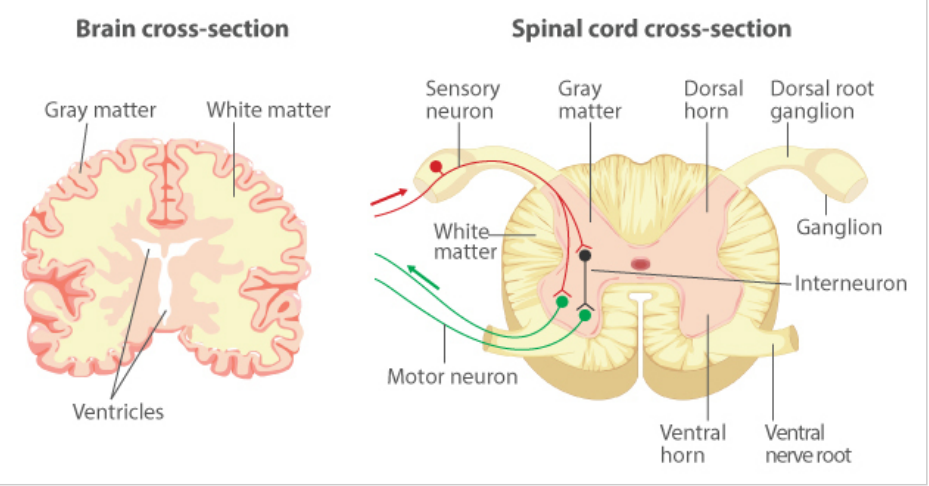


Figure 2: White matter and gray matter in the central nervous system.
White matter consists of axons wrapped in myelin sheaths. Gray matter consists of neuronal cell bodies, dendrites, and unmyelinated axons.
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Many reflexes are automatic responses produced by the spinal cord without input from the brain. For example, when the patellar ligament in the knee is tapped with a mallet, a healthy leg responds with an involuntary kick. This reflex is called the patellar, or knee-jerk, reflex. Afferent sensory neurons that detect the stimulus project directly to the spinal cord through the dorsal horn where they connect directly to efferent motor neurons that leave through the ventral horn and stimulate the appropriate muscle response. Importantly however, the same afferent sensory neurons also stimulate inhibitory interneurons in the spinal cord that hyperpolarize and inhibit other efferent motor neurons that project to muscles that are inherently antagonistic to this response. In this way, only the muscles important for the knee jerk reflex are stimulated while other muscles in the leg that are not important for this response are inhibited.

Test Yourself

What type of neuron begins the knee-jerk reflex?

Submit

The peripheral nervous system.

As discussed in the previous section, afferent neurons carry information from the PNS to the CNS, and efferent neurons carry information from the CNS to the PNS (Figure 3). Efferent neurons are separated into two categories based on the type of movement they control. Efferent neurons of the motor (somatic) system control voluntary muscles such as those found in the arms and legs. Efferent neurons of the autonomic nervous system control involuntary movement, such as beating of the heart, and are responsible for maintaining physiological homeostasis.

The autonomic nervous system is further divided into the parasympathetic, sympathetic, and the enteric divisions, which regulate organs and glands of the body. The parasympathetic and sympathetic nervous systems have antagonistic effects. The **parasympathetic nervous system** causes relaxation responses, sometimes referred to as "rest and digest." When the parasympathetic nervous system is activated, heart rate slows, and digestion speeds up. The **sympathetic nervous system** causes arousal, sometimes referred to as the "fight-or-flight" response. When the sympathetic nervous system is activated, heart rate increases, digestion is suppressed, and energy stores are mobilized. The sympathetic nervous system also stimulates the release of the hormone epinephrine (adrenaline) from the adrenal medulla. The **enteric nervous system** regulates digestive processes, including peristalsis and secretion of digestive fluids.

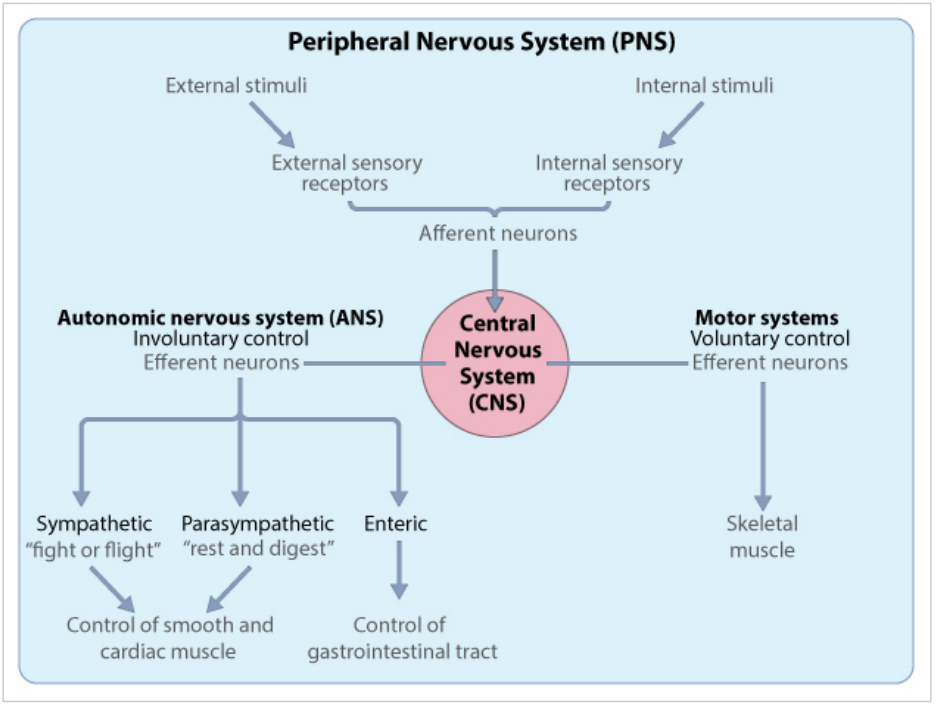


Figure 3: Components of the peripheral nervous system.
The PNS is composed of afferent neurons that provide sensory input to the CNS and efferent nerves that trigger a response in the body. Efferent neurons are placed in different divisions based on the response they trigger.
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Parasympathetic nerves originate in the brainstem and the sacral (tailbone) region of the spinal cord. Sympathetic nerves originate in the areas in

between the tailbone region and the brainstem: the thoracic and lumber regions of the spinal cord (Figure 4).

