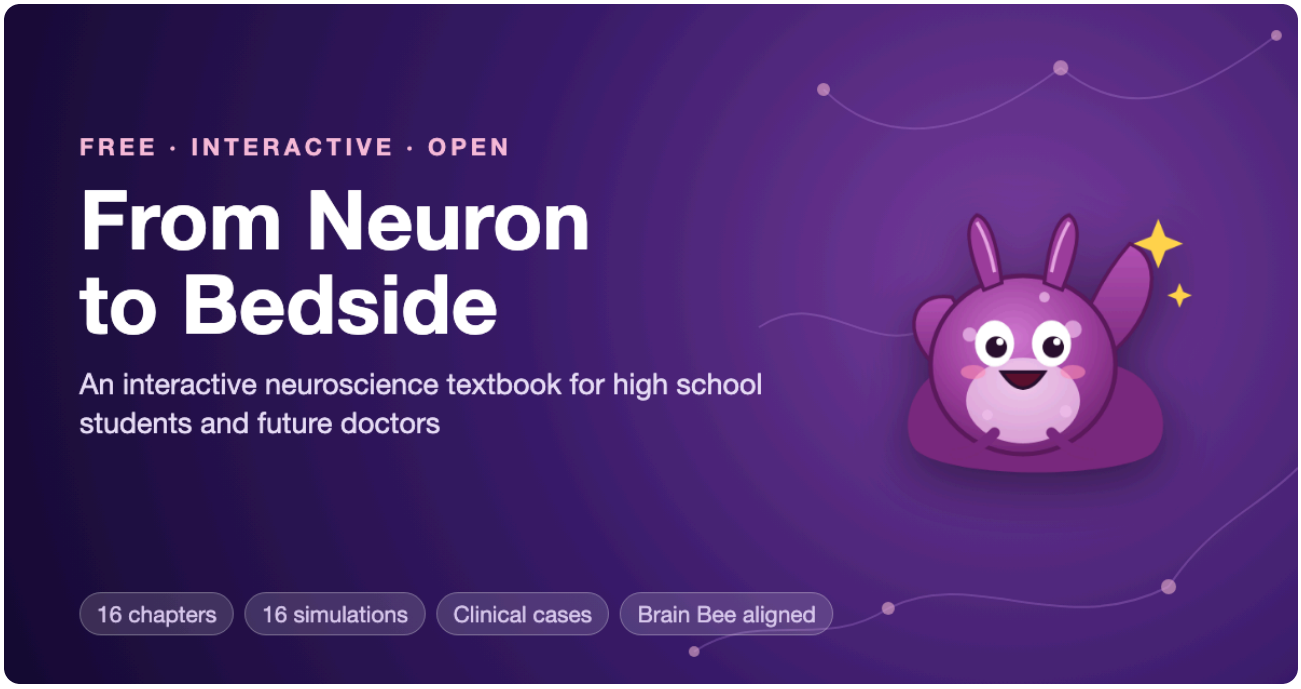


From Neuron to Bedside

An Interactive Neuroscience Textbook for High School Students and Future Doctors

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Aaryav Sharma · Version 1.1 · October 2026
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Chapter 1: Neurons, Glia, and the Nervous System

Summary

Your nervous system is built from two families of cells. **Neurons** carry messages as electrical and chemical signals, and **glial cells** keep those neurons fed, insulated, protected, and clean. This chapter tours the parts of a neuron, the three jobs neurons do, the glial cells that support them, and the blood-brain barrier that guards the brain. It ends at the bedside with multiple sclerosis, a disease in which the immune system attacks myelin, the insulation that lets signals travel fast.

Concepts Covered

1. Cell Membrane
2. Ion
3. Protein
4. Concentration Gradient
5. Nervous System
6. Central Nervous System
7. Peripheral Nervous System
8. Neuron
9. Dendrite
10. Cell Body (Soma)
11. Axon
12. Axon Terminal
13. Myelin Sheath
14. Node of Ranvier

15. Glial Cell
16. Astrocyte
17. Oligodendrocyte
18. Schwann Cell
19. Microglia
20. Sensory Neuron
21. Motor Neuron
22. Interneuron
23. Blood-Brain Barrier
24. Multiple Sclerosis

Prerequisites

- None beyond one year of high school biology.

Hi, I'm Ply!



I'm Ply, a California sea slug (*Aplysia californica*), and scientists learned how memories form by studying nerve cells just like mine. I only have about 20,000 neurons and you have billions, so I'm counting on you to put yours to good use! In this chapter you'll meet the cells that make every thought possible, and by the end you'll be able to explain why one patient's blurry vision traces back to a missing layer of fat. Every big idea starts at a single synapse!

Here's how I'll show up in every chapter:

1. **Welcome:** I tell you why the chapter matters.
2. **Thinking:** I flag a big idea worth pausing on.
3. **Tip:** I share a shortcut for remembering or checking something.
4. **Warning:** I point out a common mistake and how to avoid it.
5. **Encourage:** I cheer you through the hard parts.
6. **Celebrate:** I sum up what you just mastered.

If I'm not doing one of those six things, I'm not in the chapter.

1.1 Maya's Alarm Clock

It's 6:30 on a Tuesday morning. Maya, a 16-year-old soccer player who is studying for the Brain Bee, is fast asleep when her phone alarm starts to buzz. Before she is even fully awake, a chain of events has already begun. Tiny sensors in her ears turn the sound into electrical signals. Those signals race along nerve fibers into her brain. Her brain recognizes the sound ("ugh, the alarm"), decides what to do ("snooze it"), and sends a command down her spinal cord and out to the muscles of her arm. Her hand slaps the phone. All of this happens in well under a second, and Maya barely notices.

How can a lump of soft tissue do something so fast and so precise? The answer lives in its cells. Your brain contains about **86 billion** neurons, the cells that carry messages, plus a roughly equal number of other cells, mostly helper cells called glia (Azevedo et al., 2009). In this chapter you'll learn what these cells look like, what each part does, and what goes wrong when one small part, a fatty wrapping called myelin, is damaged.

1.2 A Quick Chemistry Refresher

Before we meet neurons, we need four ideas from basic biology and chemistry. Neurons use all four, all the time.

Think about a crowded school hallway between classes, with a classroom door. If the hallway is packed and the classroom is nearly empty, people naturally drift into the classroom when the door opens. Nobody has to push them. They spread out because there's more room on the other side. Hold on to that picture.

The cell membrane. Every cell, including a neuron, is wrapped in a **cell membrane**: a thin, flexible barrier made mostly of fat molecules (lipids). It acts like the wall of the hallway. It keeps the inside of the cell separate from the outside, and most charged particles can't slip through it on their own.

Ions. An **ion** is an atom (or small molecule) that carries an electric charge because it has gained or lost electrons. Your body fluids are full of ions. The ones neurons care most about are sodium (Na^+), potassium (K^+), chloride (Cl^-), and calcium (Ca^{2+}). Because ions are charged, moving them around moves electric charge. That is the key to how neurons make electrical signals.

Proteins. A **protein** is a large molecule built from a chain of amino acids that folds into a specific shape. The shape decides the job. Some proteins in the cell membrane act as doors (channels) that let only certain ions through. Others act as pumps that use energy to push ions across the membrane.

Concentration gradients. A **concentration gradient** is a difference in how crowded a substance is in two places, like the packed hallway next to the empty classroom. Substances tend to move "down" their gradient, from crowded to less crowded, whenever a path opens. Neurons keep a steady gradient across their membranes. There is much more sodium outside the cell than inside, and much more potassium inside than outside.

The table below pulls these four ideas together and shows why each one matters for a neuron.

Idea	Everyday picture	Why neurons need it
Cell membrane	The wall of a hallway	Keeps ions separated, so charge can build up
Ion	A charged particle	Moving ions moves charge, which creates electrical signals
Protein	Doors and pumps in the wall	Channels let specific ions through; pumps rebuild the gradients
Concentration gradient	A crowded hallway next to an empty room	Stored "push" that drives ions through open channels

Chapter 2 shows how a neuron opens and closes its ion channels to fire a signal. For now, remember the big idea: a neuron controls the flow of charged particles across its membrane, and that flow is the language of the nervous system.

1.3 The Big Picture: Your Nervous System

Imagine a city. It has a downtown headquarters where decisions are made, and a huge web of roads and cables that reach every house. Messages travel in from the houses ("there's a fire on Elm Street") and out from headquarters ("send a fire truck"). Your body works the same way.

The **nervous system** is the body's communication network. It is the set of all the cells, tissues, and organs that sense the world, process information, and control the body. It has two main divisions:

- The **central nervous system (CNS)** is the headquarters. It is made of the brain and the spinal cord. The CNS receives information, makes sense of it, and decides what to do.
- The **peripheral nervous system (PNS)** is the road network. It includes all the nerves that branch out from the brain and spinal cord to the rest of the body: your skin, muscles, eyes, ears, heart, and gut. The PNS carries information into the CNS and carries commands back out.

A **nerve** is a bundle of many axons (long fibers from neurons, which you'll meet in the next section) wrapped together like wires in a cable. There are twelve pairs of cranial nerves that connect directly to the brain, and many more spinal nerves that branch from the spinal cord.

Here is how the two divisions compare.

	Central nervous system (CNS)	**Peripheral nervous system (PNS)**
What it includes	Brain and spinal cord	Nerves outside the brain and spinal cord, and clusters of nerve cells along them
City analogy	Headquarters	Roads and cables to every house
Main job	Process information and make decisions	Carry information in and commands out
Protected by	Skull, spine, and the blood-brain barrier	Mostly by surrounding tissue
Glial cell that makes myelin	Oligodendrocyte	Schwann cell

In Maya's alarm story, the sound sensors in her ears and the nerves to her arm belong to the PNS. Recognizing the alarm and deciding to hit snooze happen in the CNS. Keep the last row of the table in mind; it matters later.

1.4 The Neuron: A Cell Built to Send Messages

Picture an uprooted tree lying on its side: spreading branches at one end, a thick base, a long trunk, and a tangle of roots at the far end. Now imagine messages flowing through it one way: in through the branches, down the trunk, and out through the roots to touch the next tree. That is a surprisingly good picture of a neuron.

A **neuron** (nerve cell) is a cell specialized to receive, process, and send information using electrical and chemical signals. Neurons come in many shapes, but most have four main parts.

1. **Dendrites** are the "branches." A **dendrite** is a short, branching extension that receives messages from other neurons and passes them toward the cell body. A single neuron can have many dendrites, which lets it listen to many other neurons at once.
2. The **cell body**, or **soma**, is the "base of the trunk." The **cell body (soma)** contains the nucleus (with the cell's DNA) and the machinery that builds most of the neuron's proteins. It also adds up all the incoming messages from the dendrites.
3. The **axon** is the "trunk." An **axon** is a single long, thin fiber that carries the neuron's own signal away from the cell body. A neuron usually has just one axon, though it may branch near its end. Axons can be extremely long. Some, such as those that run from the lower end of the spinal cord to the muscles of the foot, are about a meter long. The spot where the axon leaves the cell body is a cone-shaped region called the axon hillock. Here and at the start of the axon, the neuron "decides" whether the incoming messages add up to enough to fire.
4. **Axon terminals** are the "roots." An **axon terminal** is one of the small, swollen tips at the end of the axon's branches. This is where the neuron hands its message to the next cell, usually by releasing chemical messengers across a tiny gap. That gap, the synapse, is the star of Chapter 3.

Information in a typical neuron flows one way, in this order:

1. Dendrites receive messages from other cells.
2. The cell body adds up those messages.
3. If the total is strong enough at the axon hillock and the start of the axon, the neuron fires a signal.
4. The signal travels down the axon.
5. The axon terminals pass the message on to the next neuron, a muscle, or a gland.

Don't mix up neuron and nerve



A common trap is using "neuron" and "nerve" as if they mean the same thing. A neuron is one single cell, while a nerve is a cable made of the axons of hundreds or thousands of neurons bundled together. If you can picture one wire versus a whole power cord, you'll never mix them up again.

Where the "neuron" idea came from

It wasn't always obvious that the brain is made of separate cells. In the late 1800s, scientists argued about whether the nervous system was one giant connected web or a collection of individual cells. The Spanish scientist Santiago Ramón y Cajal stained brain tissue, studied it under the microscope, and drew detailed pictures of neurons by hand. His work showed that neurons are separate cells that communicate at contact points. He shared the 1906 Nobel Prize in Physiology or Medicine with the Italian scientist Camillo Golgi, whose staining method Cajal used and improved (Nobel Prize, 1906). Ironically, Golgi himself favored the "one giant web" idea (Wikipedia: Neuron doctrine).

Scientists also learn from animals with simpler nervous systems. The sea slug *Aplysia* (Ply's species) has relatively few neurons, and many are large and easy to identify. Eric Kandel used *Aplysia* to show how connections between neurons change during learning, work that earned him a share of the 2000 Nobel Prize in Physiology or Medicine (Nobel Prize, 2000). You'll come back to Ply's neurons in Chapter 9.

1.5 Three Jobs for Neurons

It's afternoon, and Maya is at soccer practice. A ball flies toward her, she sees it, and she traps it with her foot. Three kinds of neurons make that happen, each defined by the direction its messages travel.

- A **sensory neuron** carries information *from* the body and the outside world *toward* the CNS. Sensory neurons start at receptors that detect light, sound, touch, temperature, stretch, or chemicals. When light from the ball hits Maya's eyes, sensory neurons carry the news inward. (Sensory neurons are also called afferent neurons. "Afferent" means "carrying toward.")
- A **motor neuron** carries commands *from* the CNS *out* to muscles (and glands). Motor neurons in Maya's spinal cord send long axons down her leg to the muscles that move her foot. (Motor neurons are also called efferent neurons. "Efferent" means "carrying away.")
- An **interneuron** connects other neurons to each other inside the CNS. Interneurons sit between sensory input and motor output. They compare, combine, and route information. Much of the work of judging where the ball will land and choosing how to move happens in circuits of interneurons in Maya's brain and spinal cord.

Here is a side-by-side comparison of the three types you just met.

Neuron type	Direction of message	Where the cell body usually sits	Maya example
Sensory neuron	Body → CNS	Outside the spinal cord, in clusters along nerves, or in sense organs	Light from the ball reaches her eyes
Interneuron	Neuron → neuron, within the CNS	Brain and spinal cord	Her brain predicts where the ball will land
Motor neuron	CNS → muscle or gland	Brainstem and spinal cord (taking orders from motor areas of the brain)	Her leg muscles contract to trap the ball

A memory trick for direction



Here's a shortcut: **S**ensory starts at the **S**urface and heads in; **M**otor moves **M**uscles and heads out. Interneurons are the "in-between" cells that link the two.

1.6 Myelin and Nodes of Ranvier: Insulation for Speed

Think about your phone's charging cable. Inside is a copper wire, and around it is a plastic coating that keeps the electricity from leaking out. Now imagine sending a signal down a wire that leaks along its whole length. The signal would fade and slow down.

Axons face the same problem. An axon's membrane is a little "leaky": as a signal travels, some electric charge escapes. Many axons solve this problem with insulation.

The **myelin sheath** is a fatty, insulating layer wrapped many times around an axon. It is made of lipids and proteins, and it isn't made by the neuron itself. Glial cells (Section 1.7) wrap it around the axon, like electrical tape wound around a wire. Myelin is what makes the brain's "white matter" look white.

Myelin is not one continuous tube. It comes in segments, with tiny gaps between them. Each bare gap is called a **node of Ranvier**, named after the French scientist Louis-Antoine Ranvier, who described them in the 1800s. Nodes are packed with ion channels. This is where the speed comes from: the signal is renewed at full strength at each node, and the insulated stretches in between let it race ahead without leaking. The signal seems to jump from node to node. (Chapter 2 gives this jumping its official name and explains the ion channels behind it.)

Myelin makes a big difference in speed.

Kind of axon	Typical speed	Comparison
Thin, unmyelinated (for example, some pain and temperature fibers)	About 1 meter per second	Walking speed
Thick, myelinated (for example, many motor neurons)	More than 100 meters per second	Race car speed

These figures come from an open university textbook on sensation and perception (University of Minnesota, *Introduction to Sensation and Perception*). The fastest myelinated axons carry signals more than a hundred times faster than the slowest bare ones. That's why the axons that control Maya's leg muscles are myelinated.

Why insulation means speed



Notice the shortcut: the neuron only has to renew its signal at the nodes, not at every point along the axon. Think of it like a relay race where runners only need to stand at a few checkpoints instead of every few steps. If the insulation between two checkpoints is lost, the baton has to be carried slowly the whole way, and it might be dropped.

This hints at what happens when myelin is damaged. Charge leaks out of the bare stretch, so the signal slows and weakens. If the damaged stretch is long enough, the signal fades out before it reaches the next healthy node, and the message is never delivered. That idea is the key to the disease at the end of this chapter.

1.7 Glia: The Nervous System's Support Crew

A soccer team isn't only the players on the field. Coaches, trainers, medical staff, and groundskeepers never score a goal, but without them the team falls apart. Your nervous system has a support crew too.

A **glial cell** (or glia) is any cell of the nervous system that is not a neuron. Glia don't send fast electrical signals the way neurons do. Instead, they build myelin, support and protect neurons, clean up, and fight infection. The German scientist Rudolf Virchow described them in 1856 while looking for the brain's "connective tissue," and the name glia comes from the Greek word for "glue." For a long time, glia were treated as packing material. We now know they are active partners.

How many glia are there? You may have read that glia outnumber neurons ten to one. A careful review of 150 years of cell counting found that the real ratio in the whole human brain is about one to one or a little less, with fewer than 100 billion glia in total (von Bartheld, Bahney, and Herculano-Houzel, 2016). The ratio varies by brain region, but "ten to one" was never backed by good data.

This chapter covers four kinds of glia.

Astrocytes. An **astrocyte** is a star-shaped glial cell of the CNS. ("Astro" means star.) Astrocytes are multitaskers. They give neurons structural and metabolic support, and recycle chemical messengers around synapses so signals stay crisp (OpenStax). Their long arms end in "end-feet" that wrap around the brain's tiny blood vessels. Those end-feet come up again in Section 1.9.

Oligodendrocytes. An **oligodendrocyte** is a glial cell of the CNS that makes myelin. ("Oligo" means few and "dendro" means branch.) Each oligodendrocyte sends out several arms, and each arm wraps one segment of myelin around a nearby axon. One oligodendrocyte can myelinate segments of many different axons, by some counts up to about 40.

Schwann cells. A **Schwann cell** is a glial cell of the PNS that makes myelin. Unlike an oligodendrocyte, each Schwann cell wraps just one segment of one axon. So a long peripheral axon needs a whole row of Schwann cells along its length. Schwann cells are named after the German scientist Theodor Schwann.

Microglia. Microglia are small immune cells that live in the CNS. Microglia constantly patrol the brain, find and swallow invaders and dead or damaged cells, and help trim away

unneeded connections between neurons as the brain develops. You can think of them as the brain's security guards and cleanup crew rolled into one.

So many new words!



If the glia names feel like a vocabulary avalanche, that's normal; most people need a couple of passes. Try sorting them by just two questions: "Brain and spinal cord, or body?" and "What's its one main job?" The table below does exactly that, so use it as your cheat sheet.

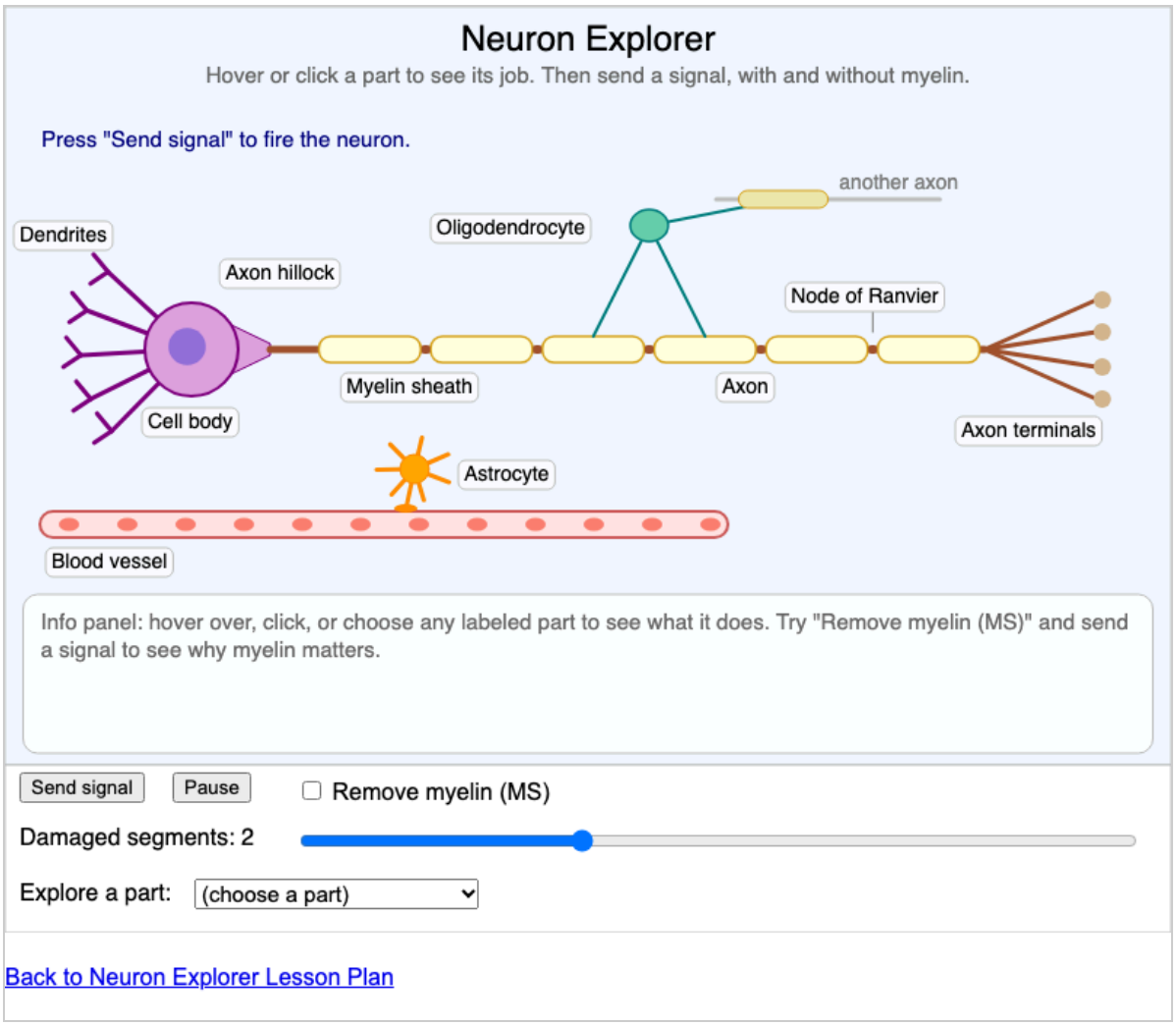
Here are the four glial cells, sorted by where they live and what they do.

Glial cell	Where it lives	Main job	Easy picture
Astrocyte	CNS	Supports and feeds neurons, cleans up around synapses, wraps blood vessels	Star-shaped caretaker
Oligodendrocyte	CNS	Makes myelin for segments of many axons	One octopus wrapping many wires
Schwann cell	PNS	Makes myelin for one segment of one axon	One roll of tape per segment
Microglia	CNS	Immune defense and cleanup	Security guard and janitor

1.8 Putting It Together: Explore a Neuron

You now know every part in the simulation below. It shows a neuron with its dendrites, cell body, axon hillock, axon, myelin sheath, nodes of Ranvier, and axon terminals. Nearby are an oligodendrocyte, whose arms wrap myelin around the axon (and around a second axon), and an astrocyte, whose end-foot touches a blood vessel.

Diagram: Neuron Explorer



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch01-neuron-explorer/

Open the Neuron Explorer fullscreen

MicroSim specification: Neuron Explorer

Type: microsim **sim-id:** ch01-neuron-explorer
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: explain
Learning Objective: The learner will explain the job of each part of a neuron and two nearby glial cells, and explain why losing myelin slows a signal or blocks it.

Parts with info-panel text (hover, click, or menu): dendrites, cell body (soma), axon hillock, axon, myelin sheath, node of Ranvier, axon terminals, oligodendrocyte, astrocyte, blood vessel (capillary).

Controls: Send signal (button); Pause/Resume (button); Remove myelin (MS) (checkbox, default off); Damaged segments (slider, min 1, max 4, step 1, default 2); Explore a part (menu).

Behavior (simplified, illustrative model): The axon has 6 myelinated segments. A signal crosses a healthy segment in 8 frames and is renewed to 100% at each healthy node. With Remove myelin (MS) checked, the chosen number of segments (starting under the oligodendrocyte) lose myelin. A bare segment takes 40 frames to cross, and the signal's strength falls by a factor of 0.55 per bare segment. If it reaches a healthy node with strength >= 25%, it is renewed to 100%; if strength drops below 25% first, the signal is blocked. Result: 1 or 2 damaged segments = arrives late; 3 or 4 damaged segments = blocked. The sim starts paused with no signal.

Chapter Anchors: 1 or 2 damaged segments slow the signal; 3 or 4 block it. Speeds and fading are illustrative, not measured.

First, hover over or click each labeled part and read its job in the info panel. Then press **Send signal** with healthy myelin and watch the signal flash at each node as it races to the axon terminals. Notice that the oligodendrocyte's arms reach two segments of this axon *and* a segment of another axon, so damage to one oligodendrocyte can affect more than one pathway.

Next, check **Remove myelin (MS)** and send the signal again with 2 damaged segments. The signal crawls through the bare stretch, weakens, and arrives late. Now slide to 3 or 4 damaged segments. This time the signal fades out before it reaches a healthy node, and the message never arrives. If this axon carried information from the eye, what would the person notice in each case?

1.9 The Blood-Brain Barrier: The Brain's Security Checkpoint

Think about airport security: travelers with tickets get through to the gates, and many other things are stopped. The brain has its own security checkpoint, built into the walls of its blood vessels.

In most of the body, the walls of the smallest blood vessels (capillaries) have small gaps, so many substances leak out of the blood into the tissue. The brain and spinal cord are different. The **blood-brain barrier** is a protective filter between the blood and the fluid around the brain's cells. It is formed mainly by the cells lining the brain's capillaries, which are sealed tightly together, with support from astrocyte end-feet wrapped around the vessels and other support cells embedded in the vessel walls (Wikipedia: Blood-brain barrier).

The blood-brain barrier does two jobs at once:

- **It lets in what the brain needs.** Oxygen and some other small molecules pass through easily. Special transport proteins carry in glucose (the brain's main fuel) and amino acids.
- **It keeps out what could cause harm.** Most germs, many large molecules, and many substances that dissolve easily in water are blocked.

This protection matters, because the brain is a very hungry organ. It makes up only about 2 to 3 percent of body weight but uses roughly 20 to 25 percent of the body's energy (OpenStax, *Introduction to Behavioral Neuroscience*; Scientific American, 2008). It needs a steady, carefully controlled supply.

The barrier has a downside for medicine: because it blocks so much, many drugs that might help brain diseases can't get in. And as you'll see next, in multiple sclerosis, immune cells that are normally kept out manage to cross into the brain and spinal cord, where they cause damage.

At the Bedside: Blurry Vision and Tingling Legs

Meet the patient

Jordan is a 28-year-old graphic designer. Over three days, the vision in her right eye has become blurry and "washed out," as if she's looking through frosted glass. It hurts a little when she moves that eye. When she mentions it to her doctor, she adds something she had brushed off: a year ago, both of her legs tingled and felt numb for about two weeks, and then the feeling went away on its own. She also says her symptoms seem worse after a hot shower.

What the doctor checks: The doctor tests Jordan's vision and finds that her right eye sees less sharply and that colors look faded in that eye. A full neurological exam checks strength, sensation, reflexes, coordination, and walking. The doctor orders an MRI scan of the brain and spinal cord, which shows several small spots of damage (lesions) in the white matter, in more than one place. Other tests that doctors may use include a lumbar puncture (a sample of the fluid around the spinal cord, to look for signs of inflammation) and evoked potential tests, which measure how quickly the nervous system responds to stimulation such as a flashing pattern (NINDS, Multiple Sclerosis).

Where is the problem? (localization): Painful, blurry vision in one eye points to the optic nerve, the cable of axons that carries signals from the eye to the brain. This is called optic neuritis (inflammation of the optic nerve). Despite its name, the optic nerve is technically a tract of the CNS, and its myelin is made by oligodendrocytes, not Schwann cells (Wikipedia: Optic nerve). The earlier tingling in *both* legs points somewhere else: the spinal cord, where sensory pathways from both legs travel close together. So Jordan has had problems in at least two parts of the CNS, at two different times, and both are made of myelinated axons wrapped by oligodendrocytes. "Different places, different times, white matter" is a classic pattern that makes doctors think of one disease.

Diagnosis: Multiple sclerosis (MS), relapsing-remitting type. **Multiple sclerosis** is a long-lasting autoimmune disease in which the immune system mistakenly attacks myelin in the central nervous system. It also damages the axons and nerve cell bodies themselves over time. "Sclerosis" refers to the scar-like patches (plaques or lesions) that form where myelin has been attacked, which are visible on MRI. Symptoms usually begin between ages 20 and 40, and women are affected more often than men (NINDS). One large study of health insurance records estimated that about 727,000 U.S. adults were living with MS in 2010, with women affected about 2.8 times as often as men. Extending their numbers forward, the same researchers estimated roughly 850,000 to 914,000 by 2017, and they warned that this extension should be read with caution (Wallin et al., 2019). A 2023 study using a similar

method found about 745,000 U.S. adults with MS (Hittle et al., 2023), but its records also date from 2008 to 2010, so these remain the most detailed national counts this book could find as of 2026. Most people with MS are first diagnosed with the relapsing-remitting form, in which attacks are followed by full or partial recovery.

Why it happens: This is the Neuron Explorer in real life. In MS, immune cells cross into the CNS and attack myelin and the oligodendrocytes that make it. Where myelin is stripped away, charge leaks out of the bare axon, and signals slow, weaken, or fail, just as in the sim. Slowed or blocked signals in the optic nerve cause blurry, washed-out vision. Blocked signals in the spinal cord's sensory pathways cause tingling and numbness. Symptoms can improve after an attack as inflammation calms down and the nervous system partly recovers. Many people with MS notice that heat temporarily makes symptoms worse (NINDS). Notice that the attack happens in the CNS, which is why the oligodendrocyte, not the Schwann cell, is the glial cell in trouble.

Treatment today: There is no cure yet, but treatment has improved a lot. For a sudden attack, doctors may give corticosteroids (strong anti-inflammatory medicines) for a few days to speed recovery, although these don't change the long-term course. To prevent future attacks and slow the disease, neurologists prescribe disease-modifying therapies, which calm or redirect the immune system. Some are pills, some are injections, and some are infusions. Physical and occupational therapy, treatment of symptoms like fatigue and stiffness, and staying active also help (NINDS). Most people with MS have a normal life expectancy.

What's new in research: One of the biggest advances has been B-cell depletion. B cells are a type of white blood cell, and drugs that remove many of them from the blood reduce MS attacks. In March 2017, the FDA approved ocrelizumab, a B-cell-depleting antibody, for relapsing MS and for primary progressive MS, making it the first approved disease-modifying therapy for the primary progressive form (Genentech, 2017). Other B-cell-depleting drugs have followed for relapsing MS, including ofatumumab (FDA approval, August 2020; Novartis, 2020) and ublituximab (FDA approval, December 2022; Pharmacy Times, 2023).