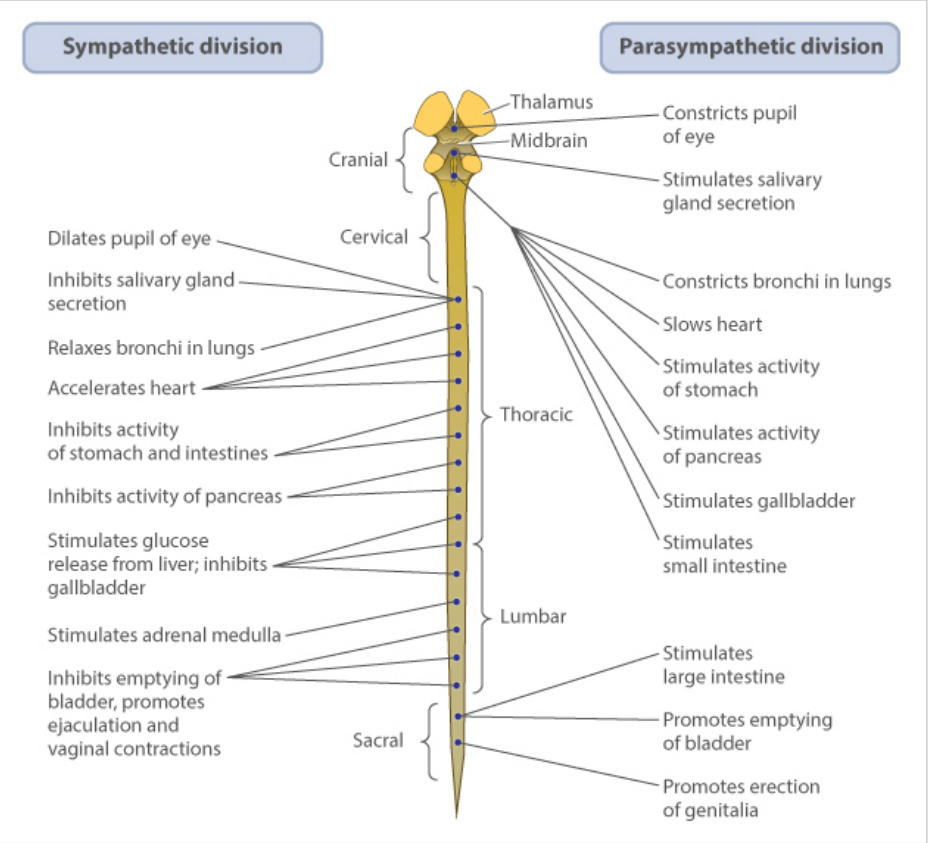


Figure 4: Parasympathetic and sympathetic divisions of the autonomic nervous system.
Efferent neurons of the parasympathetic and sympathetic divisions of the autonomic nervous system, which have antagonistic effects, originate in different parts of the brain and spinal cord, as indicated.
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Test Yourself

How does activation of the parasympathetic nervous system affect a person's pulse?

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IN THIS MODULE

- **The Two Divisions of the Vertebrate Nervous System**
- The Human Brain
- Summary
- Test Your Knowledge

WHY DOES THIS TOPIC MATTER?



Stem Cells
Stem cells are powerful tools in biology and medicine. What can scientists do with these cells and their incredible potential?

PRIMARY LITERATURE

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The Human Brain

The human brain forms from a structure called the neural tube. During embryonic development, the neural tube differentiates into three separate regions: the forebrain, midbrain, and hindbrain (Figure 5).

The structure of the human brain.

The **forebrain** develops into the cerebrum, thalamus, and hypothalamus. The **cerebrum**, which controls skeletal muscle contraction, memory, learning, and emotions, is divided into right and left **cerebral hemispheres**. The left side of the cerebral cortex controls the muscles and senses on the right side of the body, and the right side of the cerebral cortex controls those on the left side of the body. The **thalamus** is a gatekeeper that sorts the sensory signals going to the cerebrum. The **hypothalamus** maintains body temperature and physiological homeostasis and also mediates thirst and hunger. The pituitary gland, which projects from the hypothalamus, regulates various physiological processes such as growth and temperature regulation through the secretion of hormones.

The **brainstem**, which sits atop the spinal cord, includes the midbrain and parts of the hindbrain, including the medulla oblongata (or simply medulla) and the pons. All information that arrives from the spinal cord must move through the brainstem first. The pons and medulla also coordinate skeletal muscle movements and autonomic functions such as breathing, heart rate, and digestion. The hindbrain also forms the cerebellum, which facilitates motor learning and coordinates movement and balance.

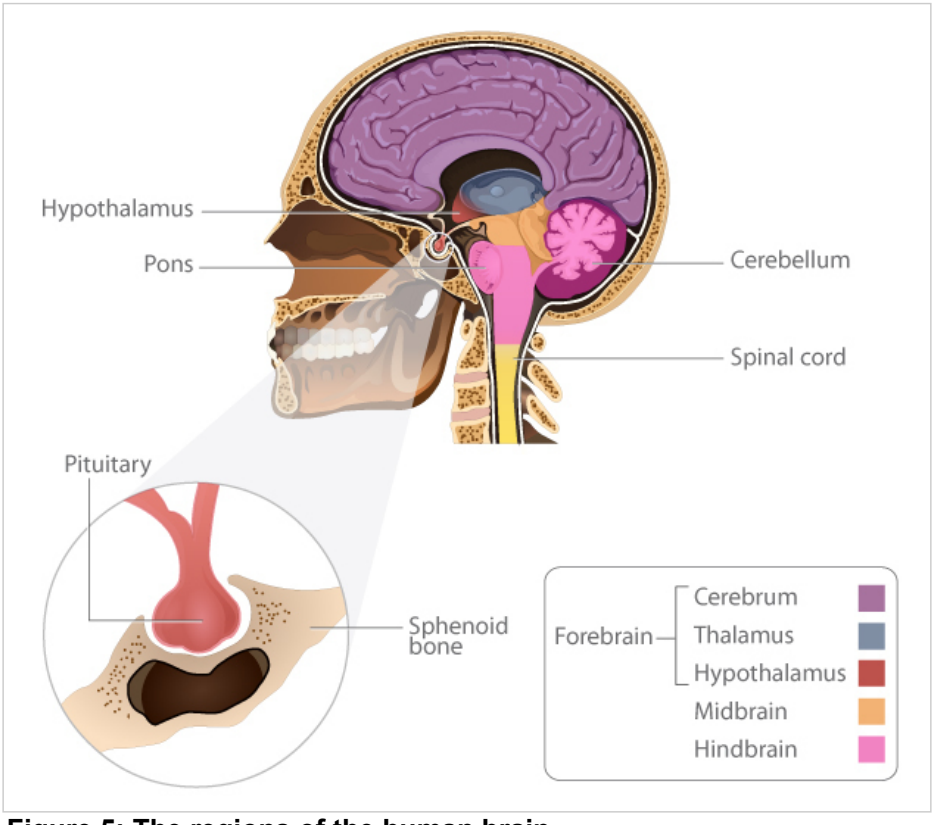


Figure 5: The regions of the human brain.
The cerebrum, thalamus, and hypothalamus, which are derived from the forebrain, form the upper and front parts of the brain. The hypothalamus includes the pituitary gland that projects into the sphenoid bone. The midbrain, which is located immediately under the thalamus, forms part of

the brainstem. The other two parts of the brainstem, the pons and the medulla oblongata, are formed from the hindbrain. The hindbrain also forms the cerebellum. Together, the pons, medulla, and cerebellum form the bottom portion of the brain.

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Test Yourself

What brain structure contains the cerebrum, thalamus, and hypothalamus?

Submit

The cerebral cortex.

The cerebrum is larger in humans than in any other vertebrate. The outermost layer of the cerebrum, which is called the cerebral cortex, engages in cognitive functioning. The cerebral cortex is separated into four lobes based on function: the frontal lobe, parietal lobe, temporal lobe, and occipital lobe (Figure 6). The **frontal lobe** contains the motor cortex, which controls skeletal muscle contraction. The frontal lobe is also involved in forming speech and in planning and decision-making, which are sometimes referred to as "executive functions." The **parietal lobe** integrates sensory information and contains the somatosensory cortex, which processes information regarding the sense of touch. The **temporal lobe** is involved in processing auditory information. The **occipital lobe** processes visual information and is involved in pattern recognition.

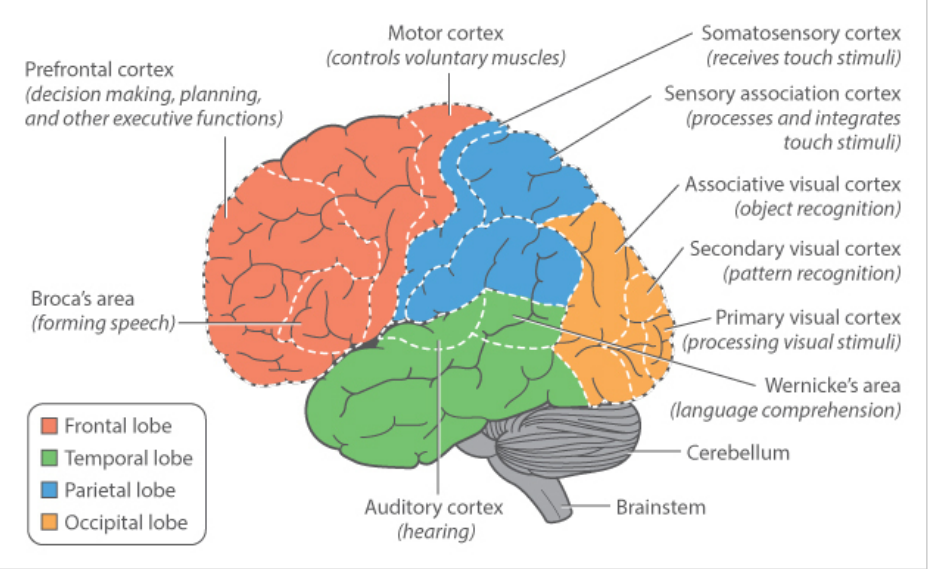


FIgure 6: The four lobes of the human cerebral cortex.
The cerebral cortex can be divided into four lobes, each with distinct functions.

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Certain brain functions involve more than one lobe. For example, the fusiform cortex, which is involved in recognition of faces, colors, and words, is formed from both the temporal and occipital lobes. A disorder that causes failure to recognize even close family members or one's own image by sight is believed to result from damage to the fusiform cortex.

The **limbic system** is a portion of the brain that surrounds the thalamus. The limbic system, which is formed from a variety of brain structures, mediates emotions, long-term memory, and behavior. It interacts with the cerebral cortex to provide emotional context to everyday occurrences. The hippocampus, thalamus, hypothalamus, and amygdala are all part of the limbic system. The amygdala is an important component of this system and

is involved in the acquisition of emotional memories as well as mediating emotional responses.