A newer kind of pill, called a BTK inhibitor (it blocks BTK, an enzyme that some immune cells use to pass signals inside the cell), crosses the blood-brain barrier and calms immune signaling inside the CNS, including in microglia. Its approval status differs by country, so dates matter. In December 2025, the FDA declined to approve tolebrutinib for secondary progressive MS without relapses (Pharmacy Times, 2025). In 2026 the European Union

approved it for that form of MS, with liver injury listed as a known risk that needs close monitoring (NeurologyLive, 2026). As of 2026, it is not approved in the United States.

Researchers are also asking what triggers MS. A 2022 study that followed more than 10 million young adults in the U.S. military found that the risk of MS rose 32-fold after infection with Epstein-Barr virus (the virus that causes mononucleosis), but not after other viruses. That makes the virus a leading suspected cause (Bjornevik et al., 2022, *Science*). Most people who catch the virus never get MS, so other factors, such as genes and vitamin D, are also involved.

Your turn: diagnose a variation

A 45-year-old man had a stomach bug two weeks ago. Now, over a few days, his feet and hands tingle and his legs have become weak, climbing up toward his arms. His reflexes are gone. An MRI of his brain and spinal cord is normal, but tests of the nerves in his arms and legs show that signals travel very slowly along them. Like MS, this is an immune attack on myelin. Which part of the nervous system is affected, and which glial cell's myelin is under attack?

Answer: The peripheral nervous system. The normal brain and spinal cord MRI and the slowed signals in the limb nerves point to the PNS, so the myelin under attack is made by Schwann cells. This pattern fits Guillain-Barré syndrome, a rare disorder in which the immune system attacks the peripheral nerves, most commonly their myelin (NINDS, Guillain-Barré Syndrome). It is a medical emergency because weakness can spread to the breathing muscles. MS and Guillain-Barré both strip myelin, but they strike opposite sides of the CNS/PNS border.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: The brain is made only of neurons.
Reality: The brain contains about as many non-neuron cells as neurons. Most of these are glia, and the rest include the cells that make up blood vessels (Azevedo et al., 2009). A brain made only of neurons would have no myelin, no immune defense, and no blood-brain barrier.

Myth: Glia are just "glue" that holds neurons in place.
Reality: The name is a leftover from the 1800s. Glia make myelin, feed neurons, clean up

chemical messengers at synapses, help form the blood-brain barrier, and fight infection. When glia fail, as oligodendrocytes do in MS, the nervous system stops working properly.

Myth: Glia outnumber neurons ten to one.
Reality: A review of 150 years of cell counting found that the ratio of glia to neurons in the whole human brain is about one to one or a little less, and the "ten to one" claim was never supported by solid data (von Bartheld et al., 2016).

Myth: We only use 10 percent of our brain.
Reality: Brain imaging shows that over the course of a day, most regions of the brain are active, and some stay active even during sleep. The brain is only about 3 percent of body weight but uses about 20 percent of the body's energy, and an organ that expensive would not be mostly idle (Scientific American, 2008).

Brain Bee Practice

1. Name the four main parts of a typical neuron, in the order a message travels through them.

Dendrites, cell body (soma), axon, and axon terminals. Messages come in through the dendrites, are added up in the cell body, travel down the axon, and leave through the axon terminals.

2. Which glial cell makes myelin in the central nervous system, and which makes it in the peripheral nervous system?

Oligodendrocytes make myelin in the CNS, and one oligodendrocyte can myelinate segments of many axons. Schwann cells make myelin in the PNS, and each Schwann cell wraps one segment of one axon.

3. What are nodes of Ranvier, and why do they matter?

They are the small, bare gaps between segments of myelin along an axon. They are packed with ion channels, so the signal is renewed at each node, which lets it seem to jump from node to node and travel much faster than along an unmyelinated axon.

4. A patient has optic neuritis now and had numbness in both legs a year ago. MRI shows white matter lesions in the brain and spinal cord. What disease is most likely, and what is being attacked?

Multiple sclerosis. The immune system is attacking myelin (and the oligodendrocytes that make it) in the central nervous system, causing lesions in different places at different times.

5. What is the blood-brain barrier, and which glial cell helps support it?

It is a protective filter formed mainly by tightly sealed cells lining the brain's capillaries, which lets in needed substances like glucose and oxygen but blocks most germs and many other molecules. Astrocytes support it by wrapping their end-feet around these blood vessels.

Exercises

Remember

1. Define *cell membrane*, *ion*, and *concentration gradient* in your own words.
2. List the four kinds of glial cells from this chapter and state where each one lives (CNS or PNS).

Answer

1. The cell membrane is the thin, fatty barrier that wraps a cell and separates inside from outside. An ion is an atom or small molecule with an electric charge. A concentration gradient is a difference in how crowded a substance is in two places; substances tend to move from crowded to less crowded.
2. Astrocytes (CNS), oligodendrocytes (CNS), microglia (CNS), and Schwann cells (PNS).

Understand

1. Explain the difference between the central nervous system and the peripheral nervous system, using the "city" analogy from Section 1.3.
2. Explain why a myelinated axon carries signals faster than an unmyelinated axon of similar size.

Answer

1. The CNS (brain and spinal cord) is like a city's headquarters, where information is processed and decisions are made. The PNS (nerves throughout the body) is like the road and cable network that carries messages in from the houses and commands back out.
2. Myelin insulates the axon so that electric charge does not leak out along the way. The signal only has to be renewed at the nodes of Ranvier, so it seems to jump from node to node instead of being rebuilt at every point along the axon.

Apply

1. Maya touches a hot pan and pulls her hand away. For each step, name the type of neuron involved (sensory, interneuron, or motor): (a) heat detected in the skin of her fingertip; (b) signal relayed inside her spinal cord; (c) her arm muscles contract.
2. A new medicine works well on brain cells in a lab dish but has no effect when given to patients as a pill. Using what you know about the blood-brain barrier, suggest one reason why, and one property the medicine would need to work better.

Analyze

1. In the Neuron Explorer, removing myelin from 2 segments slows the signal, but removing it from 3 segments blocks it. Analyze why the length of a damaged stretch matters, using the ideas of leaking charge and renewal at nodes.
2. A patient has muscle weakness. Compare how you would expect the problem to look if it came from damaged motor neurons in the spinal cord versus damaged Schwann cells along the nerves to the legs. What test results might help tell them apart?

Evaluate

1. A website claims that "glia are just filler cells, so brain health is all about neurons." Evaluate this claim using at least three pieces of evidence from this chapter.
2. Which do you think is the most important job of glia: making myelin, supporting the blood-brain barrier, or immune defense? Defend your choice using an example of what goes wrong when that job fails.

Create

1. Design a one-page infographic for middle school students explaining what myelin is and why MS affects signals. Use an analogy other than this chapter's phone cable.
2. Write a short fictional case (5 to 7 sentences) of a patient whose symptoms come from a problem in the PNS rather than the CNS. Include the symptoms, one exam finding, and the clue that lets a doctor localize the problem to the PNS.

Key Takeaways

- The nervous system has two divisions: the **central nervous system** (brain and spinal cord) processes information, and the **peripheral nervous system** (nerves throughout the body) carries information in and commands out.
- Neurons send messages by controlling the flow of **ions** across their **cell membrane**, using membrane **proteins** and **concentration gradients**.
- A typical neuron receives messages through **dendrites**, adds them up in the **cell body (soma)**, sends its signal down the **axon**, and passes it on at the **axon terminals**.
- **Sensory neurons** carry information toward the CNS, **motor neurons** carry commands out to muscles, and **interneurons** connect neurons within the CNS.
- The **myelin sheath** insulates axons, and the signal is renewed at **nodes of Ranvier**, so myelinated axons can carry signals more than a hundred times faster than thin unmyelinated ones.
- **Glial cells** are roughly as numerous as neurons (about one to one, or a little fewer): **astrocytes** support neurons and the **blood-brain barrier**, **oligodendrocytes** (CNS) and **Schwann cells** (PNS) make myelin, and **microglia** defend and clean the brain.
- In **multiple sclerosis**, the immune system attacks CNS myelin, so signals slow or fail, causing symptoms such as blurry vision and tingling that depend on where the damage is.

You've met the whole crew!



You can now name every part of a neuron, sort the glial cells by job and location, and explain why a patch of missing myelin can blur someone's vision. Next, in Chapter 2, we'll zoom in on the axon and watch ions rush through their channels to create the electrical spike every neuron uses to talk!

Chapter 2: The Action Potential

Summary

Neurons send messages as brief electrical pulses called action potentials. The chapter starts with the tiny voltage that every resting neuron keeps across its membrane, then shows how sodium and potassium channels open and close in a set order to make a spike that is always the same size. You will see why a neuron needs a short rest after each spike, how the strength of a stimulus is coded as a firing rate, and why myelin makes signals travel faster. The chapter ends at the dentist's chair, where a local anesthetic called lidocaine blocks sodium channels, switches off pain, and leaves a numb lip.

Concepts Covered

1. Membrane Potential
2. Resting Potential
3. Sodium-Potassium Pump
4. Ion Channel
5. Voltage-Gated Channel
6. Depolarization
7. Repolarization
8. Hyperpolarization
9. Threshold
10. Action Potential
11. All-or-None Principle
12. Refractory Period
13. Saltatory Conduction
14. Conduction Velocity

15. Firing Rate Coding
16. Local Anesthetic
17. Neurotoxin

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System (cell membrane, ions, concentration gradients, axons, myelin, and nodes of Ranvier)

Let's get charged up



Every thought you have, every step Maya takes on the soccer field, and every twitch of my little slug body rides on the same electrical pulse. In this chapter you'll learn how a neuron makes that pulse from nothing but salt, water, and a few clever proteins. Once you get this, a lot of medicine starts to make sense, from numbing shots to nerve poisons.

2.1 The Hot Pan Problem

It's Tuesday night, and Maya is making pasta after soccer practice. Without thinking, she grabs the pot's hot metal handle. Before she knows what happened, her hand has jerked back. A split second later comes a sharp sting, and then, a little after that, a slow, burning ache that lasts for minutes.

That moment holds three puzzles. How did her hand move before she "decided" to move it? Why did the pain come in two waves? And how does a signal travel from her fingertips so quickly at all?

The first puzzle has a short answer. Pulling away from heat is a **withdrawal reflex**: skin sensors send a signal into the spinal cord, where interneurons quickly relay it to motor neurons that contract the arm muscles. Because this loop runs through the spinal cord, the arm can start moving without waiting for the brain to decide. (You will study reflexes in detail in Chapter 7.)

The second puzzle is about speed. Pain-sensing nerve fibers come in more than one type. Thin fibers wrapped in myelin, called A-delta fibers, carry signals at roughly 15 meters per second and produce the first, sharp, pricking pain. Even thinner fibers with no myelin, called C fibers, carry signals at roughly 1 meter per second and produce the slower, burning pain (Hu et al., 2014). The burning arrives later because its signal is traveling on a slower road.

The third puzzle, how the signal travels at all, is the subject of this chapter. The answer is a brief electrical pulse called the action potential. Once you understand it, you can explain Maya's two pains, a dentist's numbing shot, and why a pufferfish toxin can stop a person from breathing.

2.2 Intuition First: A Charged Battery and a Burning Fuse

A neuron at rest is like a charged battery. A battery stores energy because it keeps electric charges separated. A neuron does the same thing. Its outer skin, the cell membrane, keeps different amounts of salt particles on each side. Little protein pumps work all day to keep those salts in place, and that separation stores energy, ready to be used.

Firing is like flushing a toilet. If you press the handle gently, nothing happens. Press a little harder and, once you pass a certain point, the whole flush happens, and it is always the same flush. Pressing harder does not make a bigger flush. Afterward, you have to wait for the tank to refill before you can flush again. A neuron's signal works the same way: it either fires completely or not at all, and it needs a short recovery time afterward.

The signal travels like a burning fuse. When you light one end of a fuse, each burning spot lights the next one, so the flame moves along by itself. An action potential moves down an axon the same way: each patch of membrane that fires triggers the next patch.

Battery, flush, fuse



If you ever get lost in this chapter, ask yourself which picture you're in. Resting potential is the battery, the spike is the flush, and conduction down the axon is the fuse.

2.3 The Membrane Potential: A Tiny Battery

Recall from Chapter 1 that **ions** are atoms with an electric charge, and that the **cell membrane** is a thin, oily wall that ions cannot easily cross on their own. Inside and outside a neuron, the most important ions are sodium (Na^+) and potassium (K^+), which each carry one positive charge.

The **membrane potential** is the difference in electrical charge, measured as voltage, between the inside of a cell and the outside. Scientists measure it with a very fine electrode inside the cell and another outside. Because the voltage is small, it is measured in **millivolts (mV)**, which are thousandths of a volt. A neuron's membrane potential is written as the inside compared with the outside, so a negative number means the inside is more negative.

When a neuron is not sending a signal, its membrane potential sits at a steady value called the **resting potential**. A common textbook value is about **−70 mV**. The real number varies from neuron to neuron and between species, and many neurons rest somewhere between about −60 and −80 mV. That is the "charged battery" from Section 2.2.

Where the charge comes from

The resting potential exists because the two main ions are unevenly spread across the membrane. The table below summarizes the typical concentrations, in millimolar (mM), a unit of how crowded the ions are.

Ion	Outside the neuron (mM)	Inside the neuron (mM)	Where is it crowded?
Sodium (Na^+)	about 145	about 12	Outside, about 12 times more
Potassium (K^+)	about 4	about 155	Inside, almost 40 times more

Two things work together to turn this unevenness into a voltage.

First, a resting neuron's membrane has many open "leak" pores that let potassium through, and far fewer that let sodium through. Potassium ions are crowded inside, so some of them drift out through the leaks, following their **concentration gradient** (the tendency of particles to spread from where they are crowded to where they are not). Each K^+ ion that leaves takes

a positive charge with it. Large negatively charged molecules, such as proteins, can't follow it out, so the inside becomes negative.

Second, that growing negative charge pulls positive potassium ions back in. The resting potential is roughly where this electrical pull nearly balances the concentration push. Because a small amount of sodium also leaks in, the resting potential ends up a little less negative than it would be if only potassium mattered.

The pump that keeps the battery charged

If ions keep leaking, why doesn't the battery run down? The answer is the **sodium-potassium pump**, a protein in the membrane that uses energy from ATP (the cell's energy molecule) to move ions against their gradients. For each ATP it uses, the pump pushes **three sodium ions out** and brings **two potassium ions in**. This keeps sodium crowded outside and potassium crowded inside.

That pumping is expensive: the OpenStax *Introduction to Behavioral Neuroscience* text cites an estimate that ion pumps use about 28% of the brain's energy budget.

Optional enrichment: the Nernst equation

Each ion has a voltage at which its electrical pull exactly balances its concentration push. This is called its **equilibrium potential**. For an ion with a single positive charge at body temperature (37 °C), the Nernst equation gives it as:

$$E_{ion} = 61.5 \text{ mV} \times \log_{10}\left(\frac{[\text{ion}]_{outside}}{[\text{ion}]_{inside}}\right)$$

The 61.5 mV comes from physical constants (the gas constant, body temperature in kelvins, and Faraday's constant). Try potassium, using the values from the table above (4 mM outside, 155 mM inside):

$$E_K = 61.5 \times \log_{10}\left(\frac{4}{155}\right) = 61.5 \times (-1.59) \approx -98 \text{ mV}$$

The real resting potential (about −70 mV) is less negative than E_K because the membrane also leaks a little sodium, whose equilibrium potential is strongly positive. Notice what happens if the potassium outside the cell rises from 4 to 8 mM: E_K moves to about −79 mV, so the resting potential also becomes less negative. You can test this idea in the MicroSim later in the chapter.

2.4 Ion Channels: Doors in the Wall

An **ion channel** is a protein that forms a tiny tunnel through the cell membrane, letting particular ions pass. Many channels are picky. A potassium channel lets potassium through but mostly blocks sodium, and a sodium channel does the reverse. Ions flow through an open channel "downhill," from where they are crowded to where they are not, without using ATP.

Some channels, like the potassium leak channels in Section 2.3, are open most of the time. Others are **gated**, meaning they open and close in response to a signal. The most important gated channels in this chapter are **voltage-gated channels**: channels that open or close when the membrane potential changes. Think of them as doors with a motion sensor that responds to voltage instead of movement.

Two kinds of voltage-gated channels make the action potential.

- **Voltage-gated sodium channels** open quickly when the inside of the cell becomes less negative. They also have a second gate, called the **inactivation gate**, that swings shut very soon after the channel opens and stays shut until the membrane returns close to rest. So these channels have three states: closed and ready, open, and inactivated (shut and not ready).
- **Voltage-gated potassium channels** also open when the inside becomes less negative, but they open more slowly and stay open a bit longer.

This table compares the four membrane proteins we have met so far.

Protein	Opens when...	What moves	Job in signaling
Potassium leak channel	Mostly always open	K^+ out	Sets the negative resting potential
Voltage-gated Na^+ channel	Membrane becomes less negative (fast)	Na^+ rushes in	Drives the rising phase of the spike
Voltage-gated K^+ channel	Membrane becomes less negative (slow)	K^+ flows out	Brings the voltage back down
Sodium-potassium pump	Always running, uses ATP	3 Na^+ out, 2 K^+ in	Keeps the gradients charged over time

How we learned this: a squid's giant axon

Much of what you just read was worked out by Alan Hodgkin and Andrew Huxley, in a famous series of experiments published in 1952. They used the **squid giant axon**, a nerve fiber that can be up to about 1.5 mm wide (typically about 0.5 mm), wide enough to slide a wire electrode inside it. They also wrote a mathematical description of how sodium and potassium currents create the action potential. Hodgkin and Huxley shared the 1963 Nobel Prize in Physiology or Medicine with John Eccles "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition" in nerve cell membranes. Their approach became the basis for many later computer models of neurons and heart cells.

2.5 Anatomy of a Spike

An **action potential** is a brief, rapid reversal of the membrane potential, where the inside of the neuron swings from negative to positive and back again in about one to two milliseconds. It is the "flush" from Section 2.2. Neuroscientists often call it a **spike** because of its sharp shape on a graph.

First, three words for the direction the voltage moves. All three compare the membrane potential to the resting potential.

- **Depolarization** means the inside becomes *less negative* (moving up toward zero or above). "Polarized" means charges are separated; *de*polarizing means reducing that separation.
- **Repolarization** means the voltage is moving back down toward the resting potential after a depolarization.
- **Hyperpolarization** means the inside becomes *more negative* than the resting potential.

Up is 'de,' down past rest is 'hyper'



Students often mix these up because depolarization makes the number go up. Remember that "polarized" means the battery is charged, so depolarizing is like draining it toward zero, and hyperpolarizing is like overcharging it.

The key step: threshold

Small inputs, such as signals from other neurons, nudge the membrane potential by a few millivolts, and most nudges fade away. But if the inside depolarizes enough to reach a critical voltage called the **threshold**, voltage-gated sodium channels begin to open in large numbers. A common textbook value for threshold is about **−55 mV**, roughly 15 mV above rest. (Like the resting potential, the real value differs between neuron types.)

Threshold is a tipping point because of feedback. When some sodium channels open, Na^+ rushes in, which depolarizes the membrane further, which opens more sodium channels, which lets in even more Na^+. This is a **positive feedback loop**, where a change causes more of the same change. Below threshold, the leak of potassium out of the cell wins and the

voltage drifts back to rest. Above threshold, the sodium feedback loop wins and a full spike is unstoppable.

The five phases

1. **Rest (about −70 mV).** Leak channels and the pump hold the battery steady. Voltage-gated channels are closed.
2. **Rising phase (depolarization).** A stimulus pushes the membrane to threshold. Voltage-gated Na^+ channels open and sodium floods in. In less than a millisecond, the inside shoots up past zero to a peak of roughly **+30 to +40 mV**.
3. **Peak and turnaround.** Sodium channels' inactivation gates swing shut, so sodium stops entering. At about the same time, the slower voltage-gated K^+ channels are opening in large numbers.
4. **Falling phase (repolarization).** Potassium flows out through the open K^+ channels, carrying positive charge out, and the voltage drops quickly back toward rest.
5. **Undershoot (hyperpolarization), then recovery.** The K^+ channels are slow to close, so for a few milliseconds extra potassium keeps leaving and the inside dips below rest, often to around **−80 mV** or a little lower. As the K^+ channels close, the membrane settles back to rest.

This table summarizes the phases side by side.

Phase	Approximate voltage	Na^+ channels	K^+ channels	Direction
Rest	−70 mV	Closed, ready	Closed	Steady
Rising	−55 mV up to +30 to +40 mV	Open	Starting to open	Depolarization
Falling	+35 mV down to about −70 mV	Inactivated	Open	Repolarization
Undershoot	about −80 mV	Inactivated, then resetting	Still open, slowly closing	Hyperpolarization

Phase	Approximate voltage	Na^+ channels	K^+ channels	Direction
Back to rest	−70 mV	Closed, ready	Closed	Steady

The pump doesn't make the spike



A common mistake is to say the sodium-potassium pump brings the voltage back down after a spike. It doesn't. Voltage-gated K^+ channels do the fast repolarizing; the pump works slowly in the background to keep the gradients charged over many spikes.

2.6 The All-or-None Principle

Because the sodium feedback loop takes over once threshold is reached, every action potential in a given neuron, starting from the same resting conditions, has essentially the same size and shape. This is the **all-or-none principle**: a neuron either fires a full action potential or does not fire at all. There is no such thing as half a spike. (The size can change only if conditions change. The simulator in Section 2.11 shows one example: when extra potassium outside the cell keeps some sodium channels inactivated, the spikes shrink.)

Think back to the toilet handle. A stimulus that only reaches −60 mV is a gentle press: a small bump that fades. One that reaches −55 mV gives a full spike, and one three times stronger gives the *same* spike with the same peak.

But Maya can tell a warm handle from a scorching one. If every spike is the same size, how does her nervous system say "much hotter"? The answer depends on timing, starting with the refractory period.

2.7 The Refractory Period: Time to Reset

Right after an action potential, a neuron cannot fire again immediately. This recovery window is called the **refractory period**. It has two parts.

- **Absolute refractory period.** During and just after the spike, most voltage-gated sodium channels are inactivated. Their inactivation gates are shut, and no stimulus, however strong, can open them. No second action potential is possible. This is the toilet tank that has not refilled yet.
- **Relative refractory period.** A little later, many sodium channels have reset, but the membrane is still in its undershoot, and potassium channels are still open. A second action potential is possible, but it takes a *stronger than normal* stimulus to reach threshold.

The refractory period has two big consequences.

1. **It keeps signals moving forward.** As an action potential travels down an axon, the patch of membrane just behind it is refractory, so the signal cannot turn around and travel backward. The fuse cannot re-light the part that has already burned.
2. **It sets a speed limit on firing.** Because each spike needs a recovery time, a neuron can only fire so many times per second. The OpenStax behavioral neuroscience text notes that without voltage-gated K^+ channels, a typical neuron would take about two to three times as long to return to rest after a spike, which would greatly limit how often it could fire.

This is the trickiest part



If refractory periods feel slippery, that's normal. Just link each one to a channel: absolute means "sodium channels are inactivated," and relative means "sodium channels are back, but potassium is still pulling the voltage down." You'll test both in the simulator soon.

2.8 Firing Rate Coding: Louder Means Faster, Not Bigger

Now we can answer Maya's hot-versus-warm question. Since every spike is the same size, a neuron reports stimulus strength mainly by **how often** it fires. This is called **firing rate coding**: a stronger stimulus produces more action potentials per second, while each individual spike stays the same size.

Suppose a sensory neuron is pushed by a steady stimulus. After each spike, the membrane drops into the undershoot and then climbs back toward threshold. A weak stimulus makes

that climb slow, so spikes are spread out. A strong stimulus makes the climb fast, so the next spike comes sooner. The refractory period sets the upper limit: no matter how strong the stimulus, the next spike can't come before the sodium channels have reset.

The illustrative numbers below come from this book's simulator model, not a measured neuron, but the pattern (stronger stimulus, more spikes, same height) is what real neurons show.

Steady stimulus (simulator units)	Spikes per second (simulator)	Peak of each spike
5	0 (never reaches threshold)	none
6	about 50	about +35 mV
8	about 80	about +35 mV
10	about 110	about +35 mV

So when Maya grabs a scorching handle, her heat- and pain-sensing neurons fire faster than they would for a warm one, and her brain reads the higher rate as "much hotter."

2.9 Traveling Down the Axon: Conduction Velocity and Myelin

An action potential's job is to *travel*, sometimes a long way. Some axons in the sciatic nerve run from the base of the spinal cord all the way to the big toe.

When one patch of axon fires, positive charge from the incoming sodium spreads a short distance inside the axon and depolarizes the next patch to threshold. That patch fires, and so on, like the burning fuse. Because each patch makes a brand-new spike, the signal arrives as large as it started.

Conduction velocity is how fast an action potential travels along an axon, usually measured in meters per second (m/s). Two features of an axon raise it.

- **Diameter.** A wider axon has less resistance to current flowing along its inside, so the charge spreads farther and faster. The squid's giant axon, for example, helps control the jet of water the squid uses to move quickly.

- **Myelin.** As you learned in Chapter 1, myelin is a fatty wrapping made by glial cells (oligodendrocytes in the brain and spinal cord, Schwann cells in the rest of the body). Myelin insulates the axon so charge does not leak out, and it leaves small gaps called **nodes of Ranvier** where voltage-gated sodium channels are packed.

Saltatory conduction

In a myelinated axon, current spreads quickly under each insulated stretch and triggers a new spike at the next node, so the signal seems to jump from node to node. This is called **saltatory conduction**, from the Latin *saltare*, "to leap." Unmyelinated axons instead use slower **continuous conduction**, regenerating the spike patch by patch.

The difference is large. According to the OpenStax behavioral neuroscience text, signals in unmyelinated axons typically travel about 0.5 to 10 m/s, while saltatory conduction can reach up to about 150 m/s. That's fast for biology, but nowhere near the speed of light (roughly 300 million m/s).

A quick calculation

This explains Maya's two pains. Imagine the path from her fingertip to her spinal cord is about 1 meter long (a round number for an adult arm and shoulder, used here only for easy math).

- Sharp pain on A-delta fibers at about 15 m/s: $\frac{1\ \text{m}}{15\ \text{m/s}} \approx 0.07\ \text{s}$, or about 70 milliseconds.
- Burning pain on C fibers at about 1 m/s: $\frac{1\ \text{m}}{1\ \text{m/s}} = 1\ \text{s}$.

The burning signal arrives roughly a whole second behind the sharp one, which matches the "sting, then burn" that Maya felt.

> **Connection to Chapter 1**
>
> In multiple sclerosis, the immune system attacks myelin in the brain and spinal cord. Without that insulation, current leaks out between nodes, so action potentials can slow down or fail to reach the next node. That is one reason MS can cause vision problems, numbness or tingling, and muscle weakness.

2.10 Blocking the Signal: Local Anesthetics and Neurotoxins

Every action potential depends on voltage-gated sodium channels, so blocking them stops the signal. Medicine uses this on purpose; nature uses it as a weapon.

Local anesthetics

A **local anesthetic** is a drug that blocks nerve signals in one area of the body, causing numbness without making the person unconscious. Lidocaine, the most familiar example, works by binding inside voltage-gated sodium channels and blocking them. If enough sodium channels in a stretch of axon are blocked, that stretch cannot reach threshold, so pain signals from the treated area never get past it to the brain.

A pharmacology review on local anesthetics in dentistry explains a few practical details (Becker and Reed, 2012):

- Local anesthetics bind more strongly to sodium channels that are open or inactivated than to resting ones, so fast-firing fibers are blocked more easily.
- Thin fibers are blocked more easily than thick ones, because fewer channels need to be blocked to stop the signal.
- Pain fibers are more sensitive than fibers for pressure and body position. A patient may still feel pressure after pain is completely blocked.
- Adding epinephrine, which narrows the small blood vessels near the injection, slows the drug's absorption into the blood and makes the numbness last longer.

Neurotoxins

A **neurotoxin** is a poison that harms or disrupts the nervous system. Many neurotoxins target the same channels as medicines do, but without any control over dose or location.

The best-known sodium-channel neurotoxin is **tetrodotoxin (TTX)**, found in some pufferfish and other animals. TTX blocks voltage-gated sodium channels, so nerves and muscles cannot fire action potentials. After a person eats contaminated or improperly prepared pufferfish, early symptoms can include numbness or tingling around the lips and mouth, followed in severe cases by weakness, paralysis, and failure of the breathing muscles. There is no specific antidote. Treatment is supportive care, such as helping the person

breathe with a ventilator until the body clears the toxin. TTX is heat-stable, so cooking the fish does not make it safe.

Both lidocaine and TTX block sodium channels. The difference is where they go: a dentist places lidocaine in one small area and it wears off in a few hours, while TTX spreads through the body and can reach the nerves that control breathing.

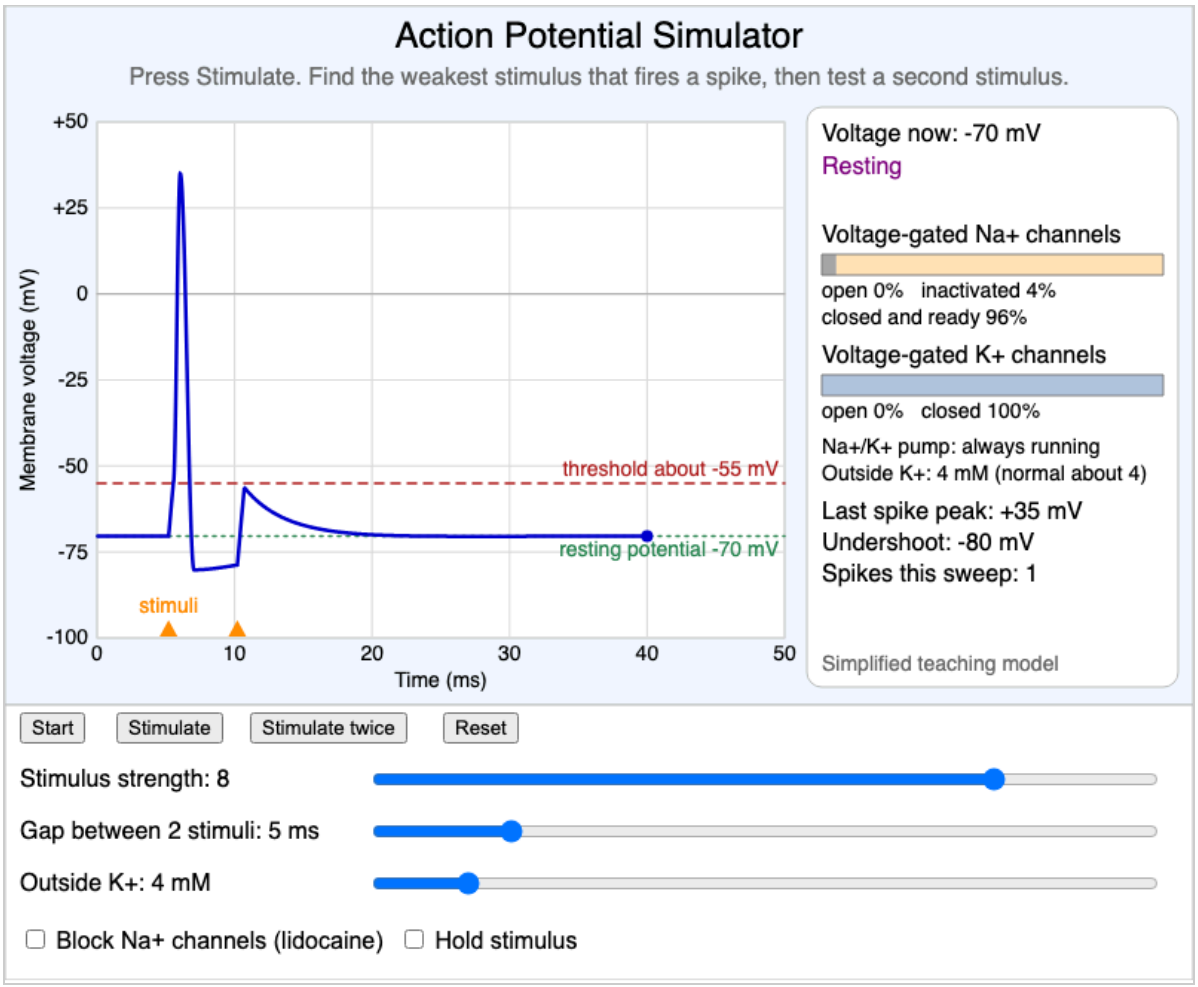
Too much potassium outside the cell

Signals can also fail if the "battery" changes. If potassium outside cells rises, less potassium leaks out, and the resting potential moves closer to threshold. At first neurons fire more easily. But if the membrane stays depolarized, more sodium channels become inactivated, and the cell gets *harder* to fire or cannot fire at all. In the body, a high blood potassium level (normally about 3.7 to 5.2 mEq/L, which is the same as mM for potassium) can become a medical emergency, mainly because it can disturb the heart's rhythm.