Future perspectives.

Recent research indicates that communicating emotions through facial expressions plays an important role in experiencing emotion, suggesting that the conscious mind is anchored to body movements and the immediate environment. For example, in 2009, Bernhard Haslinger and colleagues at the Munich University of Technology blocked the ability of volunteer subjects to frown by administering Botox (botulinum toxin) injections to the facial muscles. The treatment reduced activity in the amygdala, the part of the limbic system that mediates emotion. The results suggest that an angry facial expression contributes to a negative emotional state. In 2010, Arthur Glenberg of Arizona State University and graduate student David Havas of University of Wisconsin-Madison found that when Botox was used use to eliminate the ability to form facial expressions, it took longer for people to comprehend sentences with emotional content. These results suggest that formation of facial expressions may help facilitate the comprehension of emotional content.

Brain damage.

Damage to specific regions of the brain can impair specific functions. However, if the damage occurs while the brain is still developing, then healthy areas of the brain can often compensate for the damage, allowing the individual to regain normal or nearly normal function. Even adult brains have some ability to recover lost function by creating or using new circuits through a variety of processes often collectively referred to as neuroplasticity. The extent of recovery depends on age and genetic and environmental factors. One of the most common causes of brain damage is stroke. Figure 7 shows how a stroke may affect different regions of the brain.

Figure 7: Symptoms of a stroke.
The symptoms that a stroke victim displays depend on where in their brain the stroke occurred.

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Test Your Knowledge

1. What is a primary function of the frontal lobe of the cerebral cortex?

- auditory processing
- higher-order information processing
- visual information processing
- touch stimuli processing
- recognition of faces and words

2. Which of the following is the largest part of the human brain?

- cerebrum
- parietal lobe
- cerebral hemisphere
- cerebellum
- cerebral cortex

3. Which of the following statements about the parasympathetic nervous system is true?

- Nerves from the CNS that are connected to the parasympathetic nervous system originate in the middle section of the spine.
- The parasympathetic nervous system stimulates the "fight-or-flight" response.
- The parasympathetic nervous system slows the heartbeat down.
- The parasympathetic nervous system causes secretion of epinephrine (adrenaline).
- The parasympathetic nervous system slows down digestion.

4. What are the three main regions from which the vertebrate brain originates?

- the hindbrain, midbrain, and forebrain
- the brainstem, medulla oblongata, and pons
- the forebrain, hypothalamus, and thalamus
- the thalamus, cerebral cortex, and limbic system
- the midbrain, tectum, and tegmentum

5. The autonomic division of the PNS is divided into which systems?

- sympathetic, parasympathetic and enteric systems
- motor and parasympathetic systems
- motor and sympathetic systems
- the sympathetic and central nervous systems
- None of the answers are correct.

6. Which of the following is true about gray matter and white matter?

- Gray matter and white matter are part of the peripheral nervous system.
- Gray matter and white matter are both made up of myelinated axons but gray matter also has cell bodies and dendrites.
- Gray matter is composed of unmyelinated axons dendrites and cell bodies, while the white matter is made of bundles of myelinated axons.
- White matter forms an H shape in a cross-section of the spinal cord, and gray matter surrounds the white matter.
- None of the answers are correct.

7. What is the relationship between the PNS and the CNS?

- The PNS receives commands from the CNS, and the CNS receives information about the external environment from the PNS.
- The CNS receives commands from the PNS, and the PNS receives information about the external environment.
- The spinal nerves of the PNS are physical supports for the spinal column of the CNS.
- The spinal cord and nerves of the PNS receive information from the brain of the CNS.
- None of the answers are correct.

Submit

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The discipline of phrenology was developed by German physician Franz Joseph Gall in 1796 and became popular in the nineteenth century. Phrenologists believed that the human brain was divided into at least 35 organs and that many of these organs were shared with other animals. Phrenologists also believed that a person's character depended on the relative size of each organ and that organ size could be determined by measuring the size of the skull. Phrenology was not based on scientific observations and is now considered a pseudoscience. However, modern brain research has revealed that certain regions of the brain are responsible for cognitive functions and behavior. For example, the frontal lobe of the cerebral cortex is involved in planning and decision-making. This concept that certain brain regions govern certain functions is the basis for modern cognitive neuroscience, the study of how the biological structure and function of the brain relate to mental functions and behaviors.

The Study of Cognitive Neuroscience

Due to the practical difficulties and ethical quandaries of human brain experimentation, many early discoveries in cognitive neuroscience stemmed from observations of people with debilitating injuries. One such injury occurred to Phineas Gage, a foreman of a railroad construction crew. In 1848, an explosion drove a 3 cm wide rod into Gage's skull and clear through his frontal lobe, just behind his left eye. Gage recovered with his intellect and memory intact. However, he became impatient and erratic in his behavior, and he was unable to manage normal day-to-day responsibilities. Similar personality changes were observed in patients receiving frontal lobotomies in the twentieth century. Together, these observations led scientists to conclude that the frontal lobe of the brain is involved in executive functions, which include planning and decision-making.

A French physician by the name of Pierre Broca is credited with discovering a region of the brain involved in speech recognition. In 1861, Broca performed an autopsy on a man who had normal comprehension but was unable to speak any word other than "tan." Through the autopsy, Broca found a lesion in a specific area of the left cerebral cortex. Another patient who could only say five words had a lesion in the same area. Scientists now refer to this region of the brain, which is essential for speech formation, as **Broca's area** (Figure 1). Shortly after Broca published his findings, a German physician by the name of Carl Wernicke began to study patients with deficits in understanding written and spoken language. Wernicke found that these patients had lesions in a region of the brain now called **Wernicke's area**. Wernicke's area is found adjacent to the auditory cortex in the posterior part of the temporal lobe near the boundary with the occipital lobe. These brain loci, Broca's area and Wernicke's area, were the first brain regions that could be ascribed a specific function. These loci remain central to our understanding of the neural processing of human language, and are now part of a larger and expanded language processing circuit.

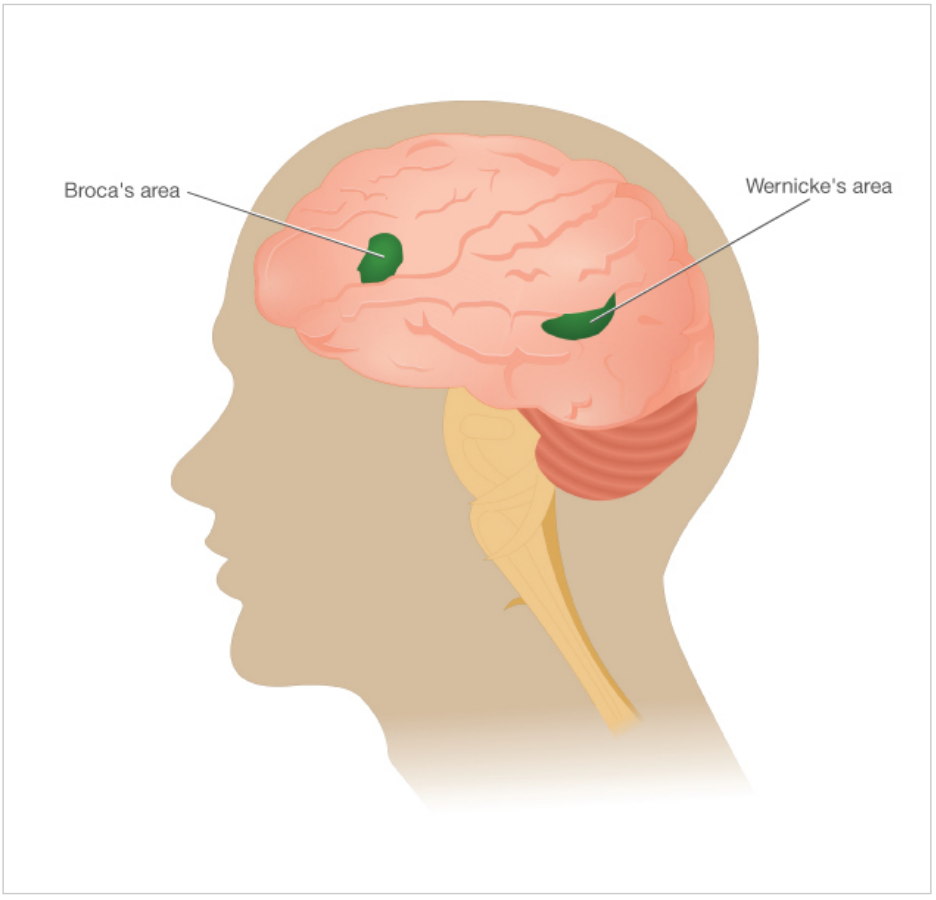


Figure 1: Broca's area and Wernicke's area.
Broca's area is involved in speech formation, and Wernicke's area is involved in speech recognition. Both areas were discovered through autopsies of patients with language deficits.
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The study of living brain tissue.

Modern techniques enable physicians and scientists to observe brain function in living patients. One of the earliest techniques used to observe brain function was electroencephalography (EEG). In EEG, scientists place electrodes on the scalp to measure electrical activity that reflects the summated electrical potential of large groups of neurons in the brain almost exclusively near the cortical surface. Using EEG, scientists have found that brain activity differs widely between subjects that are awake and subjects that are in one of the many stages of sleep. REM sleep, or rapid eye movement sleep, which is named for the eye movement that occurs during this stage of sleep, has a very distinct EEG pattern that is different from the other stages of sleep and is actually more similar to EEG patterns that are observed in an awake individual.

Today, multiple neuroimaging techniques enable scientists to produce relevant images of brain activity. One technique that is widely used to map neural activity is **functional magnetic resonance imaging (fMRI)**. fMRI is able to detect real-time changes in blood flow that are associated with brain activity. Unlike EEG, which can only detect surface electrical activity, fMRI can infer and detect regional activity throughout the brain (Figure 2). fMRI is non-invasive, does not require the administration of drugs or radiochemicals, and provides a high-resolution three-dimensional map of brain activity.

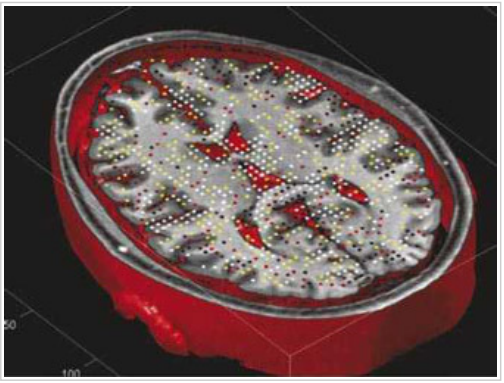


Figure 2: Real-time fMRI of the human brain.
fMRI can measure the level of activated brain tissue with relatively high resolution.
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deCharms, R. Applications of real-time fMRI. *Nature Reviews Neuroscience* 9, 720–729 (2008) doi:10.1038/nrn2414. Used with permission.

fMRI is a type of magnetic resonance imaging, or MRI, technique. MRI uses strong magnetic fields and radio waves to form images of the body. fMRI measures blood flow in different areas of the brain. Scientists measure blood flow because they have determined that it is highly correlated with neuronal activity. The method works because oxygenated blood has different magnetic properties than deoxygenated blood. Firing neurons require sugar and oxygen, and blood flow to neurons rapidly increases when they begin firing. Changes in blood flow can be translated into maps of brain activity that are often represented by different colors (figure 3).