2.11 Try It: The Action Potential Simulator

You now have every idea the simulator uses. It plots **membrane voltage (mV)** on the vertical axis against **time (ms)** on the horizontal axis, like a doctor's or scientist's recording. A side panel shows what fraction of sodium and potassium channels are open, inactivated, closed, or blocked at each moment.

Diagram: Action Potential Simulator



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch02-action-potential/

Open the Action Potential Simulator fullscreen

MicroSim specification: Action Potential Simulator

Type: microsim **sim-id:** ch02-action-potential
Library: p5.js
Status: Implemented
Bloom Level: Apply
Bloom Verb: predict
Learning Objective: The learner will predict whether a stimulus produces an action potential, given its strength, its timing after a previous spike, the outside K^+ concentration, and whether Na^+ channels are blocked by lidocaine.

Canvas: width-responsive; drawing area plus a five-row control area (iframe height 657 px).

Controls: Start/Pause; Stimulate (one 0.5 ms pulse); Stimulate twice (two pulses separated by the gap slider); Reset; Stimulus strength 0 to 10, step 1, default 3 (each unit pushes the membrane up about 2.8 mV); Gap between 2 stimuli 2 to 20 ms, step 1, default 3; Outside K^+ 2 to 20 mM, step 1, default 4; checkbox "Block Na+ channels (lidocaine)" (blocks 85% of Na^+ channels in the model); checkbox "Hold stimulus" (a steady stimulus at the chosen strength).

Behavior: Simplified teaching model (not the full Hodgkin-Huxley equations). Rest −70 mV at 4 mM K^+ (Goldman equation). A spike fires when V >= −55 mV and enough Na^+ channels are ready; peak +35 mV, undershoot about −80 mV.

Chapter Anchors: strength 5 gives no spike, 6 fires; at strength 10 a second stimulus fails at a 2 or 3 ms gap and fires at 4 ms or more; strength 8 needs 7 ms or more, strength 6 about 18 ms; hold stimulus 6, 8, 10 gives about 50, 80, 110 spikes/s with the same peak; outside K^+ 8 mM rests near −61 mV, 10 mM near −58 mV with a peak near +17 mV, 11 mM or more gives no spikes; lidocaine gives no spike even at strength 10.

Press **Stimulate** at the default strength of 3. You'll see a small bump that fades, because the membrane never reaches the dashed threshold line. Raise the strength one step at a time to find the weakest stimulus that fires (in this model, 6), then try 8 and 10. The "Last spike peak" readout stays at +35 mV no matter how hard you push: that's all-or-none. Now check **Hold stimulus** and try 6, 8, and 10. The spikes don't grow, but they come closer together: that's firing rate coding.

Next, uncheck Hold and use **Stimulate twice**. At strength 10 with a 3 ms gap, the second stimulus fails because the sodium channels are still inactivated (the gray part of the Na^+ bar). At 4 ms both fire. At strength 6, the second stimulus needs a much longer gap, because the undershoot holds the membrane far below threshold. Then check **Block Na+ channels (lidocaine)** and stimulate at full strength: the bump may cross the threshold line,

but too few sodium channels work to start the feedback loop, so no spike appears. Finally, uncheck it and slide **Outside K^+** to 8, 10, and 12 mM to watch the resting line rise and the spikes shrink, then fail.

At the Bedside: A Numb Lip at the Dentist

Meet the patient

Maya, 16, is at the dentist to fill a cavity in a lower back tooth. The dentist gives her an injection of lidocaine near the back of her lower jaw. Soon, the left half of her lower lip, her chin on that side, and part of her tongue feel thick and "rubbery." During the filling, she feels pressure and vibration from the drill but no pain. Afterward, she asks: "Did the shot hurt my nerve? And why can I still feel pushing if I can't feel anything else?"

What the doctor checks: Before starting, the dentist confirms the numbness covers the expected area on that side: the lower teeth, lower lip, chin, and part of the tongue. Maya can still move her lips normally, which shows that the nerves controlling those muscles are working.

Where is the problem? (localization): The lower teeth, lower lip, and front part of the tongue on one side all send their sensory signals through branches of the **inferior alveolar nerve** and its neighbors, which belong to the mandibular branch of the **trigeminal nerve** (cranial nerve V). The injection places lidocaine around that nerve as it enters the jaw, blocking signals from everything downstream. Lip movement is controlled by a different cranial nerve, the facial nerve, which was not blocked, so movement is normal.

Diagnosis: Expected, temporary sensory nerve block from a local anesthetic (an inferior alveolar nerve block). This is the intended effect, not an injury.

Why it happens: Lidocaine binds inside voltage-gated sodium channels in the axons of the nerve. With enough channels blocked, the axon cannot reach threshold, so action potentials from the tooth and lip cannot travel past the injection site to the brain. Pain fibers are thin and are blocked more easily than the thicker fibers that carry pressure, which is why Maya can still feel pushing but not pain.

Treatment today: Dentists commonly use lidocaine, often combined with epinephrine to make the numbness last longer. Soft-tissue numbness after a lower-jaw block can last

several hours. The main safety advice is practical: watch for accidental lip or cheek biting, including while eating, until feeling returns. This matters most for young children. Feeling comes back on its own as the drug washes away from the nerve.

What's new in research: On January 30, 2025, the U.S. FDA approved suzetrigine (brand name Journavx), a non-opioid pill for moderate to severe acute pain in adults. It is the first drug in a new class that targets one specific sodium channel type, NaV1.8, which is important in pain-sensing neurons of the peripheral nervous system. Unlike lidocaine, it is designed to quiet pain signals while leaving most other nerves alone (FDA announcement; review in *Molecules*, PMC12843740). As of 2026, it is approved only for short-term acute pain. Phase 3 trials testing it for nerve pain caused by diabetes are still enrolling patients (ClinicalTrials.gov, NCT06628908), so that use is investigational.

Your turn: diagnose a variation

A 40-year-old man eats dried pufferfish that a friend brought from overseas. Soon afterward his lips and tongue tingle and go numb, then his arms feel weak, and he starts having trouble breathing. Which channel is affected, and why are his symptoms so much more dangerous than Maya's numb lip?

Answer: This pattern suggests tetrodotoxin poisoning. Like lidocaine, TTX blocks voltage-gated sodium channels, so action potentials fail. But instead of being injected into one small spot, the toxin is absorbed into the blood and reaches nerves and muscles throughout the body, including those that control breathing. There is no specific antidote, so emergency care focuses on supporting breathing until the toxin is cleared.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: A stronger stimulus makes a bigger action potential.
Reality: Action potentials are all-or-none. Once threshold is reached, every spike in a given neuron peaks at about the same voltage. A stronger stimulus makes the neuron fire *more often* (firing rate coding), not bigger.

Myth: Nerve signals travel at the speed of light, like electricity in a wire.
Reality: Action potentials are carried by ions moving through channels, which is much

slower. Even the fastest myelinated axons reach only about 150 m/s, and unmyelinated pain fibers can be closer to 1 m/s. Light travels about 300 million m/s.

Myth: The sodium-potassium pump is what brings the voltage back down after each spike.
Reality: Voltage-gated potassium channels do the fast repolarization. The pump restores the gradients slowly in the background.

Myth: If your lip is numb after a dental shot, the nerve has been damaged.
Reality: A local anesthetic temporarily blocks sodium channels in the nerve. As the drug washes away over a few hours, the channels work again and feeling returns.

Brain Bee Practice

1. What is the approximate resting potential of a typical neuron, and which ion's leak mainly sets it?

About −70 mV (inside negative compared with outside). It is set mainly by potassium ions leaking out through open potassium leak channels.

2. Which channels open during the rising phase of an action potential, and which open during the falling phase?

Voltage-gated sodium channels open during the rising phase, letting Na^+ rush in. Voltage-gated potassium channels open during the falling phase, letting K^+ flow out and repolarize the membrane.

3. Why can't a neuron fire a second action potential during the absolute refractory period?

Most voltage-gated sodium channels are inactivated: their inactivation gates are shut and cannot reopen until the membrane returns close to rest. No stimulus, however strong, can trigger a spike.

4. What is saltatory conduction, and why is it faster?

It is the jumping of an action potential from one node of Ranvier to the next along a myelinated axon. Myelin insulates the axon so current spreads quickly between nodes, and the spike only has to be regenerated at the nodes.

5. How do lidocaine and tetrodotoxin produce their effects?

Both block voltage-gated sodium channels, so axons cannot reach threshold and action potentials fail. Lidocaine is a local anesthetic placed in one area; tetrodotoxin is a neurotoxin that can spread through the body and paralyze breathing muscles.

Exercises

Remember

1. Define *threshold* and give its approximate value in a typical textbook neuron.
2. List, in order, the five phases of an action potential described in Section 2.5.

Answer

1. Threshold is the membrane voltage at which enough voltage-gated sodium channels open to trigger a full action potential, about −55 mV in typical textbook examples.
2. Rest, rising phase (depolarization), peak and turnaround, falling phase (repolarization), undershoot (hyperpolarization) and return to rest.

Understand

1. Explain in your own words why the inside of a resting neuron is negative.
2. Explain why the refractory period makes action potentials travel in only one direction along an axon.

Answer

1. Potassium is crowded inside and leaks out through open K^+ channels, carrying positive charge out. Large negative molecules stay behind, so the inside becomes negative. The sodium-potassium pump keeps the gradients in place.
2. The patch of membrane the spike just left is refractory, with its sodium channels inactivated, so it cannot fire again right away. The spreading current can only trigger the patch ahead, which is still ready.

Apply

1. In the simulator, set the strength to 8 and use **Stimulate twice**. Predict the shortest gap that will produce two spikes, then test your prediction. Explain the result using channel states.
2. A person's sensory neuron is firing 20 times per second in response to a warm object. If the object becomes much hotter, predict what happens to the size of each spike and to the firing rate, and explain why.

Analyze

1. Compare lidocaine and tetrodotoxin: what they have in common at the molecular level, and why one is used in a dental office while the other is a dangerous poison.
2. In the simulator, raising outside K^+ from 4 to 8 mM makes the neuron *easier* to fire, but raising it to 12 mM makes it *impossible* to fire. Break this down step by step using the resting potential and sodium channel inactivation.

Evaluate

1. A classmate claims, "Myelin makes the action potential bigger, and that's why it travels faster." Evaluate this claim. What is right, what is wrong, and what is a better explanation?
2. The simulator uses a simplified model, not the full Hodgkin-Huxley equations. Judge whether this is a reasonable choice for this textbook: what does it show well, and what might it hide?

Create

1. Invent a new analogy (not the battery, flush, or fuse) that explains both the all-or-none principle and the refractory period. Say which part matches which part of the neuron.
2. Write a one-paragraph handout for a 12-year-old after a lower-jaw numbing shot, explaining why their lip is numb, how long it may last, and how to stay safe. Base every statement on this chapter.

Key Takeaways

- A resting neuron is a charged battery: its membrane potential sits near −70 mV because potassium leaks out and the sodium-potassium pump (3 Na^+ out, 2 K^+ in per ATP) keeps the gradients charged.
- Voltage-gated sodium and potassium channels open in sequence to make the action potential: Na^+ rushes in (depolarization to about +30 to +40 mV), then K^+ flows out (repolarization), with a brief undershoot (hyperpolarization).
- Threshold (about −55 mV in textbook examples) is a tipping point created by positive feedback, which is why action potentials are all-or-none.
- The refractory period, caused by sodium channel inactivation and the undershoot, keeps signals moving forward and limits how fast a neuron can fire.
- Neurons code stimulus strength mainly as firing rate, not spike size.
- Myelin and wider axons raise conduction velocity; saltatory conduction lets signals leap between nodes of Ranvier at up to about 150 m/s.
- Local anesthetics such as lidocaine and neurotoxins such as tetrodotoxin both block voltage-gated sodium channels, which shows how one molecular target can be a medicine or a poison.

You've mastered the spike!



You can now explain how a neuron fires, why it resets, and how a dentist turns pain off. But when a spike reaches the end of an axon, it hits a gap. In Chapter 3, we'll find out how neurons pass the message across that gap at the synapse, which is where my own claim to fame begins!

Chapter 3: Synapses and Neurotransmitters

Summary

Neurons do not touch each other. Between them is a tiny gap, and most signals cross it as chemicals called neurotransmitters. This chapter follows a signal from the moment an action potential reaches the end of an axon to the moment the next cell "decides" whether to fire. Along the way you will meet the major neurotransmitters, learn how drugs such as caffeine, nicotine, and antidepressants act at synapses, and see what happens when the immune system attacks the synapse between nerve and muscle in myasthenia gravis.

Concepts Covered

1. Synapse
2. Chemical Synapse
3. Electrical Synapse
4. Synaptic Vesicle
5. Neurotransmitter
6. Receptor
7. Ionotropic Receptor
8. Metabotropic Receptor
9. Excitatory Postsynaptic Pot.
10. Inhibitory Postsynaptic Pot.
11. Synaptic Integration
12. Reuptake
13. Glutamate
14. GABA
15. Acetylcholine

16. Dopamine
17. Serotonin
18. Norepinephrine
19. Neuromuscular Junction
20. Agonist and Antagonist
21. Myasthenia Gravis

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System (axon terminals, dendrites, glia, motor neurons)
- Chapter 2: The Action Potential (resting potential, threshold, ion channels, depolarization and hyperpolarization)

Welcome to the gap!



I'm a sea slug, and synapses are kind of my thing. Scientists studied my species to learn how synapses change when an animal learns. In this chapter you'll see where many brain drugs, several diseases, and even your morning coffee do their work: in the gap between two cells.

3.1 Maya's Morning Coffee

It's 7:15 a.m., and Maya has a chemistry test second period. She stayed up late studying for the Brain Bee, and her eyelids feel heavy. Her dad hands her a small coffee. Twenty minutes later she feels sharper. Nothing about her neurons' wiring changed in those twenty minutes. So how did a drink change how her brain works?

The answer is at the synapses. While Maya is awake, a molecule called adenosine slowly builds up in her brain and attaches to special proteins on her neurons. When adenosine attaches, it pushes those neurons toward sleepiness. Caffeine has a shape close enough to adenosine that it fits into the same proteins, but it does not switch them on. It just sits

there, taking up the spot, so adenosine can't deliver its "time to rest" message. Caffeine doesn't add energy. It blocks a signal that would have made Maya feel tired.

That one example holds the whole chapter in miniature. Neurons talk with chemicals. Those chemicals work by fitting into proteins on the next cell. And any outside molecule that fits those proteins, whether it's a drug, a toxin, or an antibody made by a confused immune system, can change the conversation.

3.2 The Gap Between Neurons

An everyday picture first

Picture a relay race where the runners are not allowed to touch. The first runner can't hand over the baton. Instead, she has to throw a bunch of small tennis balls across a narrow gap, and the next runner only starts if she catches enough of them. That sounds clumsy, but it has big advantages. The thrower can throw more or fewer balls. The catcher can hold out more or fewer hands. And a third person standing nearby could block the throw, swap in fake balls, or sweep the balls away. All of those are ways to control the race.

That is roughly how most neurons communicate.

Naming the parts

A **synapse** is a junction where a neuron passes a signal to another cell. The other cell might be a neuron, a muscle fiber, or a gland cell. The cell sending the signal is the **presynaptic** cell ("before the synapse"). The cell receiving it is the **postsynaptic** cell ("after the synapse"). In Chapter 1 you met the axon terminal, the swollen tip at the end of an axon. Most synapses form where an axon terminal sits next to a dendrite or cell body of the next neuron.

The word "synapse" is older than most people guess. The British physiologist Charles Sherrington introduced it in 1897, when scientists were still arguing about whether neurons were separate cells at all.

Two kinds of synapses

There are two ways to cross the gap.

A **chemical synapse** uses molecules as messengers. The presynaptic terminal releases a chemical into a narrow space called the **synaptic cleft**, which is only about 20 to 40 nanometers wide (a nanometer is a billionth of a meter). The chemical drifts across and is detected by the postsynaptic cell. Most synapses in the human brain are chemical.

An **electrical synapse** is a direct connection. At special contact points called **gap junctions**, the two cells come within about 3.5 nanometers of each other, and tiny protein tunnels link the inside of one cell to the inside of the other. Ions flow straight through, so the electrical change in one cell spreads almost instantly to the next. Electrical synapses are faster, and signals can usually flow in both directions. They are useful wherever many cells need to fire in sync or a response must be as fast as possible.

The table below sums up what we just compared.

Feature	Chemical synapse	Electrical synapse
What crosses	Neurotransmitter molecules	Ions, through gap junction tunnels
Gap between cells	About 20 to 40 nm (the synaptic cleft)	About 3.5 nm
Speed	Short delay while chemicals are released and detected	Nearly instant
Direction	One way: presynaptic to postsynaptic	Usually both ways
Can the signal be made bigger, smaller, or flipped?	Yes, in many ways	Much less so
How common in the human brain	The large majority	An important minority

If chemical synapses are slower, why does the brain use them so much? Look at the last two rows. A chemical synapse is adjustable. It can turn a signal up or down, switch excitation into inhibition, and change its strength with experience. That flexibility is what

makes learning possible, and it is also why drugs and diseases act at chemical synapses so often. The rest of this chapter is about chemical synapses.

How we learned the gap was chemical

For a long time, many scientists thought nerves must signal by electricity alone. The German pharmacologist Otto Loewi settled the question with a famous experiment in 1921, using two frog hearts. He stimulated the vagus nerve of the first heart, which slowed its beating. Then he took the fluid that had bathed that heart and put it on a second heart whose nerve had not been touched. The second heart slowed down too. Some chemical released by the nerve had carried the message. Loewi called it *Vagusstoff* ("vagus substance"). It was later shown to be **acetylcholine**, which you'll meet again soon. Loewi shared the 1936 Nobel Prize in Physiology or Medicine with Henry Dale for discoveries about the chemical transmission of nerve impulses.

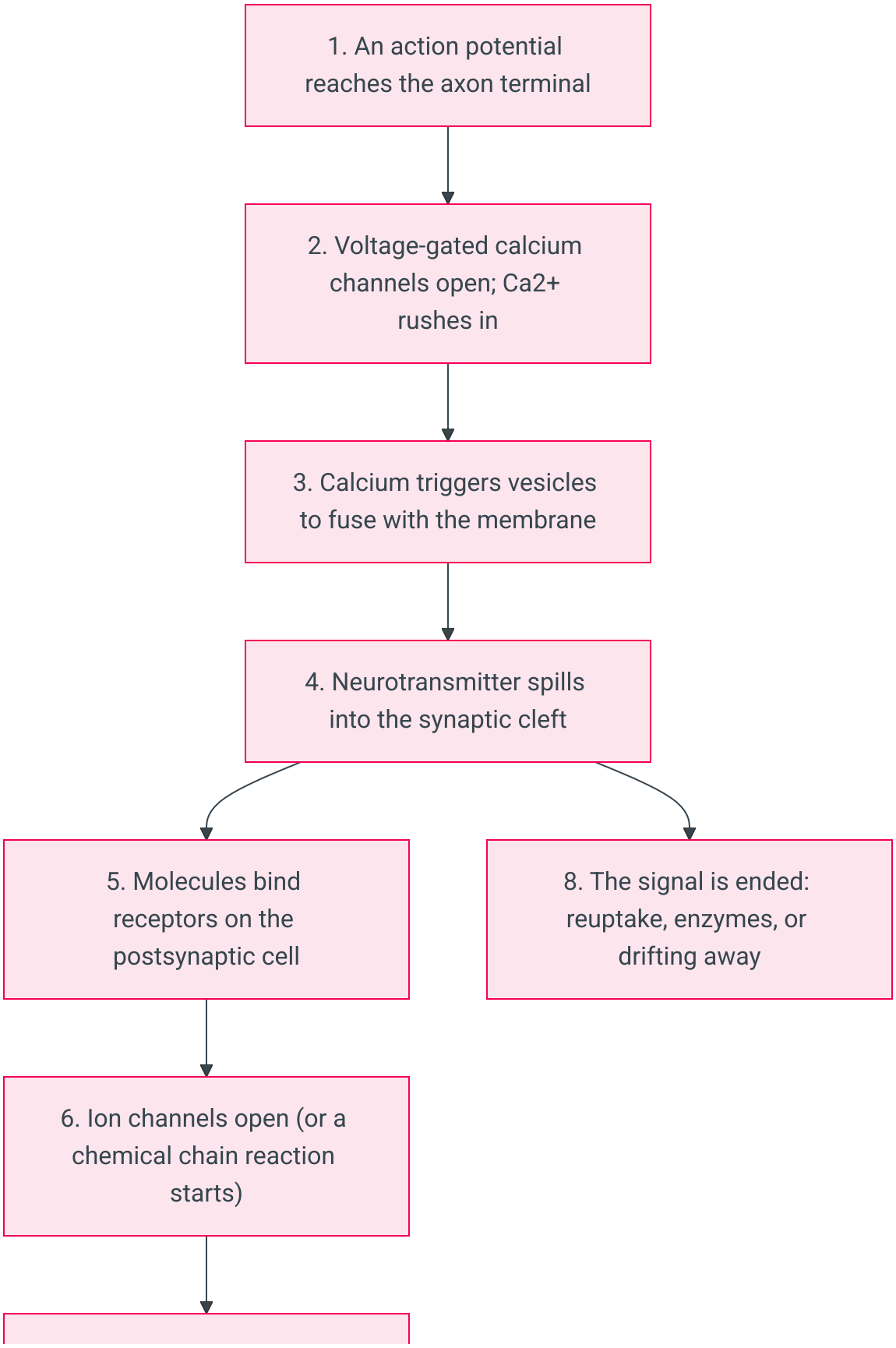
3.3 Step by Step at a Chemical Synapse

Before we walk through the steps, you need two terms.

A **neurotransmitter** is a chemical messenger that a neuron releases at a synapse to affect the next cell. Neurotransmitters are made by neurons and stored near the release site until needed.

A **synaptic vesicle** is a tiny bubble of membrane inside the axon terminal that is packed with neurotransmitter molecules. The terminal holds many vesicles, clustered close to the membrane that faces the cleft.

Now we can follow one signal across. The flowchart below shows the sequence.


1. An action potential reaches the axon terminal
2. Voltage-gated calcium channels open; Ca2+ rushes in
3. Calcium triggers vesicles to fuse with the membrane
4. Neurotransmitter spills into the synaptic cleft
5. Molecules bind receptors on the postsynaptic cell
8. The signal is ended: reuptake, enzymes, or drifting away
6. Ion channels open (or a chemical chain reaction starts)

7. The postsynaptic membrane potential changes

Here is each step in a little more detail.

1. **The action potential arrives.** In Chapter 2 you saw the action potential race down the axon. When it reaches the terminal, its depolarization does something new.
2. **Calcium enters.** The terminal membrane has voltage-gated channels for calcium ions (Ca^{2+}). Depolarization opens them, and calcium floods in, because there is far more calcium outside the cell than inside.
3. **Vesicles fuse.** Calcium-sensitive proteins attached to the vesicles change shape. That pulls docked vesicles into the cell membrane until they merge with it, a little like two soap bubbles joining.
4. **Release.** The vesicle's contents spill into the cleft. Because the cleft is so thin, the neurotransmitter concentration there shoots up for a brief moment.
5. **Binding.** Neurotransmitter molecules drift across and attach to receptors on the postsynaptic membrane.
6. **Response.** The receptors either open ion channels or start a chain of chemical reactions inside the cell.
7. **A new voltage.** The postsynaptic cell's membrane potential moves up or down.
8. **Cleanup.** The neurotransmitter must be removed quickly, or the next signal would be blurred into the last one.

Notice what happened: an electrical signal (the action potential) became a chemical signal (neurotransmitter), which then became an electrical signal again (a change in the postsynaptic voltage). Electrical, chemical, electrical. That conversion is what synaptic transmission is all about.

3.4 Receptors: The Locks on the Other Side

Lock and key

A **receptor** is a protein, usually sitting in the cell membrane, that a specific molecule can bind to and that changes the cell's activity when it does. A neurotransmitter and its receptor

fit like a key and a lock. A key cut for one lock usually won't open another. That's why a neuron can carry several kinds of receptors and respond to several messengers without mixing them up.

The receptor, not the neurotransmitter, mostly decides what happens next. The same neurotransmitter can excite one cell and calm another, depending on which receptors that cell has. Receptors come in two big families.

Ionotropic receptors: fast doors

An **ionotropic receptor** is a receptor that is also an ion channel. When the neurotransmitter binds, the protein changes shape and a pore opens right through it, letting certain ions cross the membrane. Another name for it is a *ligand-gated ion channel* ("ligand" just means the molecule that binds). The effect starts within milliseconds and ends quickly. Think of it as a door with a keyhole: turn the key and the door swings open.

Metabotropic receptors: slower, longer messages

A **metabotropic receptor** has no pore of its own. When the neurotransmitter binds, the receptor switches on a partner protein inside the cell called a **G protein**. The G protein then turns on other molecules, called **second messengers**, which spread the signal inside the cell. Second messengers might open ion channels somewhere else on the membrane, change how the cell uses energy, or even switch genes on and off. Think of it less like a door and more like a doorbell. Pressing the button doesn't let anyone in, but it starts a chain of events inside the house. Metabotropic effects are slower to start but can last much longer, from seconds to minutes or more.

	Ionotropic receptor	**Metabotropic receptor**
Is the receptor itself a channel?	Yes	No; it works through a G protein
Speed	Very fast (milliseconds)	Slower to start
How long the effect lasts	Brief	Can last much longer

	Ionotropic receptor	Metabotropic receptor
What it can change	Mainly the membrane voltage, right away	Voltage, cell chemistry, even gene activity
Example	Nicotinic acetylcholine receptor on skeletal muscle	Muscarinic acetylcholine receptor in the heart

Look at the last row. Acetylcholine binds both kinds of receptors. Your skeletal muscles use the fast ionotropic kind, so your muscles respond instantly. Your heart's pacemaker cells use the slower metabotropic kind, which is the receptor Loewi's *Vagusstoff* was acting on when it slowed the frog heart.

3.5 Adding Up the Votes: EPSPs, IPSPs, and Integration

Small nudges, not full signals

When neurotransmitter opens channels on a dendrite, the postsynaptic cell does not fire a full action potential right away. Instead, its voltage takes a small step up or down. These small steps are called **postsynaptic potentials**.

An **excitatory postsynaptic potential (EPSP)** is a small depolarization of the postsynaptic membrane. It moves the voltage up, closer to threshold, so the cell becomes *more* likely to fire. EPSPs usually happen when channels open that let positive sodium ions flow into the cell. The neurotransmitter most often behind EPSPs in the brain is glutamate.

An **inhibitory postsynaptic potential (IPSP)** is a small hyperpolarization, or a change that holds the voltage down. It moves the cell *away* from threshold, so it becomes *less* likely to fire. IPSPs often happen when channels open that let negative chloride ions in, or let positive potassium ions out. The neurotransmitters most often behind IPSPs are GABA in the brain and glycine in the spinal cord.

Postsynaptic potentials are very different from the action potentials in Chapter 2:

- They are **graded**, meaning they can be big or small depending on how much neurotransmitter arrives and how many receptors open. An action potential is all-or-none.

- They **fade** as they spread away from the synapse.
- They can **add together**. Action potentials can't.

Synaptic integration

A single neuron in your brain can receive input from thousands of synapses. Some are shouting "fire!" and others are saying "stay quiet." **Synaptic integration** is the process by which a neuron adds up all of its EPSPs and IPSPs to decide whether to fire an action potential.

There are two ways the adding happens:

- **Spatial summation:** inputs from *different* synapses arrive at about the same time and add together.
- **Temporal summation:** inputs from the *same* synapse arrive in quick succession, so each new EPSP starts before the last one has faded.

The decision is made near the **axon hillock**, the spot where the axon leaves the cell body. That region has many voltage-gated sodium channels, so it is where an action potential usually starts. If the summed voltage there reaches threshold, the neuron fires. If not, nothing leaves the cell.

A worked example

Let's use round, illustrative numbers. (Real EPSP sizes vary a lot from synapse to synapse.) Suppose a neuron rests at −70 mV and its threshold is −55 mV. It needs a total push of 15 mV.

- Three EPSPs of +6 mV arrive together: $-70 + 6 + 6 + 6 = -52$ mV. That's above −55 mV, so the neuron fires.
- Now the same three EPSPs arrive along with one IPSP of −5 mV: $-70 + 18 - 5 = -57$ mV. That's just short of threshold, so the neuron stays silent.

One "no" vote changed the outcome. Inhibition doesn't have to be loud to matter. It only has to shift the total at the right moment.

Neurons are tiny voting machines



Every neuron is constantly counting yes votes (EPSPs) and no votes (IPSPs), and only the total at the axon hillock matters. That's why a drug that only slightly boosts inhibition everywhere can make a whole brain drowsy.

3.6 Ending the Signal: Reuptake and Cleanup

A text message that kept buzzing forever would be useless. A synapse has the same problem. If neurotransmitter stayed in the cleft, the postsynaptic cell couldn't tell one signal from the next. Synapses use three main ways to clear the cleft.

1. **Reuptake. Reuptake** is the process of pumping a released neurotransmitter back into the presynaptic terminal through special proteins called **transporters**. The neuron can then repackage it into vesicles and reuse it. Reuptake ends the signal for many neurotransmitters, including dopamine, serotonin, and norepinephrine. Nearby glial cells called astrocytes (Chapter 1) also have transporters that soak up glutamate and GABA.
2. **Enzymes.** Some neurotransmitters are broken apart right in the cleft. Acetylcholine is the classic example: an enzyme called **acetylcholinesterase** splits it, and the pieces are recycled.
3. **Diffusion.** Some molecules simply drift out of the cleft and away.

Reuptake is one of the most important targets in all of medicine. If you slow it down, neurotransmitter stays in the cleft longer and keeps acting on receptors. That's exactly what many antidepressants and some drugs of abuse do, as you'll see in Section 3.8.

3.7 Meet the Neurotransmitters

More than 100 substances are known to act as neurotransmitters, but six of them come up again and again in neuroscience, in medicine, and in Brain Bee questions. Remember the rule from Section 3.4: whether a neurotransmitter excites or inhibits depends on the receptor. The descriptions below give each one's *usual* job.

Glutamate is the main excitatory neurotransmitter of the brain. It is the "go" signal at most fast excitatory synapses, and it is central to learning and memory (Chapter 9). Too much glutamate activity can damage neurons, a problem called excitotoxicity that is involved in stroke and several brain diseases (Chapters 13 and 14).

GABA (gamma-aminobutyric acid) is the main inhibitory neurotransmitter of the brain. It is used at most fast inhibitory synapses. GABA keeps excitation in check, which is why many sedative and anti-anxiety drugs work by boosting GABA's effects. In the spinal cord, a related amino acid, glycine, does much of the inhibitory work.

Acetylcholine (often written ACh) is the neurotransmitter motor neurons use to tell skeletal muscles to contract. It also slows the heart, as Loewi discovered. In the brain, it helps with alertness, attention, and memory. The loss of acetylcholine-producing neurons is associated with the memory problems of Alzheimer's disease (Chapter 13).

Dopamine has several separate pathways in the brain. One, starting in a region called the substantia nigra, helps control movement; losing those neurons causes most of the movement symptoms of Parkinson's disease (Chapter 7). Another pathway is involved in motivation and reward, the drive to seek out things we want. Many addictive drugs raise dopamine signaling in that pathway (Chapter 15).

Serotonin helps regulate mood, sleep, appetite, and body temperature, among other things. Surprisingly, most of the body's serotonin (roughly 90%) is made in the gut, where it helps control digestion, not in the brain.

Norepinephrine (also called noradrenaline) prepares the brain and body for action. In the brain, much of it comes from a small cluster of neurons in the brainstem called the locus coeruleus, and it raises arousal, alertness, and attention. Its levels are lowest during sleep and highest during stress or danger, as part of the fight-or-flight response.

Now that you've met all six, here they are side by side.

Neurotransmitter	Usual effect	Main jobs	A medical connection
Glutamate	Excitatory	Fast "go" signals; learning and memory	Excitotoxicity in stroke
GABA	Inhibitory	Fast "stop" signals; calming circuits	Sedatives that boost GABA

Neurotransmitter	Usual effect	Main jobs	A medical connection
Acetylcholine	Excitatory at muscle; varies elsewhere	Muscle contraction; heart rate; attention, memory	Myasthenia gravis; Alzheimer's disease
Dopamine	Depends on receptor	Movement; motivation and reward	Parkinson's disease; addiction
Serotonin	Depends on receptor	Mood, sleep, appetite	Target of SSRI antidepressants
Norepinephrine	Depends on receptor	Arousal, alertness, fight-or-flight	Stress responses (Chapter 11)

3.8 Drugs at the Synapse: Agonists and Antagonists

Now we can return to Maya's coffee with better words for what happened.

An **agonist** is a molecule that binds a receptor and activates it, mimicking the natural neurotransmitter. An **antagonist** is a molecule that binds a receptor without activating it, so it blocks the natural neurotransmitter from doing its job. In the lock-and-key picture, an agonist is a copied key that turns the lock. An antagonist is a key that fits in the lock but won't turn, and it's jammed in there so the real key can't get in.

Caffeine is an antagonist at adenosine receptors. That's why it doesn't give you energy so much as hide your tiredness.

Drugs can also act at other steps of synaptic transmission. Some change how much neurotransmitter is released. Others change how fast it is cleared. Each example in the table below works at one of the steps you learned in Sections 3.3 to 3.6.

Substance	What it does	Step it affects
Caffeine	Antagonist at adenosine receptors	Receptor binding
Nicotine	Agonist at nicotinic acetylcholine receptors	Receptor binding
Heroin and other opioids	Mimic natural opioid chemicals and activate opioid receptors (agonists)	Receptor binding
Naloxone	Opioid antagonist; reverses an opioid overdose	Receptor binding
Curare	Antagonist at the acetylcholine receptors on muscle; causes paralysis	Receptor binding
SSRIs (selective serotonin reuptake inhibitors)	Block the serotonin transporter	Reuptake
Cocaine	Interferes with transporters, so neurotransmitters such as dopamine are not recycled normally	Reuptake
Botulinum toxin	Stops the release of acetylcholine at the neuromuscular junction	Vesicle release
Pyridostigmine	Slows the enzyme that breaks down acetylcholine	Enzyme cleanup

Two of these deserve a closer look.

SSRIs are a common class of antidepressant medicines. By blocking the serotonin transporter, they keep serotonin in the cleft longer. The improvement in mood usually takes several weeks to appear. That delay is one clue that SSRIs probably work through gradual changes in brain signaling and in receptors, not just "more serotonin right now."

Naloxone shows how powerful an antagonist can be. In an opioid overdose, opioid drugs activate so many opioid receptors that breathing slows or stops. Naloxone binds tightly to those same receptors without activating them. It pushes the opioids off and blocks them from binding again, which can quickly restore breathing. You'll study this in Chapter 15.

An antagonist is not an 'opposite'



A common mistake is to think an antagonist does the reverse of the neurotransmitter. It doesn't produce its own opposite effect. It just blocks the receptor, so the result is "less of the normal signal," not "the opposite signal."

3.9 The Neuromuscular Junction

Every movement you make, from a soccer kick to a blink, starts at a special chemical synapse. The **neuromuscular junction** (often shortened to NMJ) is the synapse between a motor neuron and a skeletal muscle fiber.

It works exactly like the synapses you've studied, with a few special features:

- The neurotransmitter is **acetylcholine**.
- The muscle fiber's receptors are **nicotinic acetylcholine receptors**, which are ionotropic. When acetylcholine binds, the channel opens and positive ions rush in, depolarizing the muscle membrane.
- The cleft is filled with **acetylcholinesterase**, the enzyme that splits acetylcholine almost as soon as it has acted. So at the NMJ, the signal is ended by an enzyme rather than by reuptake.
- In a healthy NMJ, one action potential in the motor neuron reliably triggers one action potential in the muscle fiber. The junction releases more acetylcholine, and has more receptors, than it strictly needs to reach threshold. Neurologists call that extra margin the **safety factor**.

That safety factor is easy to overlook until it's gone. With fewer working receptors, each nerve impulse produces a smaller depolarization in the muscle. It may still reach threshold at first. But when a nerve fires again and again, the amount of acetylcholine released with

each impulse naturally drops a bit. In a healthy junction that small drop doesn't matter. In a junction with too few receptors, it can push the response below threshold, and some muscle fibers stop responding. Keep that idea in mind. It is the key to the bedside case.

Brain Bee tip: my famous synapse

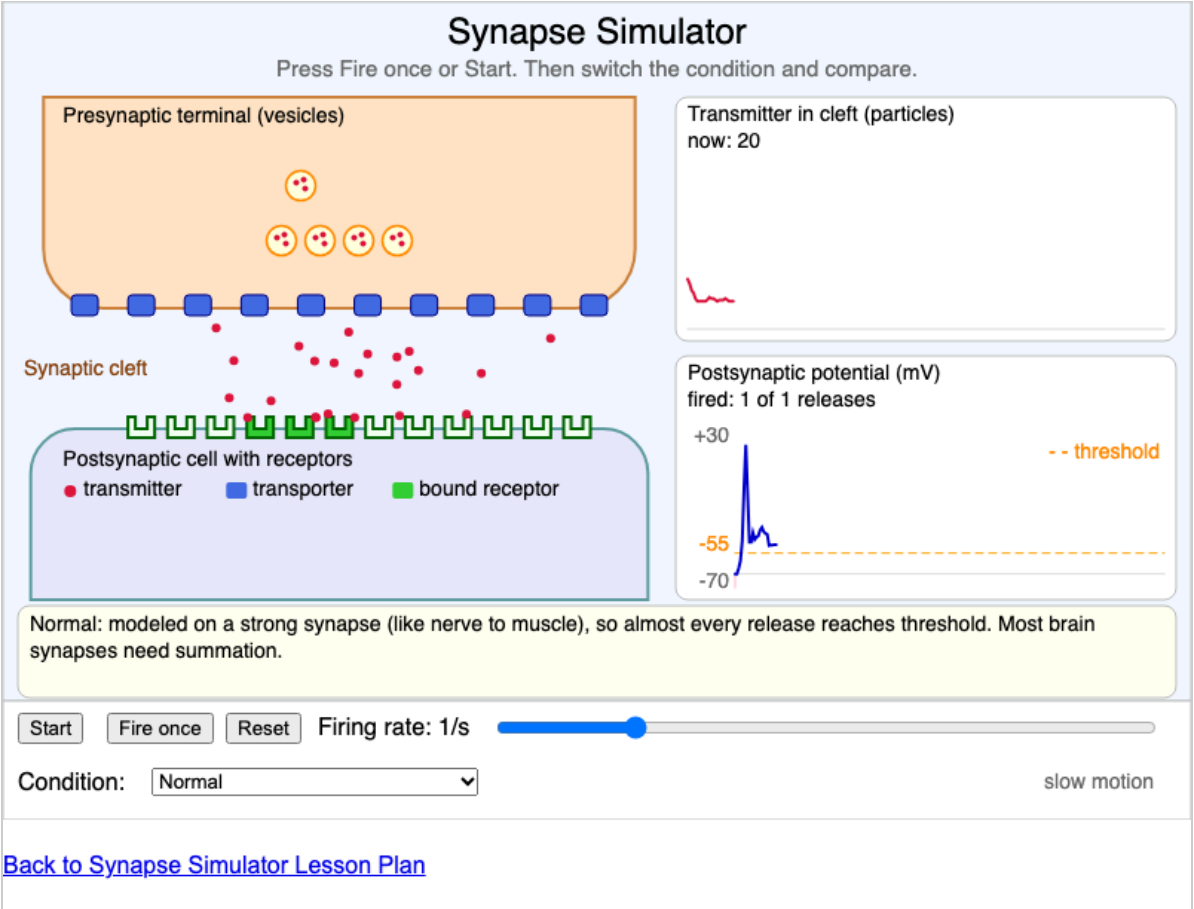


My species, *Aplysia californica*, has only about 20,000 large neurons, so Eric Kandel could study single synapses in its gill-withdrawal reflex. He found that serotonin strengthens a key synapse when the slug learns, and he shared the 2000 Nobel Prize with Arvid Carlsson and Paul Greengard for discoveries about signaling in the nervous system. You'll see this again in Chapter 9.

3.10 Try It: The Synapse Simulator

Now you can run a synapse yourself. The simulator shows one strong excitatory chemical synapse in slow motion. Red dots are neurotransmitter molecules. Blue blocks on the terminal are reuptake transporters. Green cups on the postsynaptic membrane are receptors, which turn bright green while a molecule is bound. On the right, one graph tracks how much transmitter is in the cleft, and the other tracks the postsynaptic membrane potential in millivolts, with a dashed threshold line.

Diagram: Synapse Simulator



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch03-synapse/

Open the Synapse Simulator fullscreen

MicroSim specification: Synapse Simulator

Type: microsim **sim-id:** ch03-synapse
Library: p5.js
Status: Implemented
Bloom Level: Apply
Bloom Verb: predict
Learning Objective: The learner will predict how a reuptake blocker, a receptor antagonist, and a loss of receptors each change the amount of neurotransmitter in the cleft and the size and duration of the postsynaptic potential, then check each prediction in the simulator.

Canvas: 470 px drawing area plus 80 px control area (iframe height 552 px); width responsive.

Controls: Start/Pause button; "Fire once" button (one presynaptic action potential); Reset button; firing-rate slider (0 to 5 per second, step 1, default 1, slow motion); condition menu with Normal, Reuptake blocker (like an SSRI), Receptor antagonist, and Fewer receptors (myasthenia-like).

Behavior: Each firing releases transmitter particles from vesicles; the releasable store shrinks with each release and refills over about 2 seconds, so release falls at high firing rates. Particles diffuse, bind free receptors briefly, unbind, and are removed by transporters (or slowly drift away). The postsynaptic potential rises with the number of bound receptors; reaching −55 mV triggers one postsynaptic spike to about +30 mV, from a resting potential of −70 mV. Reuptake blocker: transporters disabled, so transmitter lingers and the response lasts longer. Antagonist: 8 of 12 receptors capped by a drug. Fewer receptors: 6 of 12 receptors removed. A counter shows how many releases made the postsynaptic cell fire.

Chapter Anchors: resting potential −70 mV; threshold −55 mV; spike peak about +30 mV; 12 receptors in the normal synapse; antagonist blocks 8 of 12; fewer-receptors condition keeps 6 of 12. All other quantities are illustrative and qualitative.

Try these four experiments. Before each one, predict what the two graphs will do.

1. **Normal.** Press **Fire once** a few times. Watch the dots cross, bind, and disappear into the blue transporters. The cleft graph spikes and quickly falls, and almost every release pushes the postsynaptic cell past threshold. That is because the simulator models a strong synapse, like the nerve-to-muscle junction in Section 3.9, where one release is normally enough. Most synapses in the brain are weaker. There, a single EPSP falls short, and the cell fires only when many EPSPs add up, as in Section 3.5.
2. **Reuptake blocker.** Switch the condition and press **Start**. The transporters get a gray X. Compare the cleft graph with the normal one. The transmitter piles up and lingers, and

the postsynaptic potential stays raised for longer. This is the basic idea behind an SSRI, although real SSRIs act on serotonin synapses in the brain over weeks.

3. **Receptor antagonist.** Gray caps cover most receptors. The surprise is that the cleft graph looks about normal, because the transmitter is still released and cleared. But few receptors can bind it, so the postsynaptic potential stays small and usually misses threshold.
4. **Fewer receptors.** Half of the receptors are gone, the way antibodies remove them in myasthenia gravis. Count how many releases succeed at a firing rate of 1 per second, then at 5 per second. With fewer receptors, failures become more common at high firing rates, because the smaller release per impulse is no longer enough. (At a real neuromuscular junction, acetylcholinesterase clears acetylcholine. The simulator keeps the same cleanup method in every condition so that only one thing changes at a time.)

The big lesson: a drug or disease can change synaptic transmission by acting on the *amount* of neurotransmitter, on *how long* it stays, or on the *receptors* that detect it. The cleft graph and the response graph tell you which one is happening.

Stuck on which graph changed?



If the cleft graph changes, the drug is acting on release or cleanup. If the cleft looks normal but the response shrinks, the problem is with the receptors. Sort every drug in this chapter with that one question and you've got it.

At the Bedside: Eyelids That Droop by Evening

Meet the patient

Elena is 35 and teaches middle school math. For about two months, her eyelids have been drooping, mostly in the late afternoon. Some evenings she sees double while grading papers or driving home. Her eyelids look almost normal when she wakes up. Lately, her jaw gets tired partway through dinner, and she has to rest before she can finish chewing. She feels fine otherwise and has no numbness or pain.

What the doctor checks: The neurologist asks Elena to look up at a fixed point without blinking. After about a minute, her eyelids begin to sag, and her double vision returns. Her muscle strength is normal at first but fades with repeated testing, then improves after a short rest. Her sensation is normal. The doctor orders a blood test for antibodies against the acetylcholine receptor. She also orders **repetitive nerve stimulation**, a test that zaps a nerve with a series of small electrical pulses while recording the muscle's response, and a chest CT scan to look at the thymus gland.

Where is the problem? (localization): The weakness gets worse with use and better with rest. It affects eye and chewing muscles. And there is no numbness. A stroke or tumor in the brain would not usually come and go with exercise, and a damaged nerve would usually affect feeling too. Weakness that fatigues points to the neuromuscular junction, where each nerve impulse has to be turned into a muscle action potential.

Diagnosis: Myasthenia gravis. Her blood test is positive for acetylcholine receptor antibodies, and repetitive nerve stimulation shows the muscle's response shrinking with each pulse in the train.

Why it happens: Myasthenia gravis is a chronic autoimmune disease in which the immune system makes antibodies that block, alter, or destroy acetylcholine receptors at the neuromuscular junction. Less often, the antibodies target a related protein called MuSK. With fewer working receptors, the safety factor shrinks. Each nerve impulse still releases acetylcholine, but the muscle's depolarization is smaller. With repeated use, release per impulse dips, and more muscle fibers fail to reach threshold. That is why Elena's muscles are strongest in the morning and weakest after a day of use. Eye muscles are often affected first, partly because their neuromuscular junctions have a smaller safety factor to begin with. The thymus gland, which trains immune cells, is often abnormal in people with myasthenia gravis and is thought to help start the faulty immune response. The condition most commonly begins in women under 40 and men over 60, but it can start at any age.

Treatment today: There is no cure yet, but most people with myasthenia gravis live a normal life span. A common treatment is pyridostigmine, an acetylcholinesterase inhibitor. It slows the enzyme that breaks down acetylcholine, so each burst of acetylcholine lasts longer and has more chances to find the remaining receptors. Doctors also use medicines that calm the immune system, such as prednisone, and surgery to remove the thymus (thymectomy) helps many patients. For severe flare-ups, plasma exchange removes harmful antibodies from the blood, and intravenous immunoglobulin (IVIG) temporarily changes how the immune system behaves. The FDA has also approved complement inhibitors, such as

eculizumab, for some people with generalized myasthenia gravis who test positive for acetylcholine receptor antibodies. Eculizumab was first approved for adults with this form in 2017, and in 2025 its approval was extended to children 6 and older (Practical Neurology, 2025). About 15 to 20% of people with myasthenia gravis have at least one **myasthenic crisis**, when the breathing muscles become too weak to work. That is a medical emergency that may require a ventilator.

What's new in research: A newer class of drugs lowers the level of harmful antibodies directly. Antibodies are normally rescued from breakdown by a protein called the neonatal Fc receptor (FcRn). Drugs that block FcRn let the body clear antibodies faster, including the ones attacking the neuromuscular junction. In December 2021, the FDA approved the first of these, efgartigimod (brand name Vyvgart), for adults with generalized myasthenia gravis who test positive for acetylcholine receptor antibodies. In the phase 3 ADAPT trial (Howard et al., *Lancet Neurology*, 2021), 68% of antibody-positive patients improved on a measure of daily function during the first treatment cycle, compared with 30% on placebo (FDA announcement). Other FcRn blockers, rozanolixizumab (approved in 2023) and nipocalimab (approved in 2025 for people 12 and older), have followed. In 2026, the FDA widened efgartigimod's approval to adults whose blood tests show no acetylcholine receptor antibodies (Muscular Dystrophy Association, May 2026). A different approach targets the B cells that make the antibodies: inebilizumab (brand name Uplizna) was approved for adults with generalized myasthenia gravis in December 2025 (Amgen announcement). As of October 2026, more drugs are still under FDA review. None of these treatments is a cure.

Your turn: diagnose a variation

A 50-year-old man has surgery for a broken leg. During the operation, the anesthesiologist gives him a curare-like muscle relaxant, a drug that acts as an antagonist at the acetylcholine receptors on muscle, so his muscles stay still. At the end of surgery, the anesthesiologist gives a drug called neostigmine, and his strength returns. Using this chapter, explain (1) why the first drug caused weakness, and (2) how neostigmine, which is closely related to Elena's pyridostigmine, could reverse it.

Answer: (1) The muscle relaxant binds the nicotinic acetylcholine receptors without opening them, so acetylcholine released by motor neurons can't depolarize the muscle enough to reach threshold. This is a drug-made version of Elena's problem: too few *usable* receptors. (2) Neostigmine is an acetylcholinesterase inhibitor. With the enzyme slowed, acetylcholine builds up in the cleft and lasts longer, so it can outcompete the antagonist for the receptors that remain, and the muscle reaches threshold again. Neostigmine is used in exactly this way at the end of many surgeries.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Dopamine is the brain's "pleasure chemical."
Reality: Dopamine is more about *wanting* and *motivation* than about pleasure itself. In a classic set of rat experiments, animals whose dopamine was almost completely depleted still showed normal "liking" reactions to sweet tastes (Berridge and Robinson, 1998). The researchers concluded that dopamine matters more for how strongly a reward is *wanted* than for how good it feels. Dopamine also controls movement, which is why losing dopamine neurons causes Parkinson's disease.

Myth: Serotonin equals happiness, and depression is just "low serotonin."
Reality: Serotonin helps regulate mood, but also sleep, appetite, and digestion, and most of the body's serotonin is in the gut. A 2022 umbrella review of the research found no consistent evidence that depression is caused by low serotonin (Moncrieff et al., *Molecular Psychiatry*). That does not mean antidepressants don't help people. It means depression is more complicated than a single chemical running low.

Myth: Neurons physically touch and pass electricity straight from one to the next.
Reality: At most synapses, there is a real gap of about 20 to 40 nanometers, and the signal crosses it as chemicals. Electrical synapses, where ions flow directly between cells, exist but are the minority.

Myth: Each neurotransmitter always has the same effect, so glutamate always "excites" and dopamine always "rewards."
Reality: The receptor decides. Acetylcholine excites skeletal muscle through ionotropic receptors but slows the heart through metabotropic ones. Dopamine has several receptor types and several pathways with very different jobs.

Myth: Caffeine gives your brain extra energy.
Reality: Caffeine is an antagonist. It blocks adenosine receptors, so the "you've been awake a long time" signal can't get through. The tiredness is hidden for a while, not erased.

Brain Bee Practice

1. What ion's entry into the axon terminal triggers neurotransmitter release?

Calcium (Ca^{2+}). When the action potential depolarizes the terminal, voltage-gated calcium channels open, and the incoming calcium causes vesicles to fuse with the membrane.

2. Name the enzyme that breaks down acetylcholine at the neuromuscular junction.

Acetylcholinesterase. Drugs that inhibit it, such as pyridostigmine, are used to treat myasthenia gravis.

3. What is the difference between an ionotropic and a metabotropic receptor?

An ionotropic receptor is itself an ion channel that opens when the neurotransmitter binds, giving a fast, brief response. A metabotropic receptor works through a G protein and second messengers, giving a slower but longer-lasting response.

4. Which neurotransmitter is the main excitatory transmitter in the brain, and which is the main inhibitory one?

Glutamate is the main excitatory neurotransmitter. GABA is the main inhibitory neurotransmitter in the brain (glycine plays that role in much of the spinal cord).

5. A patient's eyelids droop more as the day goes on, and blood tests show antibodies against acetylcholine receptors. What is the diagnosis, and where is the problem?

Myasthenia gravis. The problem is at the neuromuscular junction, where antibodies reduce the number of working acetylcholine receptors on the muscle.

Exercises

Remember

1. List the three main ways a neurotransmitter's signal is ended at a synapse.
2. Name the scientist who showed in 1921 that nerves can signal with chemicals, and the neurotransmitter his experiment revealed.

Answer

1. Reuptake by transporters, breakdown by enzymes, and diffusion away from the cleft.
2. Otto Loewi. The chemical was acetylcholine (he called it *Vagusstoff*).

Understand

1. Explain why a postsynaptic potential can be graded, but an action potential is all-or-none.
2. In your own words, explain why the same neurotransmitter can excite one cell and inhibit another.

Answer

1. A postsynaptic potential depends on how many receptors open, which depends on how much neurotransmitter arrives, so its size can vary. An action potential happens only when threshold is reached, and then voltage-gated channels produce the same full-size spike every time.
2. The effect depends on which receptor the cell has. Different receptors for the same neurotransmitter can open different ion channels or start different chemical chains inside the cell.

Apply

1. A neuron at −70 mV with a threshold of −55 mV receives two EPSPs of +5 mV and one IPSP of −3 mV at the same time. Will it fire? Show your work. Then decide what single extra input would change the answer.
2. In the Synapse Simulator, predict what would happen to the cleft graph and the response graph if a drug blocked half the transporters *and* half the receptors. Explain your prediction step by step.

Analyze

1. Botulinum toxin and curare both cause muscle weakness. Compare where each one acts at the neuromuscular junction. Would an acetylcholinesterase inhibitor be more likely to help with one than with the other? Explain.

2. Elena's weakness is worst in the evening, and repetitive nerve stimulation shows the muscle response shrinking pulse by pulse. Connect these two observations to the idea of the safety factor.

Evaluate

1. A website claims, "Boost your dopamine to feel happier." Using evidence from this chapter, evaluate this claim. What is accurate about it, and what is misleading?
2. A friend says SSRIs "just flood your brain with serotonin, so they should work in an hour." Judge this statement using what you know about reuptake and about how long SSRIs take to help.

Create

1. Design a new analogy (not the relay race in this chapter) that explains the difference between an agonist, an antagonist, and a reuptake blocker. Your analogy should map each part clearly to the real synapse.
2. Write a short clinical case for a classmate in which the problem is at a synapse. Include the symptoms, one test result, and the answer key explaining which step of synaptic transmission is affected.

Key Takeaways

- A **synapse** is where a neuron passes a signal to another cell. Most are **chemical synapses**, which turn an electrical signal into a chemical one and back again. **Electrical synapses** pass ions directly through gap junctions and are faster but less adjustable.
- At a chemical synapse, an action potential opens calcium channels, **synaptic vesicles** release **neurotransmitter** into the cleft, and the transmitter binds **receptors** on the postsynaptic cell.
- **Ionotropic receptors** are fast ion channels. **Metabotropic receptors** act through G proteins and second messengers and give slower, longer effects. The receptor, not just the transmitter, decides the effect.
- **EPSPs** push a neuron toward threshold and **IPSPs** push it away. Through **synaptic integration**, the neuron adds them up, and it fires only if the total at the axon hillock

reaches threshold.

- **Glutamate** (main excitatory), **GABA** (main inhibitory), **acetylcholine**, **dopamine**, **serotonin**, and **norepinephrine** are the main neurotransmitters to know, each with typical jobs and links to disease.
- **Agonists** activate receptors, **antagonists** block them, and other drugs change release or **reuptake**. Caffeine, nicotine, opioids, naloxone, SSRIs, and botulinum toxin each act at a specific step.
- At the **neuromuscular junction**, acetylcholine triggers muscle contraction with a safety margin. In **myasthenia gravis**, antibodies remove that margin by attacking acetylcholine receptors, causing weakness that worsens with use.

You crossed the gap!



You now know how one cell talks to the next, which is the step where so much of medicine happens. Next, in Chapter 4, we'll zoom out from single synapses to tour the whole brain and see which regions do what.

Chapter 4: A Tour of the Brain: Neuroanatomy

Summary

This chapter is a guided tour of the human brain. You will learn the "map language" of anatomy, then visit the four lobes of the cortex, the deep relay centers, the brainstem, cerebellum, spinal cord, and cranial nerves. You will see how the brain is protected and fed, and how the autonomic nervous system runs your organs on autopilot. The chapter ends at the bedside with Phineas Gage and a modern patient whose car crash injured the same part of the brain.

Concepts Covered

1. Anatomical Directions
2. Brain Planes and Sections
3. Gray Matter
4. White Matter
5. Cerebral Cortex
6. Frontal Lobe
7. Parietal Lobe
8. Temporal Lobe
9. Occipital Lobe
10. Corpus Callosum
11. Thalamus
12. Hypothalamus
13. Brainstem
14. Cerebellum
15. Spinal Cord

16. Cranial Nerves
17. Ventricles and CSF
18. Meninges
19. Cerebral Blood Supply
20. Autonomic Nervous System
21. Sympathetic vs Parasympathetic
22. Localization of Function
23. Prefrontal Cortex

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters

Welcome to the big city



I'm Ply, a sea slug with about 20,000 neurons. Yours has about 86 billion, packed into a three-pound brain with dozens of named neighborhoods. Knowing those neighborhoods is how doctors trace symptoms to their source, and it's a big part of the Brain Bee. Let's take the tour!

4.1 An Iron Rod and a Changed Man

At about 4:30 in the afternoon on September 13, 1848, a 25-year-old railroad foreman named Phineas Gage was blasting rock for a new rail line near Cavendish, Vermont. As he packed explosive powder into a hole with a long iron bar called a tamping iron, the powder exploded. The iron shot upward like a spear. It was about 3 feet 7 inches long, 1¼ inches thick, and weighed about 13¼ pounds. It entered the left side of his face, passed behind his left eye, tore through the front of his brain, and flew out the top of his skull. It landed roughly 80 feet away.

Within minutes, Gage was talking. He rode an oxcart back to town, greeted the first doctor who arrived, and later survived a dangerous infection. Yet his physician, Dr. John Harlow, later reported that Gage's friends said he was "no longer Gage." The careful, reliable foreman had become impatient, rude, and unable to stick to his plans. How could damage to one part of the brain change who a person seemed to be?

More than 170 years later, Maya, a 16-year-old soccer player studying for the Brain Bee, stares at a plastic brain model and a long list of structures. "Where do I even start?" This chapter answers that question. By the end, you will be able to point to the part of the brain Gage's iron damaged, explain what it does, and separate what really happened to him from the myths.

4.2 Reading the Map: Directions, Planes, and Sections

Imagine giving a friend directions in a city. "Turn left" means nothing unless you agree which way you are facing. Anatomists solved this with **anatomical directions**: fixed terms that describe where one structure sits compared with another, no matter how the body is turned. The main pairs are:

- **Anterior** (toward the face) and **posterior** (toward the back of the head).
- **Superior** (above) and **inferior** (below).
- **Dorsal** (toward the back or top) and **ventral** (toward the belly or bottom).
- **Rostral** (toward the nose or the top of the spinal cord) and **caudal** (toward the tail).
- **Medial** (toward the midline) and **lateral** (toward the side).
- **Ipsilateral** (on the same side) and **contralateral** (on the opposite side).

There is one twist. In a dog, the brain and spinal cord form a straight line. Humans stand upright, so our nervous system bends at the top of the brainstem. Because of that bend, "dorsal" means *the top of the brain* but *the back of the spinal cord*. Picture a shark's dorsal fin on top of a swimming shark.

Now think about a loaf of bread. You can slice it three ways, and each slice shows a different face of the inside. **Brain planes and sections** are the standard ways of cutting (or imaging) the brain:

- A **sagittal** section divides the brain into left and right parts. A **midsagittal** cut runs exactly down the middle, between the two halves.
- A **coronal** section (also called frontal) divides the brain into front and back parts.
- A **horizontal** section (also called axial) divides the brain into top and bottom parts.

MRI scans show the living brain in these same three planes. The table below summarizes them.

Plane	What it separates	Everyday picture
Sagittal (midsagittal)	Left from right	Cutting a face down the nose
Coronal (frontal)	Front from back	Slicing a loaf of bread
Horizontal (axial)	Top from bottom	Lifting the lid off a jar

4.3 Cities and Highways: Gray Matter and White Matter

Picture a country from an airplane at night: bright cities where people work, and highways carrying traffic between them. A sliced brain shows the same two kinds of tissue.

Gray matter is the "city" tissue, packed with neuron cell bodies, dendrites, and synapses, where information is processed. **White matter** is the "highway" tissue: bundles of axons wrapped in myelin, the fatty insulation from Chapter 1, which makes it look white. In the brain and spinal cord, a bundle of axons is called a **tract**. Outside them, in the peripheral nervous system, it is called a **nerve**.

In the cerebrum (the big, wrinkled part of the brain), gray matter covers the outside and white matter fills the inside. The spinal cord is the reverse. Its gray matter is a butterfly-shaped core in the center, and its white matter wraps around the outside.

4.4 The Wrinkled Outer Layer: The Cerebral Cortex

The **cerebral cortex** is the thin outer layer of gray matter covering the cerebrum. The word *cortex* comes from the Latin word for "bark," because it covers the brain like bark on a tree.

It is only about as thick as two or three stacked dimes, yet it holds about 16 billion neurons. Perception, reasoning, language, planning, and voluntary movement all depend on it.

Why is the brain so wrinkled? Try fitting a tablecloth into a small box: you crumple it. Spread flat, the cortex would be roughly the size of a pillowcase, and folding lets it fit inside the skull. Each ridge is called a **gyrus** (plural *gyri*), and each groove is called a **sulcus** (plural *sulci*). A very deep groove is called a **fissure**.