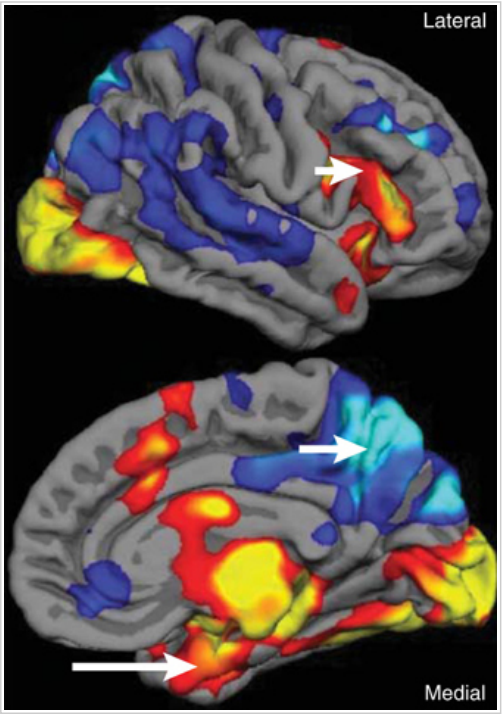


Figure 3: Three-dimensional fMRI image map of brain activity.
Colored regions indicate differential blood flow, which is associated with altered neuronal activity. Red/yellow indicates regions of increased activity while blue indicates regions of decreased activity.

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Dickerson, B. and Eichenbaum, H.
The Episodic Memory System:
Neurocircuitry and Disorders.
***Neuropsychopharmacology* 35, 86–104**
(2009) doi:10.1038/npp.2009.126.
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fMRI technology has several limitations. Because fMRI measures changes in blood flow rather than measuring brain activity (neuronal firing) directly, there can be considerable noise in the data. Also, a delay of a few seconds occurs between when the brain activity occurs and when the activity shows up in fMRI measurements.

Test Yourself

How have fMRI and other neuroimaging techniques improved our understanding of cognitive neuroscience?

Submit

Future perspectives.

In 2010, neuroscientist Adrian Owen tested a patient in a vegetative state in an fMRI machine and asked him questions. A change in blood flow in regions of the brain that were indicative of the questions being asked suggested that the man, who otherwise gave no indication of awareness, understood the questions. Based on this observation and many similar ones from other vegetative patients, scientists hope that one day fMRI may enable doctors to determine whether patients in a vegetative state still retain some level of consciousness. It is important to note that so far researchers have found that only a minority of the patients in a vegetative state that were tested retained some level of consciousness as defined by the experiments. Additionally, scientists are currently debating whether the functional output of the fMRI from these patients is an accurate indication of consciousness. Nevertheless, Dr. Owen's data are intriguing and have provided a basis for further investigation.

BIOSKILL

Case study: fMRI indicates that diet affects brain activity.

A 2012 study examined the effects of a normal versus a high-protein breakfast on brain activity in 10 teenage girls. The girls, who were overweight and typically skipped breakfast, were given either a normal-protein or a high-protein breakfast for seven days. On the seventh day, fMRI was used to measure brain activity between breakfast and lunch. The results of the fMRI indicated that neural activity in the insula and middle prefrontal cortex was higher in girls who consumed the normal-protein diet than in girls who consumed the high-protein diet (Figure 4). Previous studies have indicated that the insula and middle prefrontal cortex may play a role in hunger.

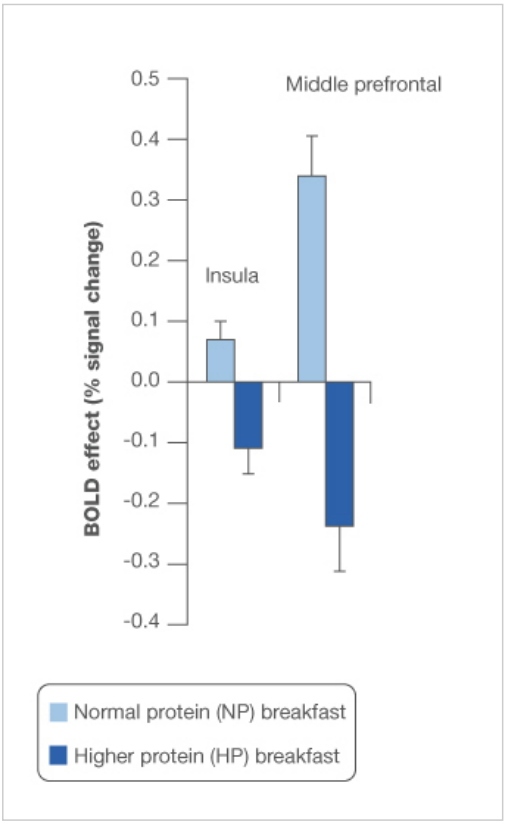


Figure 4: fMRI analysis of the effect of a high-protein breakfast on brain activity in teenage girls.
Subjects ate a normal-protein breakfast (18 ± 1 g protein) or a high-protein breakfast (50 ± 1 g) for seven days. On the seventh day, fMRI was used to measure brain activity between breakfast and lunch. The change in blood-oxygen-level-dependent (BOLD) effect is shown. The BOLD effect indicates the relative amount of blood flow.
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Test Yourself

Analyze the graph in Figure 4. Which group of girls do you think might feel hungrier, the ones who had the normal-protein breakfast or the ones who had the high-protein breakfast? Explain your answer.

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BIOSKILL

IN THIS MODULE

- The Study of Cognitive Neuroscience
- Memory and Learning
- Summary
- Test Your Knowledge

WHY DOES THIS TOPIC MATTER?



Stem Cells
Stem cells are powerful tools in biology and medicine. What can scientists do with these cells and their incredible potential?