A deep fissure down the middle splits the cerebrum into left and right **hemispheres**. Two other grooves are the most important landmarks on the side of the brain:

- The **central sulcus** runs from the top of the brain down toward the ear. It separates the frontal lobe in front from the parietal lobe behind.
- The **lateral sulcus** (also called the Sylvian fissure) is a long, deep groove that runs backward from the front. It separates the temporal lobe below from the frontal and parietal lobes above.

With these landmarks, we can divide each hemisphere's cortex into four **lobes**.

The frontal lobe, the largest lobe, sits behind your forehead, in front of the central sulcus and above the lateral sulcus. The ridge just in front of the central sulcus (the precentral gyrus) is the **primary motor cortex**, which sends commands for voluntary movement down to the brainstem and spinal cord. The rest of the frontal lobe plans, decides, and controls behavior. In most people, **Broca's area** in the left frontal lobe helps produce speech.

The parietal lobe sits behind the central sulcus, under the top of your head. The ridge just behind the sulcus (the postcentral gyrus) is the **primary somatosensory cortex** ("somato" means body), which receives touch, pain, temperature, and body-position signals. The parietal lobe also tracks where your body and nearby objects are in space.

The temporal lobe, the second-largest, sits below the lateral sulcus, near your ears. It handles hearing, understanding language, and recognizing faces. Tucked inside it is the hippocampus, which is critical for forming new memories (Chapter 9).

The occipital lobe, at the very back of the head, is mainly for vision. Strangely, the part of the brain that handles sight is the part farthest from your eyes.

Now that you have met all four lobes, the table below puts them side by side.

Lobe	Location	Main jobs	Key strip of cortex
Frontal	Behind the forehead, in front of the central sulcus	Movement, planning, judgment, speech production	Primary motor cortex (precentral gyrus)
Parietal	Top and upper back, behind the central sulcus	Touch, body position, spatial awareness	Primary somatosensory cortex (postcentral gyrus)
Temporal	Side, below the lateral sulcus	Hearing, language understanding, faces, memory	Primary auditory cortex
Occipital	Very back of the head	Vision	Primary visual cortex

Movement in front, feeling behind



My trick for the central sulcus: **movement in front, feeling behind**. The motor strip lies just in front of the groove, and the touch strip just behind it.

One more rule surprises almost everyone: each hemisphere controls and feels the **opposite** (contralateral) side of the body. The left motor cortex moves your right hand, so a stroke in the right hemisphere can weaken the left arm and leg. This happens because most motor and sensory pathways cross the midline between the brain and the body.

4.5 One Part, One Job? Localization of Function

In the 1800s, scientists argued: is the brain like a soup, where every part does a bit of everything, or like a hospital, where each department has its own job? The idea that particular brain areas do particular jobs is called **localization of function**. Evidence came from patients: if damage to one area causes one specific problem, that area probably helps with that job.

Both sides of the debate used Phineas Gage. One critic argued his survival proved the brain was *not* divided into special areas. The British neurologist David Ferrier used the same case to argue for localization. Today we can see why Gage fits the localization side: his iron missed the strips of cortex for movement and touch, so those abilities survived, while the area it hit was tied to his behavior changes.

Modern research shows that localization is real but limited. The motor cortex really does control movement. But complex abilities, like reading or deciding, depend on networks of areas linked by white matter, and the brain can reorganize. In people blind from early life, parts of the visual cortex can start responding to touch.

The **prefrontal cortex** is the part of the frontal lobe in front of the motor areas, right behind your forehead. It is the brain's executive. It helps you:

- plan ahead and set priorities,
- hold information in mind while you work with it (working memory),
- control impulses and wait for a bigger reward,
- switch strategies when something isn't working, and
- follow social rules and read other people's reactions.

These abilities are called **executive functions**. The prefrontal cortex is also one of the last regions to mature; the National Institute of Mental Health notes the brain keeps developing into the mid-to-late 20s (more in Chapter 8).

Here is the key idea for the bedside case. A person with prefrontal damage may have normal strength, senses, and even scores on many intelligence tests. What changes is how they *use* those abilities: how they plan, judge, and behave. That is why Gage could walk and talk, yet seemed like a different person.

What Really Happened to Phineas Gage

Psychologist Malcolm Macmillan, the leading Gage historian, went back to the original records. In 2000, he reported that Gage appears in about 60% of introductory psychology textbooks, but many accounts contain errors, often traits borrowed from other frontal-lobe patients. Here is what the evidence supports:

- **The injury was severe.** Dr. Harlow recorded a large wound, a dangerous infection, and loss of vision in the left eye.
- **The personality change was real, at least at first.** Harlow's detailed description, published in 1868, 20 years later, called Gage impatient, profane, stubborn, and unable to follow through on plans.
- **Gage did not become a lifelong drifter.** He worked for a horse stable and coach service in New Hampshire for about 18 months. In 1852, he moved to Chile and spent years driving six-horse stagecoaches between Valparaíso and Santiago, a job that demanded planning and skill.
- **He probably recovered more than the legend says.** Macmillan and Matthew Lena (2010) argued that Gage eventually made a surprisingly good social adjustment, helped by the daily structure of his work.
- **His health eventually failed.** He became ill in 1859 and moved to San Francisco, where his mother and sister lived. Seizures began in February 1860, and he died on May 21, 1860, at about age 36. His skull and tamping iron are displayed at Harvard's Warren Anatomical Museum.

Even the location of the damage has been debated. A famous 1994 reconstruction concluded that *both* frontal lobes were damaged, but it used a model skull shaped to match Gage's. Two later studies, Ratiu and colleagues (2004) and Van Horn and colleagues (2012), used scans of Gage's actual skull and concluded that the damage was limited to the **left** frontal lobe. The 2012 study estimated that the iron damaged about 4% of the cortex's gray matter but about 11% of the brain's white matter, cutting connections between the frontal lobe and other areas.

Don't repeat the legend



Watch out for retellings that call Gage a violent, drunken drifter for life. Those details aren't in the original records. The true story is more interesting: a severe injury, a real change in behavior, and evidence of recovery.

4.6 Linking the Hemispheres: The Corpus Callosum

Your two hemispheres need to share information. They talk mostly through the **corpus callosum**, the largest bundle of white matter in the brain: a curved band of roughly 200 to 250 million axons that crosses the midline and connects the left and right hemispheres. In a midsagittal cut, it looks like a white, C-shaped arch above the center of the brain.

In rare cases of severe epilepsy, surgeons have cut the corpus callosum to stop seizures from spreading between hemispheres. These "split-brain" patients seem normal in daily life, but in careful lab tests one hemisphere may not know what the other has seen. For example, a patient may be unable to read aloud a word shown only to the right hemisphere, yet still pick out the matching picture.

4.7 Deep in the Middle: The Thalamus and Hypothalamus

Below the corpus callosum, buried in the middle of the brain, sit two small structures with huge jobs. Together they form the **diencephalon**, which means "between brain."

Think of an airport hub, where passengers from many flights are sent to the right connecting gate. The **thalamus** is the brain's hub: a pair of egg-shaped masses of gray matter, one on each side of the midline. It receives incoming sensory signals and sends each one to the right area of cortex: vision to the occipital lobe, hearing to the temporal lobe, touch to the parietal lobe. Every sense passes through the thalamus on its way to the cortex except one: smell. The thalamus also passes signals back and forth between the cortex and the circuits that control movement.

The **hypothalamus** sits just below and in front of the thalamus ("hypo" means below). It is about the size of a pearl, but it acts as the body's thermostat, keeping internal conditions steady, a balance called **homeostasis**. It helps control body temperature, hunger, thirst, sleep, stress responses, and hormone release through the **pituitary gland**, which hangs just below it on a thin stalk.

By commanding the pituitary, the "master gland," the hypothalamus links the nervous system to the hormone system. It is also a key controller of the autonomic nervous system (Section 4.12).

Other deep structures sit nearby: the **hippocampus** (new memories), the **amygdala** (fear and emotion), and the **basal ganglia** (starting and smoothing movement). You will meet each in later chapters.

4.8 The Stalk and the Little Brain: Brainstem and Cerebellum

The brainstem

If the cerebrum is a house, the **brainstem** is the electrical panel in the basement: not glamorous, but if it fails, everything stops. It is the stalk connecting the cerebrum to the spinal cord, with three parts from top to bottom:

1. **The midbrain** helps control eye movements and reflexes to sights and sounds. Its **substantia nigra** ("black substance") holds dopamine neurons that help start movement; their loss causes most of the movement symptoms of Parkinson's disease (Chapter 7).
2. **The pons** (Latin for "bridge") links the cerebrum with the cerebellum, helps regulate breathing and sleep, and sends cranial nerves for chewing, facial expression, and eye movement.
3. **The medulla oblongata** runs life support: breathing, heart rate, and blood pressure, plus swallowing, coughing, and vomiting. Near its bottom, most motor axons from the cortex cross to the opposite side, a big reason each hemisphere controls the opposite side of the body.

A network called the reticular formation runs through the brainstem and helps keep you awake and alert. Because the brainstem packs so many vital functions into a small space, even a small injury there can be life-threatening.

The cerebellum

Tucked under the back of the cerebrum is the **cerebellum** ("little brain"). The cortex decides *what* to do, such as pass to a teammate. The cerebellum works out *how* to do it smoothly: timing, force, and balance. It compares what you meant to do with what your body did, corrects the difference, and helps you learn motor skills like a new dribbling move. It is only about 10% of the brain's volume but holds roughly 80% of its neurons.

Cerebellar damage causes **ataxia**: clumsy, poorly aimed movements and an unsteady walk, usually with normal strength. Alcohol disrupts the cerebellum, which is why sobriety tests include walking a straight line and touching the nose.

The cerebellum breaks the crossing rule



The cerebrum controls the *opposite* side of the body, but each half of the cerebellum coordinates the *same* side. Damage to the left cerebellum makes the left arm clumsy, a favorite trick in localization questions.

4.9 Cables to the Body: The Spinal Cord and Cranial Nerves

The spinal cord

The **spinal cord** is a cable of nervous tissue running down from the medulla through a tunnel in the backbone. With the brain, it forms the central nervous system. In adults, the cord ends near the top of the lower back (around the first or second lumbar vertebra), and a spray of nerve roots continues below. It has three main jobs:

- carry sensory messages **up** to the brain,
- carry movement commands **down** to muscles, and
- run simple **reflexes** on its own, like pulling your hand off a hot stove.

Thirty-one pairs of **spinal nerves** branch off the cord to reach the body. Cord damage blocks messages at the injury, so a person can lose movement and feeling below that point.

The cranial nerves

The head and face get their own wiring. The **cranial nerves** are 12 pairs of nerves that connect directly to the brain instead of the spinal cord, passing through small holes in the skull. Nerves I and II attach to the forebrain; the other ten (III through XII) attach to the brainstem, so cranial nerve problems are a clue that the brainstem may be injured. (One small exception: most of the accessory nerve, XI, actually starts in the top of the spinal cord and travels up into the skull before leaving it.) In the table, notice three groups: three nerves are purely sensory, five are purely motor, and four carry both.

#	Name	Main job	Type
I	Olfactory	Smell	Sensory
II	Optic	Vision	Sensory
III	Oculomotor	Moves most eye muscles, lifts the eyelid, narrows the pupil	Motor
IV	Trochlear	Moves one eye muscle (eye looks down and in)	Motor
V	Trigeminal	Feeling in the face; chewing muscles	Both
VI	Abducens	Moves the eye outward	Motor
VII	Facial	Facial expressions; taste from the front of the tongue	Both
VIII	Vestibulocochlear	Hearing and balance	Sensory
IX	Glossopharyngeal	Throat sensation, gag reflex, taste from the back of the tongue	Both
X	Vagus	Heart, lungs, and gut; swallowing and voice	Both
XI	Accessory	Shrugging the shoulders, turning the head	Motor
XII	Hypoglossal	Moving the tongue	Motor

Vagus means "wandering": the vagus nerve (X) wanders down to the heart, lungs, and gut, carrying much of the "rest and digest" signaling in Section 4.12.

Twelve is a lot, and that's okay



Nobody learns all 12 cranial nerves in one sitting. Start with ones you can test on yourself: I (smell), II (sight), VII (smile), VIII (hearing), and XII (stick out your tongue). Then add the eye-movement trio, III, IV, and VI.

4.10 Protecting and Feeding the Brain

The brain is soft and easily damaged, yet it survives a lifetime of bumps, headers, and falls, thanks to layers of protection, a fluid cushion, and a rich blood supply.

The meninges

Think of packing a fragile phone: a hard box, padding, then a snug sleeve. Outside the brain is the skull (and, for the spinal cord, the backbone). Inside the bone are the **meninges**, three membranes that wrap the brain and spinal cord:

1. The **dura mater** ("tough mother"): the thick outer layer against the bone.
2. The **arachnoid mater**: the middle layer, named for its spiderweb-like look.
3. The **pia mater** ("tender mother"): a delicate layer clinging to every fold of the brain.

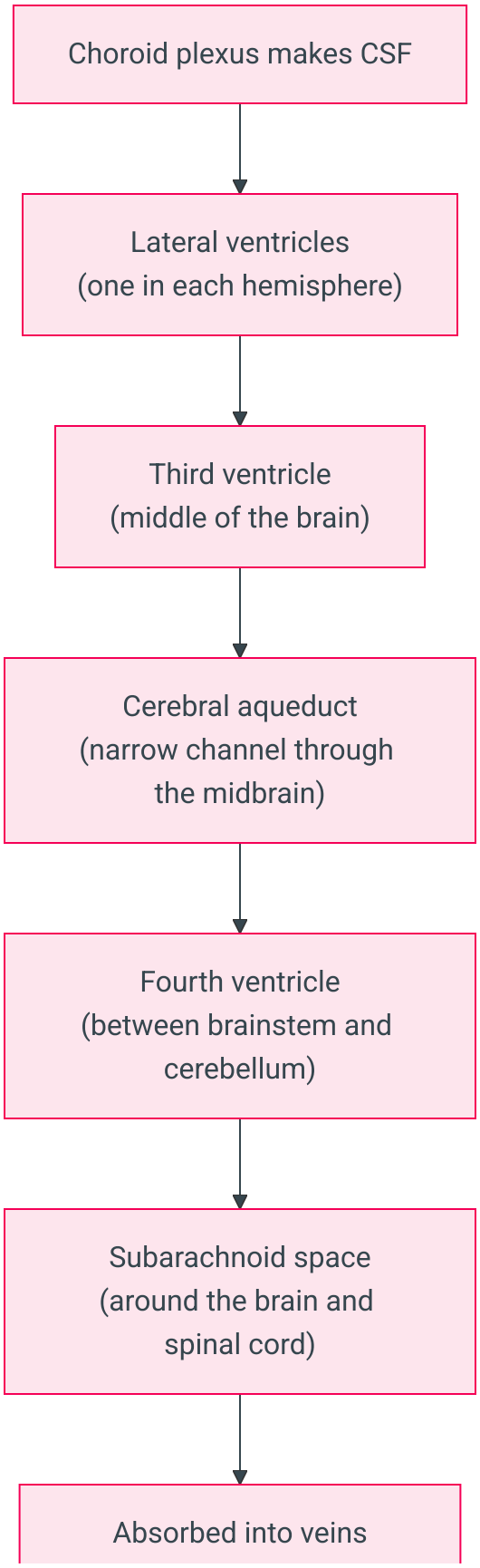
The space under the arachnoid, the subarachnoid space, is filled with fluid. Infection of the meninges is called meningitis.

The ventricles and cerebrospinal fluid

The brain floats. Deep inside are four connected spaces called **ventricles**: two large lateral ventricles (one per hemisphere), a thin third ventricle in the middle, and a fourth ventricle between the brainstem and cerebellum. They hold **cerebrospinal fluid (CSF)**, a clear liquid made from the watery part of blood. Together, the **ventricles and CSF** form the brain's built-in fluid system.

CSF is made mainly by the **choroid plexus**, a blood-vessel-rich tissue inside the ventricles. It cushions the brain, carries nutrients, and washes away waste. An adult has only about 150

mL of CSF (about 5 ounces), yet makes about 400 to 600 mL per day, so the supply is replaced several times daily. Here is the route CSF travels:


Choroid plexus makes CSF
Lateral ventricles
(one in each hemisphere)
Third ventricle
(middle of the brain)
Cerebral aqueduct
(narrow channel through
the midbrain)
Fourth ventricle
(between brainstem and
cerebellum)
Subarachnoid space
(around the brain and
spinal cord)
Absorbed into veins

through the arachnoid villi

If CSF is blocked, for example in the narrow aqueduct, it backs up. The ventricles swell and press on the brain, a condition called **hydrocephalus**. The most common treatment is a **shunt**, a thin tube that drains extra fluid to another part of the body, such as the abdomen.

The cerebral blood supply

Your brain is about 2% of your body weight but uses about 20% of the oxygen and calories your body consumes, so it needs a constant flow of blood. This **cerebral blood supply** arrives through two pairs of arteries in the neck:

- The two **internal carotid arteries** run up the front of the neck and feed the front and middle of the brain.
- The two **vertebral arteries** run up through the neck bones and join to form the **basilar artery**, which feeds the brainstem, cerebellum, and back of the cerebrum.

At the base of the brain, these vessels connect in a ring called the **circle of Willis**, named after the English physician Thomas Willis (the complete, textbook version of the ring is less common than you might think: one imaging study of 525 healthy adults found it in only about 21 percent of people, and other studies report different rates, Jalali Kondori et al., 2017). From it, three pairs of large arteries fan out over the cerebrum:

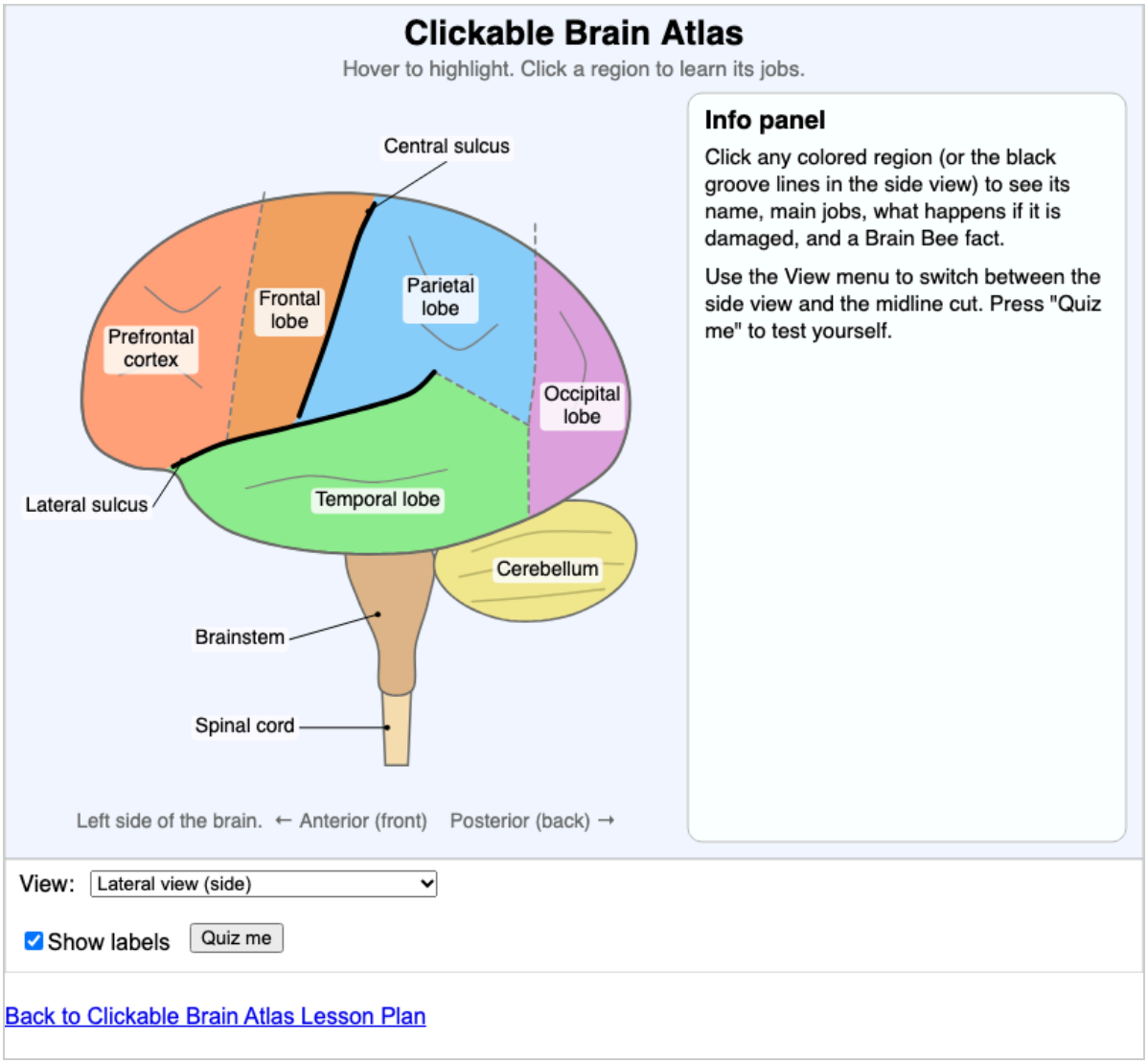
Artery	Main territory	A blockage can cause
Anterior cerebral artery	Inner (medial) surface of the frontal and upper parietal lobes	Weakness and numbness of the opposite leg
Middle cerebral artery	Most of the outer (lateral) surface of the hemisphere	Weakness of the opposite face and arm; language problems if on the left
Posterior cerebral artery	Occipital lobe and lower temporal lobe	Loss of part of the visual field

When a brain blood vessel is blocked or bursts, the result is a **stroke**. Knowing which artery feeds which lobe lets doctors predict symptoms, which you will practice in Chapter 14.

4.11 Put It Together: The Clickable Brain Atlas

You now have the vocabulary for the whole tour. Time to find the structures yourself.

Diagram: Clickable Brain Atlas



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch04-brain-atlas/

Open the Clickable Brain Atlas fullscreen

MicroSim specification: Clickable Brain Atlas

Type: microsim **sim-id:** ch04-brain-atlas
Library: p5.js
Status: Implemented
Bloom Level: Remember
Bloom Verb: identify
Learning Objective: The learner will identify 19 major brain structures and landmarks in a lateral view and a midsagittal view, with at least 80% accuracy in quiz mode.

Content: Lateral view (10): prefrontal cortex, frontal lobe (motor areas), parietal, temporal, and occipital lobes, cerebellum, brainstem, spinal cord, central sulcus, lateral sulcus. Midsagittal view (11): cerebrum, corpus callosum, thalamus, hypothalamus, pituitary, midbrain, pons, medulla, cerebellum, fourth ventricle, spinal cord. Each panel: name, main jobs, "If damaged," Brain Bee fact.

Controls: a View menu (lateral or midsagittal), a Show labels checkbox, a Quiz me button, and a Next question button.

Behavior: Hover highlights and names a region; click opens the info panel. Quiz mode hides labels and asks every structure in the view once, in random order, one attempt each. A wrong click names what was clicked, gives a location hint, and highlights the correct region in gold. The prefrontal cortex counts as correct for "Frontal lobe." A running score is shown.

Evidence of Mastery: quiz score of at least 80% in each view on the first attempt.

Start in the **Lateral view**. Before clicking, predict which region Gage's iron damaged and what its "If damaged" line will say. Then switch to the **Midsagittal view** and notice how the corpus callosum arches over the thalamus, the hypothalamus sits below and in front of the thalamus, and the three brainstem parts stack on the spinal cord.

When ready, press **Quiz me**. Labels disappear and the atlas names a structure for you to find. Aim for at least 80% in both views. If you miss one, find the landmark that would have helped: the central sulcus, lateral sulcus, or corpus callosum.

4.12 The Autopilot: The Autonomic Nervous System

It's the final minute of Maya's soccer game, and she steps up for a penalty kick. Her heart pounds, her mouth goes dry, and her pupils widen. She didn't decide any of this. It was controlled by the **autonomic nervous system**, the part of the nervous system that runs the internal organs without conscious effort: heart rate, breathing, blood pressure, digestion,

sweating, and pupil size. It acts on heart muscle, smooth muscle (in blood vessels and the gut), and glands.

It has two main branches that work like a car's gas pedal and brake. The **sympathetic** branch prepares the body for action, the "fight or flight" response. The **parasympathetic** branch calms the body and handles maintenance, "rest and digest." Most organs receive both, and the balance sets the organ's activity. The hypothalamus and brainstem are the drivers.

Sympathetic neurons leave the middle (thoracic and lumbar) spinal cord. Parasympathetic neurons leave the brainstem, through cranial nerves such as the vagus, and the bottom (sacral) spinal cord. At the target organ, most sympathetic neurons release norepinephrine, while parasympathetic neurons release acetylcholine, neurotransmitters from Chapter 3.

Now that you've seen both branches, the table below compares **sympathetic vs parasympathetic** effects:

Feature	Sympathetic ("fight or flight")	Parasympathetic ("rest and digest")
Heart	Beats faster and harder	Slows down
Pupils	Widen (dilate)	Narrow (constrict)
Saliva	Decreases (dry mouth)	Increases
Digestion	Slows down	Speeds up
Exits the CNS from	Thoracic and lumbar spinal cord	Brainstem and sacral spinal cord

After Maya scores, her parasympathetic system takes over. Her heart slows, and she realizes she's starving. A third part, the **enteric nervous system**, is a web of neurons in the gut wall that manages digestion; it has hundreds of millions of neurons, about as many as the spinal cord or more.

At the Bedside: Two Frontal Lobes, Nearly 180 Years Apart

Meet the patient

Jordan is a 19-year-old college student. Two months ago, his car was hit head-on and his forehead struck the steering wheel. He was unconscious for several minutes and spent a week in the hospital. Now he walks, talks, and remembers facts normally, but his parents are worried. He skips classes because he "didn't get around to them," starts projects and never finishes them, makes crude jokes in front of his grandmother, and spent a whole paycheck on an impulse purchase. "It's like he's Jordan, but not Jordan," his mother says.

What the doctor checks: On the neurological exam, Jordan's strength, reflexes, coordination, sensation, vision, and cranial nerves are all normal, and his memory for facts is good. On tests of executive function, though, he struggles to switch rules in a card-sorting task, plans a multistep errand poorly, and acts before thinking. His emergency CT scan showed bruises (contusions) on the underside of both frontal lobes, and a later MRI shows them more clearly.

Where is the problem? (localization): Normal strength and sensation clear the motor and touch strips around the central sulcus. Normal coordination clears the cerebellum, normal cranial nerves clear the brainstem, and normal vision clears the occipital lobe. A change in planning, impulse control, and social behavior with everything else intact points to the **prefrontal cortex**, especially its lower part above the eye sockets (the orbitofrontal region).

Diagnosis: Traumatic brain injury with contusions of both frontal lobes, causing problems with executive function and behavior. Doctors sometimes call this pattern a dysexecutive syndrome.

Why it happens: When a moving head stops suddenly, the soft brain keeps moving and hits the inside of the skull. The skull floor under the frontal and temporal lobes has rough, bony ridges, so the undersides and tips of these lobes are among the most common places for brain bruises. Damage to the prefrontal cortex and its white-matter connections disrupts the brain's executive system while sparing movement and the senses. Phineas Gage showed a similar pattern: his iron passed through the left frontal lobe and missed the motor and sensory strips, so he could walk and talk while his behavior changed.

Treatment today: Early care focuses on survival and preventing further damage: intensive care, monitoring swelling and pressure inside the skull, and surgery if needed. Recovery then depends on **rehabilitation** by a team that may include neurologists, neuropsychologists, occupational and speech-language therapists, and counselors.

Cognitive rehabilitation teaches strategies like breaking tasks into steps, using checklists and reminders, and pausing to check a plan before acting. Many people improve over months to years, although some changes can last.

What's new in research: Goal Management Training teaches patients to stop, state their goal, break it into steps, and check their progress. A 2019 meta-analysis of 21 publications found small to moderate improvements in executive function that usually lasted at follow-up (Stamenova & Levine, 2019, *Neuropsychological Rehabilitation*). Historians suggest the routine of Gage's stagecoach job may have helped him in a similar way, by structuring his days (Macmillan & Lena, 2010).

Your turn: diagnose a variation

A 58-year-old woman suddenly cannot move her right arm well, the right side of her face droops, and her speech comes out slow and broken, though she understands what people say. Her personality and judgment seem unchanged. Where is the problem?

Answer: Right-sided weakness means the **left** hemisphere (contralateral control). Face and arm weakness points to the **primary motor cortex**, just in front of the central sulcus. Slow, effortful speech with good understanding points to **Broca's area** in the left frontal lobe. Both lie in the territory of the left **middle cerebral artery**, so a stroke there is a likely cause. Unlike Jordan's injury, this damage is in the back of the frontal lobe, not the prefrontal cortex.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Some people are "left-brained" (logical) and others are "right-brained" (creative).
Reality: Some functions lean to one side; in most people, language relies more on the left hemisphere. But a 2013 study of brain scans from more than 1,000 people aged 7 to 29 found no evidence that individuals have a stronger left-brain or right-brain network overall (Nielsen et al., 2013). Everyone uses both hemispheres.

Myth: A bigger brain means a smarter person.
Reality: A 2015 meta-analysis of more than 8,000 people found a correlation of about 0.24 between brain volume and IQ, so brain size explains only about 6% of IQ differences

(Pietschnig et al., 2015). The authors warned against treating brain size as a stand-in for intelligence.

Myth: After his accident, Phineas Gage became a violent, drunken drifter for the rest of his life.
Reality: Those details aren't in the original records. Gage drove stagecoaches in Chile for years, and historians think he made a substantial social recovery (Macmillan & Lena, 2010).

Myth: Each brain function lives in exactly one spot, like files in labeled drawers.
Reality: Localization is real for basic functions like movement and vision, but complex abilities depend on networks connected by white matter. Gage's injury damaged a larger share of white matter than gray matter.

Brain Bee Practice

1. Which sulcus separates the frontal lobe from the parietal lobe, and which two strips of cortex lie on either side of it?

The **central sulcus**. The primary motor cortex (precentral gyrus) lies just in front of it, and the primary somatosensory cortex (postcentral gyrus) lies just behind it.

2. Name the three parts of the brainstem from top to bottom, and give one vital function of the lowest part.

Midbrain, pons, and medulla oblongata. The medulla controls breathing, heart rate, and blood pressure.

3. Which is the only sense that does not pass through the thalamus before reaching the cortex?

Smell (olfaction).

4. A patient has a clumsy, shaky left arm but normal strength. Which structure is most likely damaged, and on which side?

The **left** half of the cerebellum. Unlike the cerebrum, each half of the cerebellum coordinates the same side of the body.

5. Name the three layers of the meninges from outside to inside.

Dura mater, arachnoid mater, and pia mater.

Exercises

Remember

1. List the four lobes of the cerebral cortex and give one main function of each.
2. Name the structure that connects the left and right hemispheres.

Answer

1. Frontal: movement, planning, and judgment. Parietal: touch and body position. Temporal: hearing, language understanding, and memory. Occipital: vision.
2. The corpus callosum.

Understand

1. Explain why "dorsal" points toward the top of the brain but toward the back of the spinal cord.
2. Explain why someone with prefrontal cortex damage might score normally on many intelligence tests yet struggle with everyday life.

Answer

1. Humans stand upright, so the nervous system bends at the top of the brainstem. "Dorsal" is defined relative to the nervous system, so it points up in the brain but backward in the spinal cord.
2. The prefrontal cortex handles executive functions like planning, impulse control, and social judgment. Many tests measure knowledge in a structured setting, where these skills matter less; daily life requires people to organize their own behavior.

Apply

1. A patient has numbness on the left side of the body but normal strength. Predict which lobe and which hemisphere are damaged.
2. A child's scan shows very large lateral and third ventricles but a normal fourth ventricle. Using the CSF pathway, predict where the blockage is.

Analyze

1. Compare Maya's body responses before and after her penalty kick. For each, name the autonomic branch responsible and how it helps her.
2. The 1994 and 2004 reconstructions of Gage's injury disagreed about whether one or both frontal lobes were damaged. What difference in their methods could explain this?

Evaluate

1. A brain-training app claims that its games will "activate your creative right brain." Judge this claim using evidence from this chapter.
2. A textbook calls Gage "a man who became a violent drifter after his accident." Assess this using the historical evidence, and rewrite the sentence accurately.

Create

1. Design a one-page "brain map" study guide that uses one everyday analogy (a city, a school, or a sports team) for at least six structures from this chapter.

2. Write a short bedside case about damage to one structure from this chapter, with symptoms, exam findings, and localization reasoning. Trade with a classmate and diagnose each other's patient.

Key Takeaways

- Fixed direction words (anterior/posterior, dorsal/ventral, medial/lateral) and three planes (sagittal, coronal, horizontal) describe any spot in the brain.
- Gray matter holds cell bodies and synapses; white matter holds myelinated axons. In the cerebrum, gray is outside. In the spinal cord, it is inside.
- The cerebral cortex has four lobes. The central sulcus and lateral sulcus are the main landmarks, with "movement in front, feeling behind" the central sulcus.
- The cerebrum controls the opposite side of the body, but each half of the cerebellum coordinates the same side.
- The thalamus relays sensory signals (except smell), the hypothalamus maintains homeostasis and controls the pituitary, and the brainstem runs life support.
- The brain is protected by the skull and meninges, cushioned by CSF, and fed by the carotid and vertebral arteries. Sympathetic and parasympathetic branches of the autonomic nervous system run the organs on autopilot.
- Gage's left frontal injury showed that the prefrontal cortex shapes planning and behavior, but his recovery was better than the legend claims.

Tour complete!



You just toured the whole brain! In Chapter 5, we'll follow one sense, vision, from the eye all the way to the occipital lobe.

Chapter 5: Vision

Summary

Vision starts when photoreceptors in the retina turn light into electrical signals, a process called sensory transduction. The retina then cleans up and compresses that signal, and the optic nerves carry it to the brain along a pathway with one famous twist: at the optic chiasm, half the fibers cross to the other side. Because the pathway is laid out so precisely, a doctor can test which parts of a patient's vision are missing and work backward to find the damage. This chapter ends with a patient whose "clumsiness" turns out to be a pituitary tumor pressing on the optic chiasm.

Concepts Covered

1. Sensory Transduction
2. Eye and Retina
3. Photoreceptor
4. Rods and Cones
5. Color Vision
6. Optic Nerve
7. Optic Chiasm
8. Visual Pathway
9. Primary Visual Cortex
10. Receptive Field
11. Visual Field
12. Visual Field Defect
13. Ventral and Dorsal Streams
14. Pituitary Tumor

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters
- Chapter 4: A Tour of the Brain: Neuroanatomy (especially the occipital, temporal, and parietal lobes, the thalamus, and the cranial nerves)

Welcome to the Brain's Biggest Sense



I'm Ply, a sea slug, and yes, I have two tiny eyes! Yours are far fancier, and the wiring behind them is one of the best maps in all of neuroscience. Learn this one pathway well, and you'll be able to look at a patient's vision test and say where in the brain the problem is.

5.1 Maya's Blind Side

Maya is at Tuesday soccer practice. She's dribbling up the right wing with her eyes locked on the ball. Her teammate Jordan sends a pass in from the left. Maya doesn't react until the ball is almost at her feet, and it bounces off her shin. "Didn't you see that?" Jordan yells. Maya honestly isn't sure. She saw *something* move, but it was a blur.

That night, studying for the Brain Bee, she starts to worry. Is something wrong with her eyes, or with her brain? The eyes catch light, but the brain builds the picture, and a problem anywhere along that route can steal part of your vision. By the end of this chapter, you'll know how to tell the difference, and whether Maya needs to worry.

5.2 Turning Light into Language: Sensory Transduction

Think about a solar panel. Sunlight hits it, and out comes electricity that wires can carry. Your senses do the same job. The world sends you light, sound, pressure, heat, and chemicals, but neurons speak only one language: electrical signals, like the action potentials from Chapter 2. **Sensory transduction** is the process of converting a physical or

chemical stimulus into an electrical signal in a nerve cell. The cells that do this are called sensory receptors.

Every sense has its own receptor type: light-sensitive cells for vision, and hair cells, nerve endings, and chemical-sensing cells for the senses in Chapter 6. Vision is a great place to start, because scientists know its transduction steps in fine detail.

5.3 The Eye and Retina

The front of the eye: a focusing system

People often say the eye is "like a camera," and the front half really is. Light passes through the **cornea** (the clear dome at the front), the **pupil**, and the **lens**. The cornea and lens bend the light into a sharp image on the back of the eye, and tiny muscles reshape the lens to focus near or far.

Because a lens flips images, the picture on the back of your eye is **upside down and reversed left to right**. Your brain doesn't "flip it back." It simply learns what each spot on the retina means. Keep this flip in mind. It matters a lot for vision loss.

The back of the eye: a thin sheet of brain

The **retina** is the thin layer of nerve tissue that lines the back of the eye and turns light into nerve signals. Surprisingly, the retina grows out of the brain in the embryo. When an eye doctor shines a light into your eye, they're looking at a piece of your central nervous system.

The retina has layers of five main kinds of neurons. The first three pass the signal forward, in this order, and the last two link cells side to side:

1. **Photoreceptors** catch light (the next section is all about them).
2. **Bipolar cells** pass the signal forward.
3. **Ganglion cells** collect the signal and send it out of the eye. Their axons form the optic nerve.
4. **Horizontal cells** connect photoreceptors and bipolar cells side to side.
5. **Amacrine cells** connect bipolar and ganglion cells side to side.

The side-to-side cells let neighbors compare notes, which is how the retina starts finding edges (Section 5.6).

Oddly, the retina is built "inside out." Light passes through the ganglion and bipolar cell layers before reaching the photoreceptors at the back. In one small spot, those layers are pushed aside. That spot is the **fovea**, a tiny pit in the center of the retina packed with cones. It gives you your sharpest vision. When you "look at" something, you're aiming your foveas at it.

The blind spot

The ganglion cell axons leave the eye at the **optic disc**, where blood vessels also enter. The optic disc has no photoreceptors, so each eye has a **blind spot**. You don't notice it because the other eye covers that spot and your brain fills in the gap.

Find Your Own Blind Spot



Draw an X and, a few finger-widths to its right, a dot. Close your left eye, stare at the X with your right eye, and slowly move the page toward your face: at one distance the dot vanishes, because its image has landed on your optic disc.

5.4 Photoreceptors: Rods and Cones

Two cameras in one eye

Imagine owning two cameras. One is a night-vision camera that works in near darkness but takes grainy, black-and-white pictures. The other takes sharp color photos, but only in plenty of light. Your retina carries both.

A **photoreceptor** is a neuron in the retina that is specialized to detect light. Humans have two kinds, called **rods and cones**:

- **Rods** work in dim light. The human retina has about 120 million of them. They are extremely sensitive: a fully dark-adapted rod can respond to a single particle of light, called a photon. But rods don't tell colors apart, and they give blurry, low-detail vision. In

bright daylight they are "maxed out" and stop signaling changes. Rods are spread across the retina but are missing from the fovea.

- **Cones** work in bright light and give us sharp detail and color. There are about 6 million cones. They are packed most tightly in the fovea, with a thinner scattering in the rest of the retina.

(Numbers from the OpenStax textbook *Introduction to Behavioral Neuroscience*.) Rods outnumber cones about 20 to 1, yet your sharpest vision depends on the smaller cone team.

Feature	Rods	Cones
Number per retina	About 120 million	About 6 million
Best light level	Dim (night)	Bright (day)
Color?	No	Yes (three types)
Detail	Low	High
Where most dense	Outside the fovea	In the fovea

Now you can solve part of Maya's mystery. Jordan's pass came from far to her left, so its image landed far from her fovea. That part of the retina has few cones, and each of its ganglion cells collects signals from a wide area. So her side vision was blurry but good at noticing motion. That's why she saw "something move." This isn't a disease. To see details, you have to bring the image onto your fovea.

How a photoreceptor catches light

Here is where sensory transduction happens. Each rod is stuffed with a light-catching molecule called **rhodopsin**. Rhodopsin has two parts: a protein called opsin and a small molecule called retinal, which your body makes from vitamin A.

In the dark, retinal has a bent shape. When it absorbs a photon, it snaps straight. That shape change switches on the opsin protein, which starts a chain reaction inside the cell. The end result is that sodium channels in the cell membrane close.

This part surprises most people. Most neurons get *more* active when stimulated. Photoreceptors do the opposite:

- **In the dark,** sodium channels are open. Positive sodium ions flow in, so the photoreceptor sits at about −40 mV. That is less negative than the −70 mV resting potential you learned for a typical neuron. In this state, the photoreceptor releases its neurotransmitter, glutamate, all the time.
- **In the light,** sodium channels close. The cell becomes more negative (it **hyperpolarizes**), and it releases *less* glutamate.

So a photoreceptor's message is "less glutamate means light," and brighter light closes more channels. A nerve signal doesn't always mean "fire more." What matters is the *change*, and the bipolar cells downstream know how to read it.

5.5 Color Vision

Three cone types

Color vision is the ability to tell apart lights by their wavelength, which we experience as different colors. Light comes in a range of wavelengths. Shorter visible wavelengths look blue to us, and longer ones look red.

A single cone cannot tell color by itself. A cone just counts the photons it catches. A few photons at its favorite wavelength and many photons at a wavelength it barely absorbs can produce the same response. With one cone type, you'd see only shades of gray.

The fix is to compare. Humans have three types of cones, each with a slightly different opsin protein that is best at catching a different part of the spectrum:

Cone type	Nickname	Peak sensitivity
S (short wavelength)	"Blue" cone	About 420 nm
M (medium wavelength)	"Green" cone	About 534 nm
L (long wavelength)	"Red" cone	About 564 nm

For comparison, rod rhodopsin peaks near 498 nm. (A nanometer, nm, is one billionth of a meter.) These values are from OpenStax.

Your brain works out color by comparing how strongly the three cone types respond to the same patch of light. If S cones respond strongly and L cones barely respond, the light is toward the blue end. A TV screen uses this trick: mixing just red, green, and blue pixels can make a wide range of colors. Most mammals, including dogs and cats, have only two cone types, so your pet doesn't see colors the way you do.

Opponent colors

The three cones are only the first step. Neurons in the retina and thalamus then compare the cones in "opponent" pairs. Some cells take the difference between L and M cones, a red versus green signal. Others compare S cones against L and M cones added together, a blue versus yellow signal. In the 1800s, these were rival theories: Hermann von Helmholtz argued for three color receptors (trichromacy), and Ewald Hering argued for opposing color pairs. Both turned out to capture part of the truth, at different stages: three cone types at the start, opponent comparisons after that (Shevell and Martin, *Journal of the Optical Society of America A*, 2017). Opponent pairs help explain afterimages. Stare at a red square and then at a white wall, and you see a greenish afterimage. The parts of the system that signal red have adapted (tired out), so the green side of the pair "wins" for a moment.

Color blindness

Some people are born with only two working cone types, or with one cone pigment that is slightly off. They can't tell apart some colors that most people see as different. The most common type makes red and green hard to tell apart.

The National Eye Institute reports that about 1 in 12 men have a color vision deficiency. OpenStax gives about 8% of males and 0.4% of females for the red-green type. Why the big difference? The genes for the red and green cone pigments sit on the X chromosome. Males have only one X, so one faulty copy is enough to cause color blindness. Females have two X chromosomes, so a working copy on the other X usually covers for a faulty one.

5.6 Receptive Fields: The Retina Finds Edges

A retina that edits

The retina doesn't send every "pixel" to the brain. Each eye has over 100 million photoreceptors but only one to two million ganglion cells, so the retina has to summarize. What it sends is mostly news about **edges**, places where light changes to dark.

To see how, we need one idea. A **receptive field** is the specific area of the sensory world that can change a particular neuron's activity. For a ganglion cell, that's a small patch of the visual scene. (The idea started with touch: a nerve fiber in your skin responds only to touch on its own small patch of skin.)

Center and surround

In 1953, Stephen Kuffler recorded from single ganglion cells in the cat retina. He found that their receptive fields are circles with two zones: a **center** and a **surround** ring. The two zones have opposite effects:

- An **on-center** cell fires a burst when light hits its center, and is quieted by light on its surround.
- An **off-center** cell is the reverse. It fires most to a dark spot surrounded by light.

When the whole receptive field is lit evenly, the center says "fire!" and the surround says "stop!" They mostly cancel, and the cell barely responds. But when an edge puts light on the center and darkness on part of the surround, the cell responds strongly. Horizontal cells help build the surround. That's why a cartoon of a few lines is easy to recognize: your visual system cares more about edges than overall brightness.

Out of the eye: the optic nerve

Bipolar cells are so short that they signal with graded voltage changes, not action potentials. Ganglion cells must send signals a long way, so they are the first retinal cells to fire action potentials.

The **optic nerve** is the bundle of ganglion cell axons that carries visual signals from one eye to the brain. You met it in Chapter 4 as cranial nerve II. Most of its fibers head toward the thalamus for conscious vision. Some go to the midbrain to help steer the eyes. A small group, fewer than 1 in 100 ganglion cells in the human retina, sense light themselves and report brightness to the brain's body clock.

5.7 The Visual Field: What You Can See Right Now

Hold your gaze on one spot straight ahead. Everything you can see without moving your eyes, from the center out to the edges, is your **visual field**. Doctors split it into halves using a vertical line through the point you're looking at:

- the **left visual field** (everything to the left of that line)
- the **right visual field** (everything to the right)

Each eye has its own visual field, and the two overlap a lot. Cover your right eye: your left eye still sees things on both your left and your right. Each eye's field has an inner part, toward the nose (the **nasal** field), and an outer part, toward the temple (the **temporal** field).

Now combine this with the upside-down, reversed image from Section 5.3. Light from your **left** visual field lands on the **right** half of each retina. For the left eye, that's the half closest to the nose, the **nasal retina**. For the right eye, it's the outer half, the **temporal retina**.

Read that twice. It's the most important idea in this chapter for understanding vision loss:

- **Temporal visual field → nasal retina**
- **Nasal visual field → temporal retina**

Retina Halves and Field Halves Are Opposites



A classic mistake on lesion questions is mixing up "temporal retina" with "temporal field." Because the lens flips the image, the temporal (outer) field always lands on the nasal (inner) retina, and the nasal field lands on the temporal retina.

5.8 The Visual Pathway

The crossing rule

The **visual pathway** is the chain of nerve fibers and brain areas that carries signals from the retina to the visual cortex. First, an analogy.

Picture two delivery trucks, one from each eye, heading to a city with a Left Warehouse and a Right Warehouse. The rule: packages about the left side of the world go to the Right Warehouse, and packages about the right side go to the Left Warehouse. Each truck carries both kinds, so at a big intersection the trucks swap half their loads.

That intersection is the **optic chiasm**, the X-shaped spot at the base of the brain where the two optic nerves meet and some of their fibers cross to the other side. The rule is:

- Fibers from the **nasal** half of each retina **cross** to the other side.
- Fibers from the **temporal** half of each retina **stay** on the same side.

Since the nasal retina of the left eye and the temporal retina of the right eye both see the left visual field, this rule sends all left-field information to the right side of the brain. Roughly half the fibers cross. The result: **each side of the brain sees the opposite half of the world, using input from both eyes.**

One Rule Explains Almost Everything



Nasal fibers cross, temporal fibers stay. If you remember that one line, plus the fact that the retina sees the world flipped, you can figure out every lesion pattern in this chapter instead of memorizing them.

After the chiasm

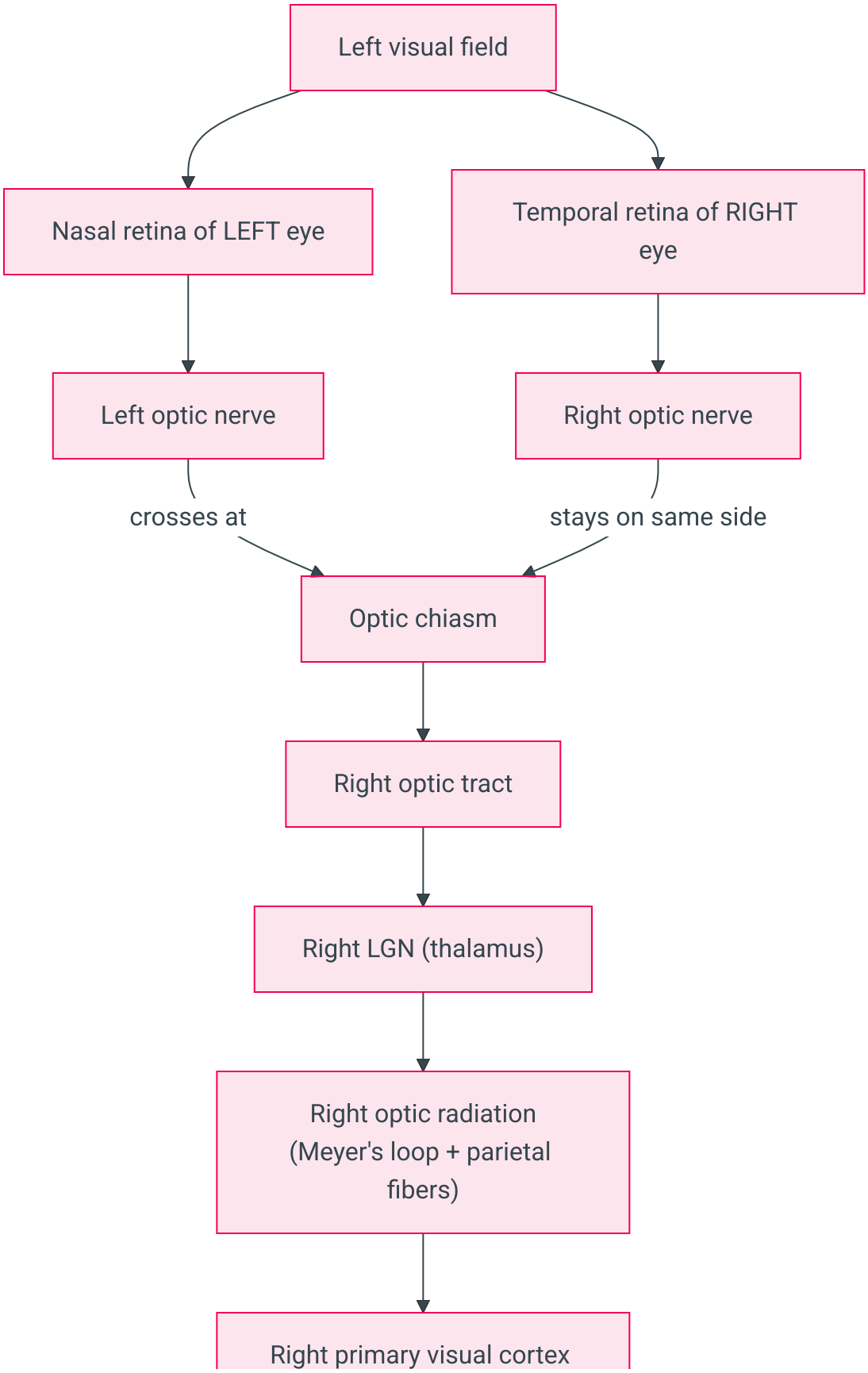
After the chiasm, the bundle on each side is called an **optic tract**. Each tract holds fibers from both eyes, all about the opposite visual field. It ends in the **lateral geniculate nucleus (LGN)**, a six-layered part of the thalamus, the sensory relay station from Chapter 4. The two eyes' fibers go to separate LGN layers, so their signals are still kept apart here.

From the LGN, a broad fan of axons called the **optic radiation** sweeps back to the primary visual cortex in the occipital lobe. It has two main parts:

- The upper fibers travel under the **parietal lobe**. They carry the **lower** part of the opposite visual field.
- The lower fibers take a detour. They loop forward into the **temporal lobe** before turning back. This detour is called **Meyer's loop**, and it carries the **upper** part of the opposite

visual field. (The image on the retina is upside down, so lower retina means upper field.)

The flowchart below traces the path for information about the *left* visual field.


Left visual field
Nasal retina of LEFT eye
Temporal retina of RIGHT eye
Left optic nerve
Right optic nerve
crosses at
stays on same side
Optic chiasm
Right optic tract
Right LGN (thalamus)
Right optic radiation (Meyer's loop + parietal fibers)
Right primary visual cortex

(V1)

5.9 The Primary Visual Cortex

Where seeing becomes shapes

The **primary visual cortex**, also called **V1**, is the first area of the cerebral cortex to receive visual signals from the thalamus. It lies in the occipital lobe, mostly along the inner surface between the two hemispheres. You may also see it called "striate cortex" because it looks striped under a microscope.

V1 keeps a map of the visual field, called a **retinotopic map**: neighboring points in the world are handled by neighboring patches of V1. The map is stretched in the middle. Because so many ganglion cells serve the fovea, it gets a huge share of V1. Your center of gaze gets the most brainpower.

Hubel and Wiesel's lines and edges

In 1958, David Hubel and Torsten Wiesel began recording from single neurons in the visual cortex of cats, and later monkeys. Small spots of light, which work well for retinal cells, often did little. Then, as Hubel told the story, they slid a glass slide out of their projector. Its faint straight edge swept across the screen, and the neuron suddenly fired rapidly.

They had found that many V1 neurons respond best to **lines or edges at a particular angle**. One cell might love vertical edges, and its neighbor might prefer edges tilted slightly. They described "simple cells," which need the edge in an exact spot, and "complex cells," which respond to a correctly tilted edge anywhere in their receptive field. Many complex cells also care about the direction the edge moves.

Their explanation shows receptive fields building on each other. Wire several center-surround cells lined up in a row to one V1 cell, and that cell fires most when a bar at just the right angle covers the whole row. In 1981, Hubel and Wiesel shared the Nobel Prize in Physiology or Medicine for their discoveries about how the visual system processes information. (Roger Sperry received the other half of that year's prize for his work on the two brain hemispheres.)

Cell type	Receptive field shape	Best stimulus
Retinal ganglion cell	Circle with center and surround	Spot of light or dark (an edge on the center)
V1 simple cell	Long, narrow zones	Bar or edge at one angle, in one exact spot
V1 complex cell	Larger area	Bar or edge at one angle, anywhere in the field, often moving

5.10 Ventral and Dorsal Streams: What and Where

V1 is only the start. Visual information then flows into many other areas, organized into two main routes called the **ventral and dorsal streams**.

- The **ventral stream** runs from the occipital lobe down into the lower temporal lobe. It answers **"What is it?"** It recognizes objects, colors, and faces. Deep in this stream, some neurons respond best to faces, and an area in the human temporal lobe called the fusiform face area becomes active when we look at faces.
- The **dorsal stream** runs from the occipital lobe up into the parietal lobe. It answers **"Where is it, and how do I act on it?"** It tracks position and movement. One area in this stream, called MT, is packed with neurons tuned to the direction of motion.

A memory trick: **v**entral is "**v**hat" (what), and **d**orsal is "where/do."

In 1982, Leslie Ungerleider and Mortimer Mishkin proposed this "what versus where" split, based partly on monkeys with damage to one stream. In 1992, Melvyn Goodale and David Milner argued that the dorsal stream is really about guiding action, or "how." A key patient, known as D.F., had brain damage from carbon monoxide poisoning. She couldn't say how a slot was tilted, yet she could post a card through it at the correct angle. Her "what" system was damaged, but her "how" system still worked.

Maya uses both streams every time she plays. Her ventral stream recognizes Jordan's face and jersey. Her dorsal stream tracks the ball's path and guides her foot to meet it.

5.11 Visual Field Defects: Reading the Map Backward

A **visual field defect** is a missing area in a person's visual field caused by damage somewhere along the visual pathway, from the retina to the cortex. Because the pathway is so orderly, the *shape* of the missing area tells a doctor *where* the damage is. This is called **localization**, and it's one of the most satisfying skills in neurology.

Doctors test the visual field one eye at a time. At the bedside, the doctor may wiggle fingers in each part of the field ("confrontation testing"). A machine called a perimeter is more precise: the patient stares at a center dot and presses a button whenever a faint light flashes.

Visual field maps are always drawn **as the patient sees them**: the left eye's map on the left, with the patient's left side on the left of each circle.

Two words will help you name the patterns:

- **Hemianopia** means loss of half of the visual field (the half on one side of the vertical line).
- **Homonymous** means the *same* side is lost in *both* eyes (for example, the left half in each eye).

Now apply the crossing rule:

- **In front of the chiasm** (optic nerve), only fibers from one eye are present, so the damage affects **only that eye**.
- **At the chiasm**, the damage hits the crossing fibers, which come from both nasal retinas. Nasal retinas see the temporal fields, so both eyes lose their **outer halves**. This is **bitemporal hemianopia**.
- **Behind the chiasm** (optic tract, radiation, or cortex), each side carries the opposite field from both eyes, so damage causes a **homonymous** loss on the opposite side.

Lesion site	Field defect	Typical description
Left optic nerve	Left eye blind; right eye normal	Monocular vision loss

Lesion site	Field defect	Typical description
Center of optic chiasm	Outer half lost in each eye	Bitemporal hemianopia
Right optic tract	Left half lost in both eyes, often uneven between eyes	Left homonymous hemianopia
Left Meyer's loop (temporal lobe)	Upper-right quarter lost in both eyes	Right superior homonymous quadrantanopia ("pie in the sky")
Left parietal optic radiation	Lower-right quarter lost in both eyes	Right inferior homonymous quadrantanopia ("pie on the floor")
Right occipital cortex (V1)	Left half lost in both eyes, center often spared	Left homonymous hemianopia with macular sparing

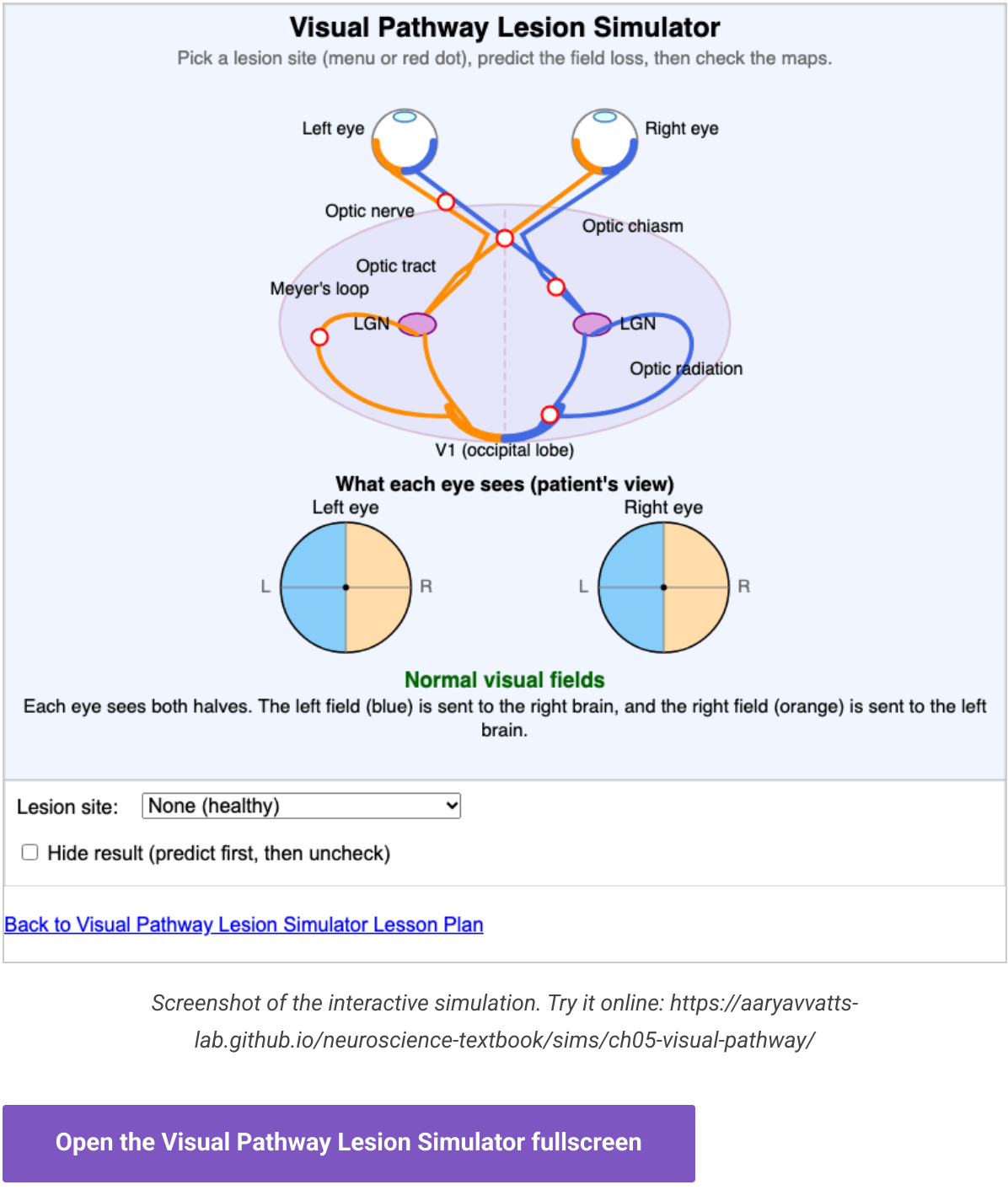
Two details are worth knowing. Meyer's loop damage often comes from surgery in the front of the temporal lobe, and people often don't notice the "pie in the sky" loss at first. Damage to the occipital cortex is usually from a stroke. In many of those patients, the very center of vision, served by the macula (the area around the fovea), is spared. One common explanation is that the tip of the occipital lobe, where central vision is mapped, can get blood from a second artery. But scientists still debate the reason, and sparing doesn't happen in every patient.

Localization Takes Practice



If this feels like a lot, that's normal: doctors in training practice these maps over and over. Use the simulator below, predict before you peek, and the patterns will start to feel obvious.

Diagram: Visual Pathway Lesion Simulator



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch05-visual-pathway/

Open the Visual Pathway Lesion Simulator fullscreen

MicroSim specification: Visual Pathway Lesion Simulator

Type: microsim **sim-id:** ch05-visual-pathway
Library: p5.js
Status: Implemented
Bloom Level: Analyze
Bloom Verb: differentiate
Learning Objective: The learner will differentiate the visual field defects caused by lesions at five sites (left optic nerve, optic chiasm, right optic tract, left Meyer's loop, right occipital cortex) and predict the defect in each eye before revealing it.

Canvas: responsive width; 620 px drawing area plus 85 px control area.

Controls: "Lesion site" menu (None plus the five sites); clickable red dots for the same sites; "Hide result" checkbox for predict-first use.

Behavior: Top-down schematic with retina halves color-coded (blue = left visual field, orange = right visual field). A lesion turns cut fibers gray and dashed, and two field maps (drawn as the patient sees them) shade lost areas. Results: optic nerve = monocular blindness; chiasm = bitemporal hemianopia; optic tract = left homonymous hemianopia; Meyer's loop = right superior homonymous quadrantanopia; occipital cortex = left homonymous hemianopia with macular sparing. Maps are idealized.