PRIMARY LITERATURE

Classic paper: The discovery of *Australopithecus africanus* (1925)
Australopithecus africanus: The Man-Ape of South Africa.
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Phrenology
Eric Kandel explains phrenology

Memory and Learning

The total neuronal connectivity and organization of the CNS is largely established during embryonic development. However, specific changes in the connections between neurons can occur in the CNS during an organism's lifetime. These changes are referred to as neural plasticity. Neural plasticity enables an animal to acquire memories and learn.

Types of memory.

Memory is the ability to store information. **Short-term memory** is used to store new pieces of information for brief periods of time. For example, after looking up a number for a pizza delivery service, you use short-term memory to dial the number. **Long-term memory** is used to store information for a long period of time. If you order a pizza from the same restaurant every week, you may use long-term memory to store the number. Both short-term and long-term memory are stored in the cerebral cortex, albeit in different cortical areas. However, short-term memory is very limited and is easily lost if not transferred to long-term memory. The hippocampus is required for the transfer of short-term memory to long-term memory.

Synaptic plasticity refers to neural plasticity, or changes in connectivity, that occurs specifically at the synapse. **Long-term potentiation (LTP)** is a long-lasting enhancement of synaptic transmission that is associated with synaptic plasticity and can be initiated through either presynaptic or postsynaptic mechanisms. For example, LTP can occur at a synapse when certain receptors that are normally sequestered in the cell fuse with the membrane of a postsynaptic neuron. These receptors do not replace ones that are already present but work in concert with them to increase the strength of the signal. LTP can also be mediated from the presynaptic neuron through an up-regulation of neurotransmitter release. LTP is believed to be an important underlying principle required for memory.

Memory can be classified according to the type of information being stored. **Declarative memory** is used to store pieces of information that can be consciously recalled. Two types of declarative memory are semantic memory and episodic memory. Semantic memory is used to remember facts. Episodic memory is used to remember information in a particular context. Personal memories and emotions as well as knowledge of the world are stored as episodic memory. **Procedural memory**, which does not require conscious recall, is used to memorize motor skills, such as those needed to ride a bicycle or play the piano.

Various studies indicate that a region of the human brain called the amygdala plays an important role in the memory of emotional stimuli. For example, subjects who saw a particular image repeatedly and were simultaneously subjected to a mild shock developed a fearful response to the image. Their heart rate increased and they began to sweat, indicating that the parasympathetic division of the autonomic nervous system, which is responsible for the "fight-or-flight" response, was aroused. Subjects with damage to the amygdala recalled the image but did not exhibit a fearful response to it.

Types of learning.

Human neurological disorders and diseases constitute the basis for much of the current knowledge of how human brains make and recall memories. One well-known case from the 1950s involved Henry Molaison, identified as H.M.

in research records. He had severe epilepsy, and, to treat the disorder, doctors performed a bilateral lobectomy, which included a complete removal of the hippocampus. After the surgery, H.M. was no longer able to transfer information to his long-term memory. For example, if he met a person who then left the room and returned a few minutes later, H.M. would not be able to recall their previous meeting. He could recall events that occurred before the surgery, however, indicating that his long-term memory remained undamaged. These observations suggested that the hippocampus plays an essential role for moving information from short-term memory to long-term memory. In addition, H.M. had difficulty with declarative memories. **Declarative memory** keeps track of people, places, and things and is recalled only through conscious effort. In contrast, H.M. had no problem with **procedural memory**, which is a subconscious memory of how to perform a task or procedure. In fact, when learning a new motor skill, H.M. could not remember the previous lessons, yet showed daily improvement in the specific motor skill. These combined observations suggest that the hippocampus plays a role in declarative memory but is not involved in procedural memory at all.

Learning is the process by which we acquire and modify knowledge and behaviors based on past experiences. Learning in humans occurs in different ways. One type of learning, called **habituation**, occurs when an animal gets used to a stimulus and eventually fails to respond to it. For example, a dog may initially bark at a doorbell ring on a TV show, but after hearing the doorbell on TV several times, the dog becomes habituated to the sound and no longer barks. Habituation is a type of **non-associative learning**; there is less and less response to a stimulus as the stimulus is repeated over time. Habituation occurs regularly with humans. A person might look up at the sound of an airplane flying overhead; however, in the case of someone living near an airport, the sound of airplane engines fails to stimulate a response, unless the plane happens to be unusually loud or low-flying. Another type of non-associative learning is called **sensitization**, and it is characterized by a heightened response after multiple exposures to certain intense or unpleasant stimuli. For example, if a cat has been painfully poked by a child on one or more occasions, it may subsequently exhibit an excessive response to even a slight touch.

Another type of learning is called **associative learning**. In associative learning, an organism makes an association between two stimuli or between a behavior and a stimulus. The two main types of associative learning are classical conditioning and operant conditioning. In **classical conditioning**, an unconditioned stimulus (one that normally evokes a response) is consistently paired with a neutral stimulus (one that would not normally evoke a response). Russian psychologist Ivan Pavlov conducted a well-known classical conditioning study in the 1920s. In this study, Pavlov gave hungry dogs small amounts of food and simultaneously rang a bell. The dogs, which salivated at the food, were eventually conditioned to salivate at the sound of the bell, even in the absence of the food.

In **operant conditioning**, reward or punishment (the stimulus) results in a change in behavior. Psychologist B. F. Skinner used operant conditioning to change the behavior of rats. He placed rodents in special cages that had levers the animals could depress to access food. After acquiring food accidentally a few times by inadvertently moving the lever, the rodents learned to depress the bar intentionally when hungry.

One very important animal model used to study learning is the sea slug, *Aplysia californica* (Figure 5). *Aplysia* is particularly useful due to its large neurons and straightforward neural circuitry. To study how learning occurs, researchers can examine the physiology of the activated neurons together with the behavior of the animal itself. In this way, the activity of specific

neurons can be linked to specific behaviors. Many studies with *Aplysia* have looked at classical conditioning by pairing a normally harmless stimulus with something that is unpleasant, such as an electric shock. The sea slug learns to withdraw from the harmless stimulus as it begins to associate it with the unpleasant one.