What to try. Start with "None" and trace the blue fibers: they come from the *inner* half of the left eye and the *outer* half of the right eye, and both end in the right side of the brain. Then check **Hide result**, pick a lesion, and sketch what each eye will lose before you uncheck the box.

What to notice. Only the optic nerve lesion affects just one eye. Every lesion behind the chiasm takes away the *same side* in both eyes, opposite the damaged side of the brain. Try it in reverse: if both eyes lose the upper-right quarter, which red dot did you click?

Back to Maya

So, does Maya have a field defect? Her optometrist checks each eye separately and finds a full visual field in both. Maya's "blind side" was ordinary peripheral vision. Jordan's pass landed on a part of her retina built for catching motion, not for detail. Her coach's advice, to scan the field with quick glances instead of staring at the ball, is good neuroscience: each glance points her foveas at something new.

At the Bedside: The Driver Who Kept Bumping Door Frames

Meet the patient

Mr. Alvarez is a 47-year-old delivery driver. Over the past year, he keeps bumping his shoulders on door frames and clipping his van's side mirror on gateposts. Twice a car seemed to "come out of nowhere" in the next lane. He also has dull headaches. He can still read signs and his phone, so he figures he's just tired and clumsy. His wife insists he see a doctor.

What the doctor checks: His sharpness of vision (visual acuity) is normal in each eye. During confrontation testing, with one eye covered, he can't see the doctor's fingers wiggling in the *outer* half of his field, and the same thing happens with the other eye. Formal perimetry confirms it: the left eye has lost the left (temporal) half of its field, and the right eye has lost the right (temporal) half. The rest of his eye exam is normal.

Where is the problem? (localization): Only one place holds the fibers for *both* temporal fields: the crossing fibers in the middle of the optic chiasm. An optic nerve lesion would affect only one eye, and a lesion behind the chiasm would take the *same* side from both eyes. The pituitary gland sits just below the chiasm, so a mass growing up from there is the prime suspect.

Diagnosis: An MRI with contrast shows a large **pituitary tumor** pushing up out of its bony pocket and pressing on the optic chiasm. A pituitary tumor is an abnormal growth in the pituitary gland, the small hormone-control gland at the base of the brain. Most are **pituitary adenomas**, which are noncancerous, grow slowly, and don't spread. Since 2022, the World Health Organization's tumor classification has recommended a new name, pituitary neuroendocrine tumor (PitNET), but many doctors and patient guides still say "adenoma" (Tsukamoto and Miki, *Japanese Journal of Radiology*, 2023). Blood tests show that his tumor isn't making extra hormones, so it's called a "nonfunctioning" adenoma. Final diagnosis: **bitemporal hemianopia caused by a nonfunctioning pituitary adenoma compressing the optic chiasm.**

Why it happens: The tumor presses on the crossing fibers in the center of the chiasm. Those fibers come from the nasal half of each retina, which sees the temporal (outer) visual field. So he loses the outer side of each eye's view and bumps into things on *both* sides. His central vision still works, which is why he could read signs and didn't notice the problem for so long.

Treatment today: Because the tumor is pressing on the visual pathway, the standard approach is surgery to remove it. Most pituitary tumors can be removed through the nose and sinuses, called **transsphenoidal surgery**, so no opening in the skull is needed. After surgery, doctors repeat visual field tests and check his hormone levels, because the pituitary may need support. Radiation is an option if the tumor can't be fully removed or grows back. One important exception: tumors that make the hormone prolactin (prolactinomas) are usually treated first with medicines called dopamine agonists, which can shrink the tumor.

What's new in research: Doctors want to predict how much vision will come back after surgery. **Optical coherence tomography (OCT)** is a quick, painless light scan that measures the thickness of the retina's nerve fiber layer (the ganglion cell axons). In a 2015 study of 107 patients, eyes with a normal-thickness layer before surgery usually recovered near-normal visual fields (81%), compared with 37% of eyes where the layer had already thinned (Danesh-Meyer et al., *Journal of Clinical Neuroscience*, 2015). A 2024 study also linked a thicker layer before surgery to better results (Han et al., *PLoS ONE*, 2024). The idea is simple: if the axons are still there, they have a better chance of working again once the pressure is removed.

Your turn: diagnose a variation

A different patient with a pituitary tumor has lost only the **upper outer quarter** of each eye's visual field. Where is the tumor pressing, and why the *upper* field?

Answer: The tumor is pushing on the chiasm from **below**, so it squeezes the lower crossing fibers first. Those fibers come from the lower nasal retina. Because the image on the retina is upside down, the lower nasal retina sees the **upper temporal** field. Doctors often see this pattern early, and it can grow into a full bitemporal hemianopia if the tumor keeps growing.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: The eye works like a camera, and the brain just records the picture.
Reality: Only the front of the eye works like a camera. The retina is part of the brain and

edits the image, mostly reporting edges. Then many brain areas build what you "see": shape, color, motion, and faces. Seeing is constructed by the brain.

Myth: The left eye sends its signals to the right brain, and the right eye to the left brain.
Reality: Each *half of the visual world* goes to the opposite hemisphere. Only the nasal half of each retina crosses at the chiasm. Each hemisphere gets input from **both** eyes about the opposite side of space.

Myth: Damage to the right side of the brain makes you blind in the right eye.
Reality: Damage behind the chiasm on the right takes away the **left** half of the visual field in **both** eyes. Only damage in front of the chiasm (to the eye or optic nerve) causes blindness in one eye.

Myth: Color-blind people see only in black and white.
Reality: Almost all color-blind people see many colors. Most have trouble telling apart certain reds and greens because one cone type is missing or works differently. Seeing no color at all is very rare.

Brain Bee Practice

1. What is the name of the light-absorbing pigment in rods, and what vitamin is part of it made from?

Rhodopsin. Its light-catching part, retinal, is made from vitamin A.

2. Which retinal cells are the first to fire action potentials, and what do their axons form?

Retinal ganglion cells. Their axons bundle together to form the optic nerve (cranial nerve II).

3. A patient has lost the outer half of the visual field in both eyes. Name the defect and the most likely site of the lesion.

Bitemporal hemianopia. The lesion is at the center of the optic chiasm, often from a pituitary tumor pressing on it.

4. Damage to Meyer's loop in the right temporal lobe causes what visual field defect?

A left superior homonymous quadrantanopia, the "pie in the sky" defect: the upper-left quarter is lost in both eyes.

5. Which visual processing stream would be most important for recognizing a friend's face, and which lobe does it travel into?

The ventral ("what") stream, which travels from the occipital lobe into the lower temporal lobe.

Exercises

Remember

1. List, in order, the structures a visual signal passes through from the retina to the primary visual cortex.
2. Name the two types of photoreceptors and state which one is responsible for color vision.

Answer

1. Photoreceptors → bipolar cells → ganglion cells → optic nerve → optic chiasm → optic tract → lateral geniculate nucleus (thalamus) → optic radiation → primary visual cortex (V1).
2. Rods and cones. Cones are responsible for color vision.

Understand

1. Explain why a photoreceptor releases *more* glutamate in the dark than in the light.
2. Explain why an on-center ganglion cell responds weakly when its whole receptive field is lit evenly.

Answer

1. In the dark, sodium channels in the photoreceptor stay open, so the cell is depolarized (about −40 mV) and keeps releasing glutamate. Light triggers a chain reaction that closes those channels, so the cell hyperpolarizes and releases less glutamate.
2. Light on the center excites the cell, but light on the surround inhibits it. When both are lit, the two effects largely cancel, so the cell signals contrast (edges), not overall brightness.

Apply

1. A person has a stroke in the left occipital lobe. Use the crossing rule to predict which part of the visual field is lost in each eye.
2. A highway warning light must catch a driver's side vision at night. Based on rods and cones, should it rely on color or on flashing? Justify your answer.

Analyze

1. Two patients both say they have trouble seeing on their left. Patient A has lost all vision in the left eye. Patient B has lost the left half of the visual field in both eyes. Compare where each lesion is likely to be, and explain how the visual field test tells them apart.
2. Mr. Alvarez had normal visual acuity but a serious visual field defect. Analyze why acuity testing alone missed his problem, using what you know about the fovea and the crossing fibers.

Evaluate

1. A website claims, "Your eyes see the world, and your brain just receives the image." Evaluate this claim using at least two pieces of evidence from this chapter.
2. Imagine a driver's license office that checks only visual acuity (the eye chart). Judge whether it should also test the visual field. Consider safety, cost, and people like Mr. Alvarez.

Create

1. Write a short fictional case of a patient with a "pie in the sky" visual field defect. Include their symptoms, the exam finding, and a localization that a classmate could solve.
2. Design a one-page poster that teaches middle school students the rule "nasal fibers cross, temporal fibers stay," using an analogy of your own.

Key Takeaways

- **Sensory transduction** turns light into electrical signals. Photoreceptors do this in an unusual way: light *hyperpolarizes* them and reduces their glutamate release.
- **Rods** (about 120 million) handle dim light with low detail. **Cones** (about 6 million) handle bright light, fine detail, and **color vision**, which comes from comparing three cone types.
- The retina is part of the brain. Its **receptive fields** have a center and a surround, so it sends mostly news about edges and contrast through the **optic nerve**.
- At the **optic chiasm**, fibers from the nasal half of each retina cross and temporal fibers stay. As a result, each hemisphere sees the opposite half of the **visual field** using both eyes.
- The **visual pathway** runs through the optic tract, the LGN of the thalamus, and the optic radiation (including Meyer's loop) to the **primary visual cortex (V1)**, where neurons respond to lines and edges at specific angles.
- Beyond V1, the **ventral stream** identifies "what" and the **dorsal stream** handles "where" and "how."
- The shape of a **visual field defect** reveals the lesion site. A **pituitary tumor** pressing on the chiasm classically causes bitemporal hemianopia.

You Can Read the Map Now!



You just learned to look at a vision test and point to a spot in the brain, which is real clinical reasoning! Next, in Chapter 6, we'll see how the other senses perform their own transductions, from hair cells that "hear" to the strange case of pain in a missing limb.

Chapter 6: Hearing, Touch, Taste, Smell, and Pain

Summary

Every sense starts with a receptor cell that turns energy, such as a sound wave, a push on the skin, or a chemical, into electrical signals. This chapter follows those signals for hearing, balance, touch, body position, taste, smell, and pain. You will see how the somatosensory cortex keeps a distorted map of the body, and how doctors use skin "stripes" called dermatomes to find spinal problems. The chapter ends with a puzzle that has fascinated doctors for more than 150 years: pain in a limb that is no longer there.

Concepts Covered

1. Cochlea and Hair Cells
2. Auditory Pathway
3. Vestibular System
4. Somatosensory System
5. Mechanoreceptor
6. Dermatome
7. Somatosensory Cortex
8. Homunculus
9. Olfaction
10. Gustation
11. Nociception
12. Pain Pathway
13. Gate Control Theory
14. Phantom Limb Pain

15. Proprioception

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters
- Chapter 4: A Tour of the Brain: Neuroanatomy
- Chapter 5: Vision

Five senses? Try a lot more.



I'm a sea slug with no ears, so I rely on touch and chemical senses. You get ears that hear and balance you, skin that tells silk from sandpaper, and a nose and tongue that work as a team. In this chapter you'll learn how each sense reports to the brain, and how a doctor can touch your skin with a pin and figure out which part of your spinal cord is hurt.

6.1 A Paper Cut, a Bruise, and a Bland Slice of Pizza

Maya is 16, plays soccer, and is studying for the Brain Bee. On Tuesday she slices her fingertip on the edge of a flashcard. The cut is so tiny she can barely see it, yet it stings so sharply that she drops the cards. That afternoon a defender kicks her shin at practice, leaving a big purple bruise. It aches, but she can almost ignore it.

On Friday Maya has a cold. Her nose is stuffed up, and her favorite pizza tastes like warm cardboard. Nothing is wrong with her tongue. So why does a tiny cut hurt more than a big bruise? And why does a blocked *nose* ruin the *taste* of food? By the end of this chapter you will be able to answer both questions with real neuroscience.

6.2 How Any Sense Works: Translators at the Border

Imagine your brain as a control room sealed inside the skull. It never touches the outside world directly. All it receives are action potentials, which you met in Chapter 2. So each sense needs a translator at the border: a cell that turns outside energy into the brain's electrical language.

That translation step is called **sensory transduction**. The translator cell is a **sensory receptor**. Different senses use receptors tuned to different kinds of energy:

- Push, stretch, or vibration (mechanical energy): hearing, balance, touch, body position
- Chemicals: taste and smell
- Heat and cold: temperature sense
- Damaging or nearly damaging stimuli: pain

Action potentials all look alike. A signal from a touch receptor *feels like touch* because of **where the wire goes**: touch nerves connect to touch areas of the brain, and sound nerves connect to hearing areas. This is sometimes called the "labeled line" idea.

Same message, different wires



When someone touches my siphon, touch-sensing neurons fire and I pull my gill in to protect it. That simple reflex is what Eric Kandel studied in my species. Your brain uses the same trick I do: the meaning of a signal comes from which neurons carry it, not from the shape of the spike.

So how many senses do people have? Far more than five. The table lists the ones in this chapter, plus vision from Chapter 5.

Sense	What it detects	Receptor type
Vision	Light	Photoreceptors (rods and cones)
Hearing	Sound waves	Hair cells (mechanical)
Balance	Head turning, tilting, and speeding up	Hair cells (mechanical)
Touch	Pressure, vibration, stretch, texture	Mechanoreceptors

Sense	What it detects	Receptor type
Body position	Where your limbs are	Muscle spindles, tendon organs
Temperature	Warm and cold	Temperature-sensitive nerve endings
Pain	Damage or threat of damage	Nociceptors
Taste	Chemicals dissolved in saliva	Taste receptor cells
Smell	Chemicals floating in air	Olfactory sensory neurons

6.3 Hearing: The Cochlea and Hair Cells

Sound is a pressure wave in the air. Its **frequency**, measured in hertz (Hz), is how many waves pass each second, and we hear it as pitch. Humans hear from about 20 Hz (a deep rumble) to about 20,000 Hz (a high whine).

Before we name the parts, picture a piano keyboard rolled up like a snail shell, with low notes at one end and high notes at the other. When a sound comes in, the "key" for that pitch moves the most. Your inner ear works much like this.

Here is the path a sound takes:

1. Sound waves make the **eardrum** vibrate.
2. Three tiny middle-ear bones (malleus, incus, and stapes) pass the vibration along and amplify it.
3. The last bone pushes on a window into the **cochlea**, a snail-shaped, fluid-filled tube in the inner ear.
4. The fluid ripples, and a ribbon of tissue inside, the **basilar membrane**, moves in a traveling wave.
5. Sensory cells on that membrane bend and start the electrical signal.

Those sensory cells are **hair cells**. Each has a bundle of tiny stiff projections on top called **stereocilia**. When the basilar membrane moves, the stereocilia tilt, ion channels at their tips

open, positive ions rush in, and the hair cell releases neurotransmitter onto auditory nerve fibers. Together, the **cochlea and hair cells** are where sound becomes neural signals.

The basilar membrane is stiff and narrow at the **base** of the cochlea (near the middle ear) and floppy and wide at the **apex** (the tip of the spiral). So high sounds, around 20,000 Hz, vibrate the base most, and low sounds, around 20 Hz, travel to the apex. This map of pitch is called **tonotopy**, and it is kept at almost every station on the way to the cortex. Cochlear implants use it: electrodes near the base stimulate high-pitch nerve fibers, and deeper electrodes stimulate low-pitch fibers.

The human cochlea has about 3,500 **inner hair cells**, which do most of the job of sending sound information to the brain. Three more rows of **outer hair cells** act like tiny amplifiers. They change length very quickly and boost faint sounds at particular pitches.

Hair cells are delicate. According to the National Institute on Deafness and Other Communication Disorders (NIDCD), sounds at or below 70 A-weighted decibels (dBA) are unlikely to cause hearing loss even after long exposure, but long or repeated exposure to sounds at or above 85 dBA can cause hearing loss, mostly by killing hair cells. Birds and amphibians can regrow hair cells, but humans cannot. After loud noise, hearing can be dulled for 16 to 48 hours and then seem to recover, though some lasting damage may remain (NIDCD). An extremely loud burst, such as a gunshot or explosion, can cause permanent loss right away. Once hair cells die, that hearing loss is permanent. That is a real reason to turn your earbuds down.

6.4 The Auditory Pathway

Once hair cells fire, the signal travels along cranial nerve VIII (the vestibulocochlear nerve) into the brainstem. The route from the cochlea to the cortex is the **auditory pathway**, and it has several relay stations, each with a job.

One key job is finding *where* a sound comes from. A car honking on your left reaches your left ear a tiny bit sooner, and louder, than your right. The **superior olivary complex** in the brainstem, the first station that receives input from both ears, compares their timing and loudness.

The table lists the main stops in order.

Stop	Location	Main job
Cochlear nuclei	Brainstem, where the medulla meets the pons	First stop for every auditory nerve fiber; keeps the pitch map
Superior olivary complex	Lower brainstem (pons)	Compares the two ears to locate sounds
Lateral lemniscus	Bundle of axons in the brainstem	Carries signals upward
Inferior colliculus	Midbrain	Major relay; combines pitch, timing, and location
Medial geniculate body	Thalamus	Gateway from the brainstem to the cortex
Primary auditory cortex	Temporal lobe	Conscious hearing; pitch is still mapped in order

Because each ear's signals reach both sides of the brain, damage to one auditory cortex usually does not cause deafness in one ear. One-sided deafness usually points to the ear or the auditory nerve.

6.5 Balance: The Vestibular System

Try this. Look at a finger held at arm's length and shake your head side to side. The finger stays sharp. Now hold your head still and wave the finger at the same speed. It blurs. The difference is the **vestibular system** at work.

The vestibular system is the inner ear's balance sensor. It shares fluid, hair cells, and cranial nerve VIII with the cochlea. It has two kinds of parts:

- **Semicircular canals.** Three fluid-filled loops at roughly right angles, like the corner of a box. When you turn your head, the fluid lags behind because of inertia, like coffee in a spinning mug, and bends a gel flap holding hair cells. The canals sense rotation.

- **Otolith organs.** Two pouches, the **utricle** and **saccule**, whose hair cells sit under a gel topped with calcium carbonate grains called **otoconia**. Gravity and straight-line acceleration shift the grains, telling your brain which way is down and when you speed up.

The finger test shows the **vestibulo-ocular reflex**. When your head turns, signals from the semicircular canals reach your eye muscles through only a few synapses, so your eyes swing the opposite way fast enough to keep the world steady. This reflex is why Maya can read a defender's body while dribbling at full speed. It also explains why you feel dizzy after spinning and stopping: the fluid in your canals keeps sloshing, so your ears say "turning" while your eyes say "still."

In a common balance problem called **benign paroxysmal positional vertigo**, loose otoconia tumble into a semicircular canal and send false "spinning" signals, causing brief, intense vertigo with certain head movements, such as rolling over in bed.

6.6 Touch and Body Sense: The Somatosensory System

"Soma" means body. The **somatosensory system** is the set of receptors, nerves, and brain areas that handle touch, pressure, vibration, temperature, pain, and body position. Its receptors are spread over the whole body, not packed into one organ like the eye or ear.

Mechanoreceptors

A **mechanoreceptor** is a receptor that responds to mechanical force, such as pressure, stretch, or vibration. In the skin, many are nerve endings wrapped in capsules or attached to special cells. Force opens ion channels in the nerve ending, including a family called **Piezo** channels.

Two features make each mechanoreceptor good at a different job:

- **Depth.** Receptors near the surface have small, sharp **receptive fields**, the patch of skin that can activate them. Deeper receptors have large, blurry receptive fields.
- **Adaptation.** *Slowly adapting* receptors keep firing as long as pressure lasts, like a doorbell held down. *Rapidly adapting* receptors fire when something changes and then go quiet, like a motion-sensor light.

The table compares the four classic touch receptors.

Receptor	Depth in skin	Adaptation	Good at sensing
Merkel disk	Shallow	Slow	Steady pressure, edges, and shapes, like the dots of Braille
Meissner corpuscle	Shallow	Rapid	Light touch and slipping, like a cup sliding in your grip
Ruffini ending	Deep	Slow	Skin stretch, like bending a finger
Pacinian corpuscle	Deep	Rapid	Vibration, like a phone buzzing in your pocket

Rapid adaptation is why you stop noticing your socks soon after putting them on.

In 2021, David Julius and Ardem Patapoutian shared the Nobel Prize in Physiology or Medicine for discovering receptors for temperature and touch, including the Piezo channels.

Proprioception

Close your eyes and touch your nose. You can do it because of **proprioception**, the sense of where your body parts are and how they move. Its receptors sit in muscles, tendons, and joints. The two most important are **muscle spindles**, which sense how much a muscle is stretched, and **Golgi tendon organs**, which sense how hard a muscle is pulling on its tendon. You will meet muscle spindles again in Chapter 7, because they drive the knee-jerk reflex.

Nerve fibers: fast lanes and slow lanes

Each receptor connects to a sensory neuron whose cell body sits in a **dorsal root ganglion**, a cluster of cell bodies just outside the spinal cord. As you learned in Chapter 2, thicker axons with more myelin conduct faster. Sensory fibers come in several sizes.

Fiber type	Myelin	Approximate speed	Main signals
Aβ (A-beta)	Thick	36 to 72 m/s	Touch, vibration, pressure
Aδ (A-delta)	Thin	4 to 36 m/s	Sharp, fast pain; temperature
C	None	0.4 to 2 m/s	Slow, burning or aching pain; temperature; itch

From skin to cortex: the touch pathway

Touch and body-position signals take the **dorsal column pathway**. The sensory axon climbs the spinal cord on the *same* side to the medulla. There it synapses, and the next neuron crosses to the *opposite* side and rises to the **thalamus**, which relays the signal to the cortex. Because of that crossing, the left side of your brain feels the right side of your body.

Keep your eye on the crossing



Sensory pathways can feel like a maze of names. For each one, ask just two questions: where does it cross the midline, and where does it end? Those two answers solve most lesion puzzles.

6.7 Maps of the Body: Dermatomes, Cortex, and the Homunculus

Dermatomes: stripes on the skin

The spinal cord has 31 segments: 8 cervical (neck), 12 thoracic (chest), 5 lumbar (lower back), 5 sacral, and 1 coccygeal. Each segment has a pair of dorsal roots that bring in sensory information. A **dermatome** is the strip of skin whose sensation is carried by one spinal nerve root.

Picture a person on hands and knees. The dermatomes run in roughly horizontal bands, like zebra stripes, and get stretched out along the arms and legs.

Doctors use dermatomes like an address book. Numbness in one stripe points to a problem at that spinal level or nerve root, such as a herniated disc pressing on one root in the neck. Doctors test standard "key points," listed below.

Spinal level	Key test spot on the skin
C4	Top of the shoulder
C6	Thumb
C7	Middle finger
C8	Little finger
T4	Chest at the nipple line
T10	Belly button (umbilicus)
L3	Inner knee
L4	Inner ankle
L5	Top of the foot
S1	Outer heel

Two warnings come with this table. First, dermatome maps disagree between textbooks, and borders vary from person to person because neighboring dermatomes overlap. Treat these as standard test spots, not perfect borders. Second, the face has no spinal dermatome. Facial skin is supplied mainly by the **trigeminal nerve** (cranial nerve V).

The somatosensory cortex and the homunculus

Touch signals from the thalamus arrive at the **somatosensory cortex**. The first stop, the **primary somatosensory cortex** (S1), is a strip of cortex on the **postcentral gyrus**, the ridge just behind the central sulcus at the front of the parietal lobe (see Chapter 4).

S1 holds an orderly map of the opposite side of the body, with neighboring body parts mostly in neighboring patches. The leg and foot are near the top of the brain and on the inner (medial) wall between the hemispheres. Moving down the side of the brain, you pass the trunk, arm, hand, and fingers, then the face, lips, tongue, and throat.

The map is not to scale. Body parts with densely packed receptors, like the hands, lips, and face, get huge areas, while the trunk gets a small one. Draw a little person with each part sized by its share of cortex and you get the famous **homunculus** ("little man"), with giant hands and lips.

Neurosurgeon Wilder Penfield built this map in Montreal by stimulating the exposed cortex of awake patients during epilepsy surgery and asking what they felt. He and Edwin Boldrey published the first homunculus in the journal *Brain* in 1937, using data from 126 patients. That first drawing combined sensory and motor results in one figure. The real map is messier than the cartoon, and in 1950 Penfield himself warned against reading too much into the drawing's shapes and sizes. Still, the main idea holds: more receptors means more cortex and finer touch.

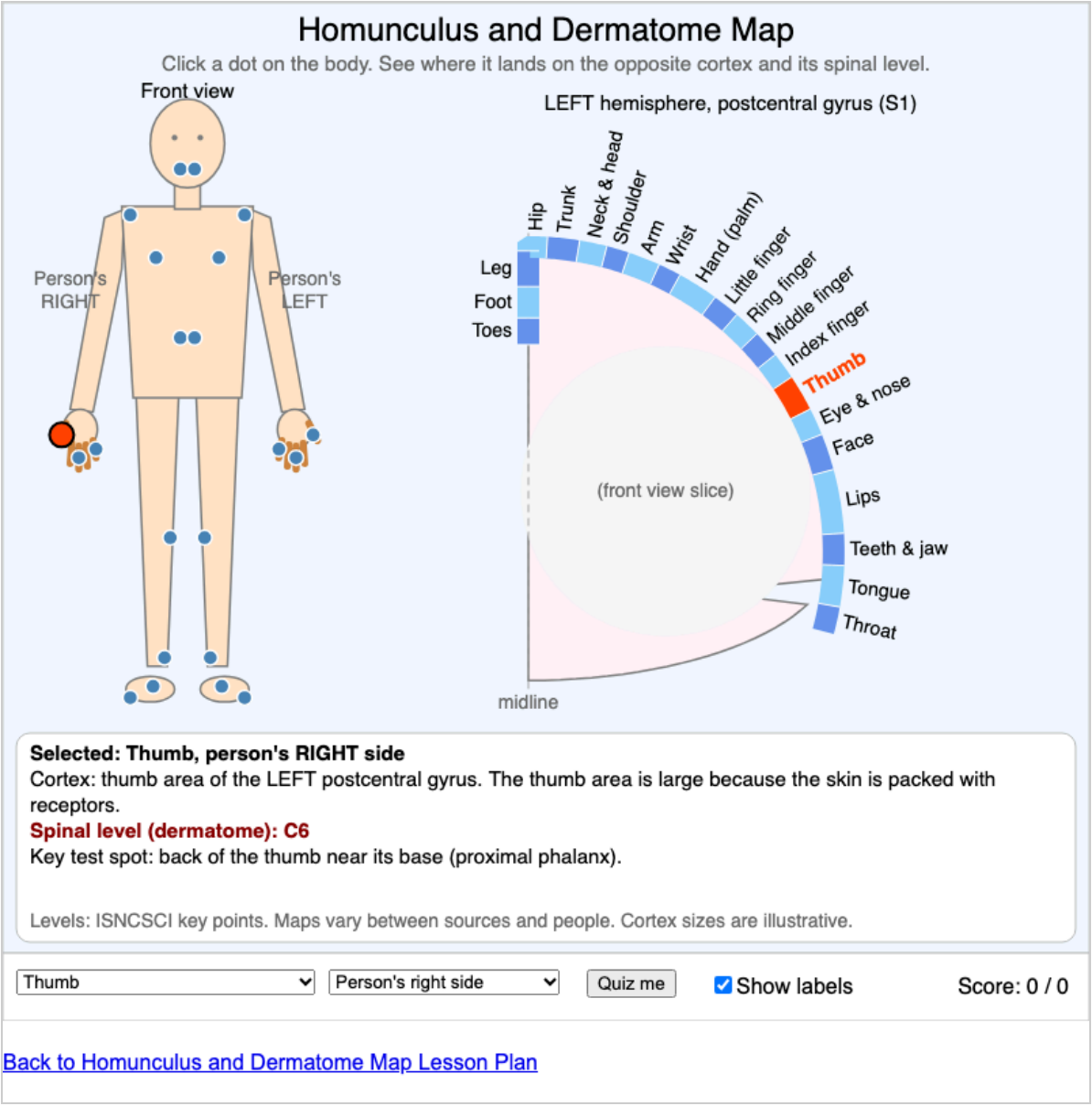
Whose left is it?



In a front view of a person, their right side is on *your* left. Then touch crosses to the opposite hemisphere. Students often flip one of these and get the wrong side, so say both steps out loud: "patient's right hand, so left hemisphere."

In the MicroSim below, click a spot on the body to see its S1 segment on the opposite hemisphere and its dermatome level.

Diagram: Homunculus and Dermatome Map



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch06-homunculus-dermatomes/

Open the Homunculus and Dermatome Map fullscreen

MicroSim specification: Homunculus and Dermatome Map

Type: microsim **sim-id:** ch06-homunculus-dermatomes
Library: p5.js
Status: Implemented
Bloom Level: Apply
Bloom Verb: locate
Learning Objective: The learner will locate where a touched body region is represented on the opposite primary somatosensory cortex and name the spinal level (dermatome) or cranial nerve that carries it.

Canvas: 700 px drawing area plus a 50 px control row; responsive width.

Controls: region dropdown (11 regions), side dropdown, "Quiz me" button, "Show labels" checkbox; clicking a body dot also selects a region.

Content: lips (trigeminal nerve), shoulder C4, thumb C6, middle finger C7, little finger C8, nipple line T4, belly button T10, inner knee L3, inner ankle L4, top of foot L5, outer heel S1 (ISNCSCI key points). Cortex segments run medial (toes) to lateral (throat); sizes are illustrative.

Behavior: the chosen region lights up on the opposite hemisphere. Quiz mode asks for a random region; first-try correct answers score; after two misses the answer is shown.

Click the person's right thumb, then their left thumb, and watch the slice flip hemispheres. Compare the thumb's share of the strip with the whole trunk's. Then click the lips: the readout names the trigeminal nerve, not a spinal level. Finally, press **Quiz me** and try to place five regions in a row on the first try.

6.8 Taste: Gustation

Gustation is the sense of taste. It detects chemicals dissolved in saliva. Taste receptor cells are grouped into **taste buds**, each a cluster of about 50 to 150 cells shaped a bit like a garlic bulb. Most sit in the bumps on your tongue, called papillae, but some are on the roof of the mouth and in the throat. A newborn has about 10,000 taste buds, and people may start to lose some after age 50.

Taste receptors respond to at least five basic taste qualities:

Taste	What it usually signals	Example
Sweet	Sugars, which mean energy	Fruit
Salty	Sodium and other minerals	Chips
Sour	Acids, which can mean spoiled or unripe food	Lemon
Bitter	Many plant toxins	Coffee, kale
Umami	Savory amino acids such as glutamate	Parmesan, broth

Taste travels on three cranial nerves: the **facial nerve** (VII) for the front two-thirds of the tongue, the **glossopharyngeal nerve** (IX) for the back third, and the **vagus nerve** (X) for the throat. All three reach the **nucleus of the solitary tract** in the medulla. Signals then pass through the thalamus to the **gustatory cortex** in the insula, tucked inside the lateral sulcus.

Different types of taste cells are scattered all over the tongue, so every part with taste buds can detect all five tastes. The famous "tongue map," with sweet at the tip and bitter at the back, is a myth. It grew out of a 1901 German study that found only small differences in sensitivity, which later textbook drawings turned into separate "zones."