Figure 5: The sea slug *Aplysia.*
The sea slug (*Aplysia californica*) has a simple nervous system and the ability to learn, making it an ideal subject for experiments on the neural basis of learning.
Martin Shields/Science Source.

This sea slug is also able to learn through operant conditioning. The esophageal nerve of *Aplysia* is stimulated when the animal eats, and scientists believe that stimulation of this nerve is associated with an internal reward mechanism. Scientists caused the animals to bite when no food was present and stimulated the esophageal nerve at the same time. For 24 hours afterward, animals that had been stimulated made significantly more bites than controls, indicating that they had learned that biting resulted in a feeling of reward.

The scientists also surgically removed a neuron associated with biting from trained (as above) and control animals and measured the neuron's threshold for activation. They found that the threshold for activation in this neuron was considerably lower in the trained animals than in the control animals. In a separate experiment, these same scientists stimulated removed neurons from untrained animals and simultaneously applied dopamine, a neurotransmitter that is involved in reward responses in both humans and animals. Over time, the threshold for activation of the neuron decreased in a manner similar to what occurred in trained animals. These results indicate that operant conditioning is associated with a change in neuron sensitivity.

Drug-addiction is a form of "learning."

Dopamine is an important neurotransmitter of the brain's reward center. It is believed that cocaine produces its psychoactive effects by blocking the cellular reuptake of dopamine after its release from presynaptic terminals, leading to an overstimulation of dopamine receptors. Many scientists believe that one of the major functions of dopamine signaling is to help the brain encode salient information. Therefore, chronic exposure to cocaine and the consistent overstimulation of certain synapses with dopamine may result in a gross misregulation of neural plasticity in the brain, and may be a key factor in promoting the addictive state and many addiction-related memories.

Alzheimer's disease is a memory disorder.

Alzheimer's disease is a neurodegenerative disease affecting up to 50% of people over the age of 85, although symptoms can present much earlier. More than half of people with dementia who display symptoms such as behavioral changes, language impairment, and cognitive decline now appear to be suffering from Alzheimer's disease. A definitive diagnosis can only be made after death, when the brain can be autopsied. Small memory lapses often mark the first sign of the disease, and these lapses can progress into problems with language and abstract thought, and more extensive memory loss. Mood swings and unprovoked emotional outbursts become common as the disease worsens. Eventually, some patients may lose nearly all motor and language function. A brain affected by Alzheimer's disease exhibits a buildup of abnormal protein deposits that form plaques between neurons and create tangles of proteins inside the nerve cells. It is believed that the plaques interrupt communication between cells, and the tangles eventually kill the neurons. Cell loss is most common in the hippocampus and parietal lobes of patients. The brains of all patients with diagnosed Alzheimer's disease have plaques and tangles; however, through the use of MRI techniques, research has shown that those formations can sometimes be found in the brains of people that do not exhibit dementia, indicating that our understanding of the causes of Alzheimer's is still far from complete.

Who is most likely to develop Alzheimer's disease in his or her lifetime? Researchers have discovered a genetic component to the disease, but that component only accounts for a very small fraction of all cases. People who have faced diabetes, heart disease, or substantial head injuries seem to be more at risk than the general population. Presently, no known cure for Alzheimer's disease exists, but one avenue of research is to target formation of the protein plaques with drugs. Another is to stimulate the body's immune response against the plaques.

IN THIS MODULE

- The Study of Cognitive Neuroscience
- **Memory and Learning**
- Summary
- Test Your Knowledge

WHY DOES THIS TOPIC MATTER?



Stem Cells
Stem cells are powerful tools in biology and medicine. What can scientists do with these cells and their incredible potential?

PRIMARY LITERATURE

Classic paper: The discovery of *Australopithecus africanus* (1925)
Australopithecus africanus: The Man-Ape of South Africa.
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Prions go toxic and cause disease
Prion propagation and toxicity in vivo occur in two distinct mechanistic phases.
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Preplay of future place cell sequences by hippocampal cellular assemblies.
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Self-organizing optic-cup morphogenesis in three-dimensional culture.
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SCIENCE ON THE WEB

Meet Aplysia
Nobel Prize Winner Eric Kandel introduces his favorite model organism, Aplysia

Aplysia's Gill Withdrawal Reflex
See a video of the slug behavior pattern that illuminated our understanding of memory in the brain

Phrenology
Eric Kandel explains phrenology

Test Your Knowledge

1. What function of the brain does Broca's area relate to?

- motor skills
- short-term memory
- long-term memory
- hearing
- speaking

2. If a person had an injury in Wernicke's area of the brain, which of the following would he or she be unable to do?

- learn a new sport
- remember a place
- read a letter
- remember a person
- make sounds

3. Which of the following statements about fMRI is true?

- fMRI measures blood flow in the brain.
- fMRI directly measures neural activity.
- fMRI requires injection of radiochemicals.
- All the answers are correct.
- None of the answers are correct.

4. Which of the following is true about types of learning?

- Habituation is a type of associative learning.
- Classical conditioning involves reward and punishment.
- Only humans exhibit associative learning.
- Classical conditioning and operant conditioning are both types of associative learning.
- Pavlov's dog experiment demonstrates habituation.

5. A child who has been stung by a bee now runs away from all flying insects. What type of learning is this?

- sensitization
- habituation
- conditioned reflex
- operant conditioning
- None of the answers are correct.

6. What type of memory does a student most likely use when studying biology?

- short-term memory
- long-term memory
- declarative memory
- procedural memory
- None of the answers are correct.

7. A person suffered a loss of declarative memory. Which situation would this person have trouble with?

- recalling the names of relatives
- speaking
- subconscious memory
- None of the answers are correct.
- All answers are correct.

Submit

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