6.9 Smell: Olfaction

Olfaction is the sense of smell. It detects chemicals called **odorants** that float in the air. The receptors are **olfactory sensory neurons**, real neurons that sit in a small patch of tissue high in the nasal cavity. Their axons pass through tiny holes in a thin bone called the cribriform plate and reach the **olfactory bulb** on the underside of the brain.

Each olfactory sensory neuron makes just one type of odorant receptor protein. Humans have about 400 working odorant receptor genes, while mice and dogs have roughly two to three times as many. Richard Axel and Linda Buck shared the 2004 Nobel Prize in Physiology or Medicine for discovering these odorant receptors and how the olfactory system is organized.

How can a few hundred receptor types tell apart thousands of smells? Think of an alphabet. Neurons with the same receptor all send axons to the same knot in the olfactory bulb, called a **glomerulus**. Each odor activates a *combination* of glomeruli, the way a word combines letters, and hundreds of "letters" make an enormous number of "words."

Smell has two unusual features:

- **A shortcut to the cortex.** Vision, hearing, touch, and taste pass through the thalamus before reaching the cortex. Smell does not. The olfactory bulb sends signals straight to the olfactory (**piriform**) cortex and has direct links to the amygdala, an emotion center. (Some smell information does reach the thalamus later, but only after the olfactory cortex.) This direct route may help explain why a smell can bring back a memory or feeling so suddenly.
- **Self-repair.** Olfactory sensory neurons are constantly replaced from stem cells in the nasal lining, which is rare for neurons. This ability declines with age.

Now for the rest of Maya's puzzle. When you chew, aromas drift from the back of your throat up into your nose. This **retronasal smell** combines with taste to create **flavor**, and much of the "taste" of pizza is really smell. A cold blocks that channel, so food tastes bland even though the tongue works fine.

6.10 Pain: Nociception and the Pain Pathway

The International Association for the Study of Pain, a worldwide group of pain researchers, updated its definition in 2020 (Raja et al., *Pain*, 2020). It defines pain as an unpleasant sensory *and emotional* experience linked to actual or possible tissue damage, or resembling such an experience. That definition separates two things that are easy to mix up:

- **Nociception** is the nervous system's detection of damaging or potentially damaging stimuli: the signal.
- **Pain** is what the brain makes of that signal, shaped by attention, mood, and context.

You can have nociception without much pain, or pain with no new tissue damage at all, as you will see with phantom limbs.

Nociceptors

The receptors for nociception are **nociceptors**: **free nerve endings**, bare branches of sensory axons with no capsule, found in skin, muscles, joints, and many organs. They respond to intense pressure, extreme temperatures, or chemicals from damaged tissue. Many use TRP ion channels. One TRP channel opens with dangerous heat and also with capsaicin, which is why chili peppers feel hot. Its discovery was part of David Julius's 2021 Nobel Prize work.

Nociceptors use two fiber types from Section 6.6. Thin myelinated **Aδ fibers** carry a fast, sharp "first pain." Unmyelinated **C fibers** carry a slower, aching "second pain." Stub your toe and you feel both: a sharp jolt, then a spreading ache.

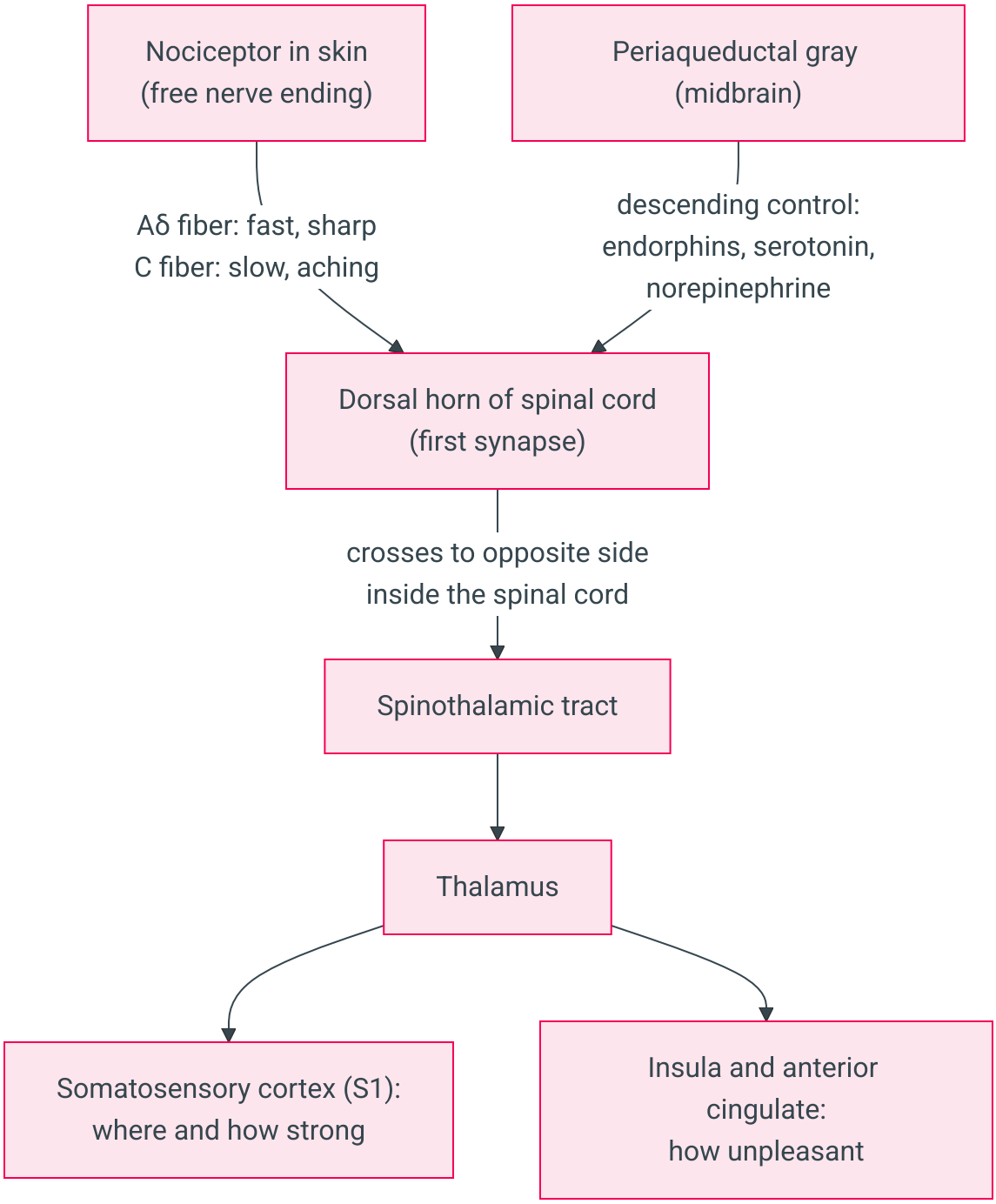
A rare genetic condition shows why nociception matters. People with **congenital insensitivity to pain**, which can be caused by changes in a sodium channel (Nav1.7) that pain fibers rely on, feel touch but not pain, so they can be badly injured without noticing.

The pain pathway

The main route for pain and temperature is the **spinothalamic tract**. It differs from the touch pathway in where it crosses.

1. A nociceptor fiber enters the **dorsal horn** of the spinal cord and synapses there.
2. The second neuron crosses to the opposite side **within the spinal cord**, close to the level where it entered.
3. It climbs the spinal cord and brainstem to the **thalamus**.
4. Thalamic neurons send the signal to S1, which tells you *where* it hurts and *how much*.
5. Other branches reach the **insula**, the **anterior cingulate cortex**, and limbic areas involved in emotion, which help make pain feel *unpleasant* and motivating.

The flowchart summarizes the **pain pathway**, including the brain's own volume control, which comes next.



The bottom arrow in the chart is the **descending pain control system**. Starting in a midbrain region called the **periaqueductal gray**, it sends signals down to the dorsal horn that can turn pain transmission down. It works through the body's own opioid chemicals, called **endorphins**, and through serotonin and norepinephrine from Chapter 3. It helps explain why soldiers and athletes sometimes feel little pain from serious injuries during intense action.

Because touch crosses in the medulla but pain crosses in the spinal cord, damage to one half of the spinal cord causes loss of fine touch and position sense on the *same* side below the injury, but loss of pain and temperature on the *opposite* side. This classic pattern is called **Brown-Séquard syndrome**.

Now we can partly answer Maya's paper cut question. Her fingertip is packed with sensory endings and owns a large territory on the somatosensory map, so her brain gets a detailed, sharply located signal, and she keeps using the finger. Her shin bruise is deeper damage in a region with a smaller cortical map, felt mostly as a dull C-fiber ache that is harder to pin down. Pain is not a simple measure of damage.

6.11 Gate Control Theory: Why Rubbing Helps

When Maya gets kicked in the shin, she rubs it, and it really does help a little. Why?

In 1965, Ronald Melzack and Patrick Wall proposed the **gate control theory** of pain in the journal *Science*. Their idea was that the dorsal horn of the spinal cord acts like a gate that controls how much pain information gets sent up to the brain. Here is a simple version of the circuit:

- Pain fibers (C and Aδ) excite the projection neuron that sends pain signals to the brain. They also *quiet* a small **inhibitory interneuron** in the dorsal horn. Both effects open the gate.
- Large touch fibers (Aβ) weakly excite the projection neuron but strongly *excite* the inhibitory interneuron, which releases inhibitory transmitters such as GABA to quiet the pain pathway. That helps close the gate.

So rubbing a bump fires many touch fibers, which boosts the inhibitory interneuron and partly closes the gate. Signals from the brain can also open or close the gate, which helps explain why distraction, stress, and expectations change how much something hurts. Some details of the 1965 model have since been revised, but its central idea, that pain signals are filtered in the spinal cord and by the brain, changed pain science.

6.12 Phantom Limbs: When the Map Outlives the Body

During the U.S. Civil War, physician Silas Weir Mitchell treated many soldiers who had lost limbs and still felt them, sometimes painfully. He is usually credited with coining the term

"phantom limb" in 1871, though earlier doctors had described the experience.

Doctors now separate three related experiences after an amputation:

- **Phantom sensation:** feeling that the missing limb is still there, sometimes with a position or tingling, but without pain.
- **Residual limb pain:** pain in the remaining part of the limb, often from an irritated nerve end at the cut.
- **Phantom limb pain:** pain that feels like it comes from the missing part, such as a clenched fist, burning, or cramping fingers.

Phantom limb pain is common. A 2020 review that combined many studies estimated that about 64% of people with amputations experience it. A larger 2026 review of 51 studies and about 13,000 people found a similar figure, about 61% (Zhang et al., *BMC Musculoskeletal Disorders*, 2026). Both reviews saw a wide range between studies.

How can a missing limb hurt? Part of the answer is the cortical map. After an arm amputation, the hand area of S1 loses its usual input, and on the homunculus the face area sits right next to it. In the 1990s, V. S. Ramachandran and colleagues reported that touching the face of some arm amputees made them feel touch on the missing hand, suggesting face inputs had spread into the silent hand territory. A 1995 brain-imaging study by Herta Flor and colleagues linked more phantom limb pain to more reorganization of the S1 map.

The story is not settled. A 2013 study found that people with more phantom pain actually kept *more* of their original hand map. Then, in 2025, a team scanned three adults before and for months to years after an arm amputation. The hand and lip maps in S1 stayed almost the same, with no sign of the lip area spreading into the hand area (Schone et al., *Nature Neuroscience*, 2025). Three people is a small study, but it challenges the classic "remapping" story. Today most scientists think phantom limb pain comes from several sources together: injured nerve endings in the residual limb, changes in the dorsal horn, and changes in the brain's representation of the missing limb.

The map is part of you



Phantom limbs show that what you feel is built by the brain's map of your body, not by the body part alone. Remove the hand, and the map can still produce a hand, sometimes a painful one.

At the Bedside: Pain in a Hand That Is No Longer There

Meet the patient

Daniel is a 32-year-old Army veteran whose right arm was amputated below the elbow eight months ago after a vehicle crash during his service. The wound has healed well. But most nights he feels his missing right hand clenched into a tight fist, fingernails "digging into" his palm, with cramping and burning pain. It is worse when he is stressed or tired, and it ruins his sleep.

What the doctor checks: The doctor examines the residual limb for infection or skin breakdown and checks the prosthetic socket fit. She taps along the nerves of the residual limb to look for a **neuroma**, a tangled, oversensitive bundle of regrowing nerve fibers that can fire a shooting pain when touched. She asks Daniel to describe three things separately: pain in the residual limb, painless feelings in the missing hand, and pain that seems to come from the missing hand. When she lightly touches his face, he feels some touches on his "missing" fingers.

Where is the problem? (localization): There is no tissue where Daniel feels the pain, so the problem must lie along the nervous system that used to serve the hand: cut nerve endings in the residual limb, pain neurons in the dorsal horn of the spinal cord segments that served the hand (about C6 to T1), and the hand area of his **left** primary somatosensory cortex, because the right side of the body is mapped on the left hemisphere. Face touches felt in the phantom hand were long explained by the neighboring face area spreading into the hand's territory, though newer brain scans (Section 6.12) question how much the map really changes.

Diagnosis: Phantom limb pain, with phantom sensations.

Why it happens: The brain's map of the right hand loses its input but does not disappear. Injured nerve endings can fire on their own and send noisy signals, dorsal horn neurons can become more excitable, and the brain's hand map, which largely stays in place, reads those signals as coming from the missing hand. With no feedback that the hand has relaxed, the brain may produce a painful, stuck posture, and stress can open the spinal "gate" further.

Treatment today: No single treatment works for everyone. Care usually combines medicines for nerve pain, physical therapy, a well-fitted prosthesis, support for sleep and stress, and sometimes surgery for a painful neuroma.

Many clinics also try **mirror therapy**: a mirror between Daniel's arms shows his left hand's reflection where his right hand used to be, so when he opens his real left hand, his brain "sees" the missing hand open too. V. S. Ramachandran and colleagues introduced the idea in the 1990s, and a small 2007 trial in people with leg amputations reported less pain with a mirror than with a covered mirror or mental imagery. The overall evidence is mixed. A 2022 combined analysis of randomized trials found a short-term benefit, but a 2023 review of only placebo-controlled trials could not conclude that it works, mainly because the trials were small and of low quality. Mirror therapy is low-risk and helps some patients, but it is not a proven cure.

What's new in research: In **targeted muscle reinnervation** (TMR), surgeons give cut nerves a new "job" by connecting them to motor nerves of nearby muscles, which may make painful neuromas less likely. In a randomized trial of 28 people with chronic pain after major limb amputation, TMR reduced phantom limb pain more than standard neuroma surgery over a year of follow-up, although one simpler comparison just missed statistical significance (Dumanian and colleagues, *Annals of Surgery*, 2019). Larger studies are still needed.

Your turn: diagnose a variation

A patient with a below-knee amputation feels a sharp, electric jolt in his residual limb whenever his prosthetic socket presses one spot, and tapping that spot reproduces it. He also feels his missing foot, but it does not hurt. What is the likely source of his pain, and is it phantom limb pain?

Answer: This sounds like residual limb pain from a **neuroma** at a cut nerve end. The pain is triggered at one spot and felt in the residual limb, so the main problem is the peripheral nerve, not the brain's map. His painless feeling of the missing foot is a **phantom sensation**, not phantom limb pain. Care would focus on the socket fit and the neuroma.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Humans have exactly five senses.
Reality: You also sense balance (vestibular system), body position (proprioception), temperature, and pain, each with its own receptors and pathways.

Myth: The tongue has separate zones for sweet, salty, sour, and bitter.
Reality: Every area of the tongue with taste buds can detect all five basic tastes. The "tongue map" came from textbook redrawings that exaggerated small differences in sensitivity found in a 1901 study.

Myth: How much something hurts tells you how much damage there is.
Reality: Pain depends on which receptors fire, how densely packed they are, how the spinal "gate" filters the signal, and what the brain attends to. A paper cut can hurt more than a large bruise.

Myth: Phantom limb pain is imaginary or "all in the patient's head."
Reality: Phantom limb pain is real, with causes in the nerves, spinal cord, and the brain's body map. Calling it imaginary can keep people from getting help.

Brain Bee Practice

1. Which part of the cochlea responds best to high-pitched sounds, and what is this pitch map called?

The base of the cochlea (near the middle ear); the apex responds to low pitches. The pitch map is called tonotopy.

2. Name the two kinds of vestibular sense organs and what each detects.

The semicircular canals detect head rotation. The otolith organs (utricle and saccule) detect gravity, head tilt, and straight-line acceleration.

3. A patient has numbness on the back of the middle finger but nowhere else. Which spinal nerve root is most likely affected?

C7. The middle finger is the standard key test spot for the C7 dermatome.

4. Why does smell differ from all other senses in how it reaches the cortex?

Olfactory signals go from the olfactory bulb straight to the olfactory (piriform) cortex without first relaying through the thalamus. Other senses pass through the thalamus first.

5. According to gate control theory, why does rubbing an injury reduce pain?

Rubbing activates large Aβ touch fibers, which excite inhibitory interneurons in the dorsal horn. These quiet the projection neurons that carry pain to the brain, partly "closing the gate."

Exercises

Remember

1. List the four classic skin mechanoreceptors and state whether each adapts slowly or rapidly.
2. Name the three cranial nerves that carry taste and the brainstem nucleus where taste signals first arrive.

Answer

1. Merkel disk (slow), Meissner corpuscle (rapid), Ruffini ending (slow), Pacinian corpuscle (rapid).
2. Facial (VII), glossopharyngeal (IX), and vagus (X); they deliver taste to the nucleus of the solitary tract in the medulla.

Understand

1. Explain why a signal from a touch receptor feels like touch rather than sound, even though all action potentials look alike.
2. Explain why food tastes bland when you have a stuffed-up nose.

Answer

1. A signal's meaning depends on where its pathway ends. Touch receptors connect to pathways ending in the somatosensory cortex, so their signals are felt as touch (the "labeled line" idea).
2. Much of flavor is retronasal smell, aromas rising from the mouth into the nose. A cold blocks that channel, so the brain gets taste but little smell.

Apply

1. A patient's left hand is touched with a cotton swab, and an fMRI scan (a brain scan that shows which areas are active) is recorded. Predict which hemisphere and which gyrus will show the strongest early response, and roughly where along that gyrus.
2. A construction worker uses a loud jackhammer all day without ear protection. Predict what will happen to his hearing over the years and explain why it cannot be reversed.

Analyze

1. After an injury that damaged the left half of the spinal cord at a mid-chest level, a patient cannot feel a pin prick on his right leg but can feel it on his left leg. He also cannot tell which way his left big toe is being moved. Use the crossing points of the two sensory pathways to explain this pattern.
2. Compare the touch pathway and the smell pathway. Identify two ways their routes to the cortex differ and one way they are similar.

Evaluate

1. A website calls mirror therapy "a proven cure for phantom limb pain." Evaluate this claim using the evidence in this chapter, and rewrite it as one accurate sentence.
2. Dermatome maps differ between textbooks. Should doctors still use dermatome key points in exams? Defend your answer with two reasons.

Create

1. Design a safe experiment, using household materials, to test whether the fingertip can tell two nearby points apart better than the back of the hand. State your hypothesis,

procedure, and how you will record results.

2. Write a short fictional case of a patient whose symptoms point to damage in one part of the auditory or vestibular system. Include the key symptom, one exam finding, and the location a classmate should identify.

Key Takeaways

- Every sense uses receptors that transduce energy into electrical signals, and the brain reads each signal by where its pathway ends. Humans have far more than five senses.
- Cochlear hair cells turn sound into neural signals, with pitch mapped from high (base) to low (apex). Lost human hair cells do not grow back.
- The vestibular system senses rotation (semicircular canals) and gravity and linear acceleration (otolith organs).
- Skin mechanoreceptors detect touch, muscle spindles and tendon organs detect body position, and nociceptors detect damage, carried by Aδ and C fibers.
- Touch crosses in the medulla and pain crosses in the spinal cord; both reach the opposite somatosensory cortex, a distorted body map called the homunculus. Dermatomes link skin areas to spinal levels, though maps vary.
- Taste detects five basic qualities across the tongue. Smell uses combinations of hundreds of receptor types, skips the thalamus, and supplies most of flavor.
- Pain is built by the brain. It can be turned down by the spinal gate and descending control, and it can even come from a missing limb.

You can map a body now!



You followed signals from ears, skin, tongue, and nose all the way to the cortex, and you can now turn a numb finger into a spinal level. In Chapter 7, we flip the direction: instead of signals coming in, you'll see how the brain sends commands out to move your muscles.

Chapter 7: Movement: Muscles, Reflexes, and Motor Control

Summary

Every movement you make, from a blink to a penalty kick, ends with muscle fibers pulling. This chapter follows a movement from the bottom up: how a muscle fiber contracts, how motor units set force, and how spinal reflexes act without waiting for the brain. Then it climbs to the top: the motor cortex and corticospinal tract send commands, the basal ganglia act as a gas pedal and brake, and the cerebellum corrects errors and helps you learn skills. It ends at the bedside with Parkinson's disease, where losing dopamine neurons makes movement slow and hard to start.

Concepts Covered

1. Skeletal Muscle Contraction
2. Motor Unit
3. Reflex Arc
4. Stretch Reflex
5. Primary Motor Cortex
6. Corticospinal Tract
7. Upper vs Lower Motor Neuron
8. Basal Ganglia
9. Substantia Nigra
10. Direct and Indirect Pathways
11. Cerebellar Coordination
12. Motor Learning
13. Parkinson's Disease

14. Levodopa
15. Deep Brain Stimulation

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters
- Chapter 4: A Tour of the Brain: Neuroanatomy

Let's get moving!



I'm a sea slug, so my top speed is not very impressive. But my slow crawl and your fastest sprint follow the same plan: decide, command, adjust, and pull. In this chapter you'll learn how a decision becomes motion, and why a doctor can often tell *where* a problem is just by watching someone move.

7.1 One Kick, Many Brain Areas

It's the last minute of a tied soccer game. Maya, a 16-year-old midfielder who is also studying for the Brain Bee, steps up to take a penalty kick. She glances at the goalkeeper, picks the bottom-left corner, takes three steps, plants her left foot, and swings her right leg through the ball. The whole thing takes about two seconds.

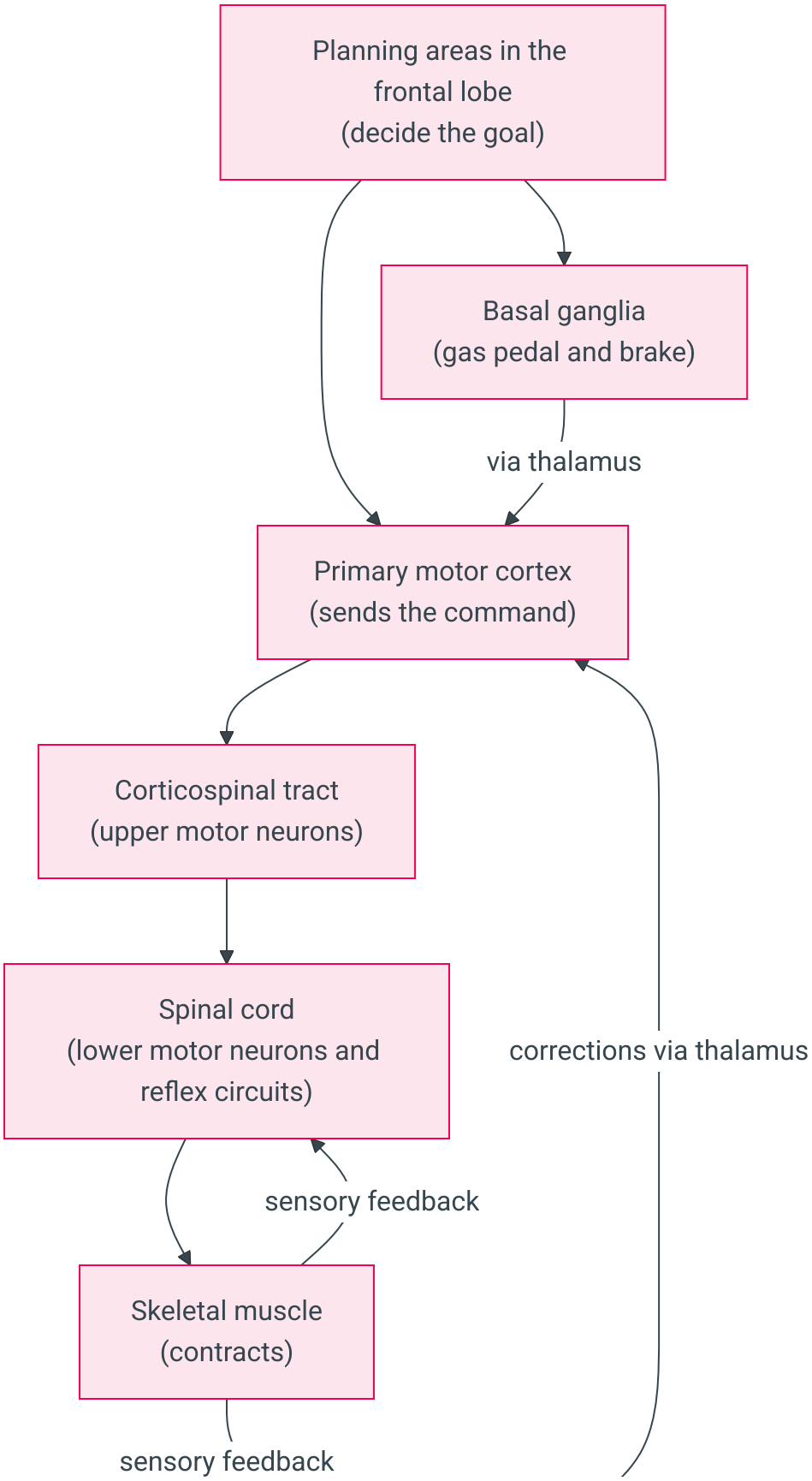
Those two seconds use a surprising amount of brain. Something had to *decide* to aim left. Something had to turn that plan into muscle commands, keep her balanced on one leg, and adjust the swing when the grass was slippery. At the very end, thousands of muscle fibers in her thigh had to pull at the right moment with the right force. Why does one kick need so many parts of the nervous system?

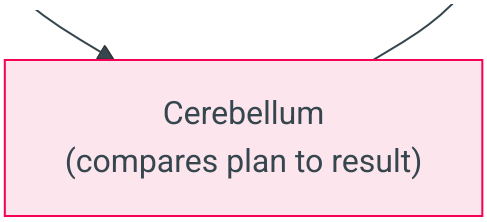
An everyday analogy: a film crew

Before naming any brain structures, picture a film crew shooting a stunt. A **director** decides what the scene should be. A **camera operator** turns the plan into specific actions. A **safety officer** keeps a hand on the brake, letting only the planned action start. A **stunt coordinator** compares each take to the plan and calls out corrections. The **stunt performers** do the physical work. And some actions, like flinching when something flies at your face, happen so fast that nobody waits for the director.

Your motor system has all of these roles. The performers are your **muscles**, the instant flinches are **reflexes** run by the spinal cord, the camera operator is the **primary motor cortex**, the safety officer is the **basal ganglia**, and the stunt coordinator is the **cerebellum**. The director's job is spread across planning areas in the front of the brain.

The flowchart below shows how these pieces connect. Planning areas decide, the motor cortex sends commands down the spinal cord, and two "advisor" loops (basal ganglia and cerebellum) shape the command.


Planning areas in the
frontal lobe
(decide the goal)
Basal ganglia
(gas pedal and brake)
via thalamus
Primary motor cortex
(sends the command)
Corticospinal tract
(upper motor neurons)
Spinal cord
(lower motor neurons and
reflex circuits)
corrections via thalamus
sensory feedback
Skeletal muscle
(contracts)
sensory feedback



We'll start at the bottom of this chart, with the muscle, and work our way up.

7.2 How a Muscle Pulls

Muscles can only pull. They never push. When you straighten your knee, muscles on the front of your thigh pull. When you bend it, muscles on the back pull. Muscles that pull in opposite directions around a joint work in pairs, so every movement is a tug-of-war that the nervous system referees.

The analogy: hands on a rope

Imagine a team hauling a boat to shore with a rope. Each person grabs the rope, pulls, lets go, reaches forward, and grabs again. No single grab moves the boat far, but thousands of quick grabs haul it in. Inside each muscle fiber, tiny protein "hands" do almost exactly this.

The real steps

Skeletal muscle contraction is the process in which an electrical signal from a motor neuron makes a muscle fiber shorten and pull on a bone. A skeletal muscle is made of long cells called **muscle fibers**. Inside each fiber are two kinds of protein filaments. **Actin** filaments are the "rope." **Myosin** filaments have little heads that act as the "hands." Here is the sequence, building on Chapter 2 and Chapter 3:

1. An action potential travels down a motor neuron to the **neuromuscular junction**, the synapse between a motor neuron and a muscle fiber.
2. The axon terminal releases **acetylcholine**, which binds to receptors on the muscle fiber and depolarizes it.
3. The muscle fiber fires its own action potential, which spreads across its membrane.
4. That electrical wave makes an internal storage compartment, the **sarcoplasmic reticulum**, release calcium inside the fiber.

5. Calcium moves a blocking protein (tropomyosin) aside, uncovering grip sites on actin.
6. Myosin heads grab actin, bend, and pull it toward the center. This is the "power stroke."
7. **ATP**, the cell's energy molecule, lets each myosin head let go and reset to grab again. When nerve signals stop, calcium is pumped back into storage and the muscle relaxes.

One surprise: ATP is needed to *release* the grip. After death, ATP runs out, myosin stays locked onto actin, and muscles stiffen. This is rigor mortis (OpenStax, Section 10.1).

The table below sums up who does what in the steps you just read.

Player	Job in contraction
Acetylcholine	Carries the signal across the neuromuscular junction
Calcium	The "on switch" that uncovers grip sites on actin
Actin	The "rope" that gets pulled
Myosin	The "hands" that grab and pull
ATP	Lets myosin let go and reset

7.3 Motor Units: How the Brain Sets the Force

Maya uses the same thigh muscle to tap a short pass and to blast a shot at the goal. How does one muscle produce both?

Each muscle fiber gets input from just one motor neuron, but one motor neuron branches to many muscle fibers. A **motor unit** is one motor neuron plus all of the muscle fibers it controls. When that neuron fires, all of its fibers contract together. A muscle contains many motor units (OpenStax, Section 10.1).

The nervous system turns up force in two ways:

1. **Fire faster.** A higher rate of action potentials releases calcium again before the fibers relax, so their pulls add up.

2. **Recruit more motor units** to pull at the same time.

Recruitment follows the **size principle**. Small motor neurons, which control few fibers, are easier to excite, so they fire first. Large motor neurons, which control many fibers, need stronger input and join only when more force is needed (OpenStax, Section 10.2). That's how you can hold an egg gently, then lift a heavy backpack with the same hand.

	Small motor units	Large motor units
Fibers per motor neuron	Few	Many
Input needed to fire	Small	Large
When recruited	First, for light tasks	Later, for more force
Example in Maya's game	A soft pass	A full-power shot

Muscles don't decide on their own



A muscle fiber has no idea how hard it "should" pull. The nervous system decides, by choosing how many motor units to recruit and how fast each one fires.

7.4 Reflexes: Shortcuts in the Spinal Cord

Remember touching a hot pan in Chapter 2? Your hand jerked away before you felt the pain. That was a reflex, handled mostly by your spinal cord.

Think of an automatic door at a grocery store. It doesn't call the manager when you walk up. A sensor detects you, a small local circuit decides "open," and a motor slides the door. Reflexes work the same way: a fast local circuit handles a predictable situation, and the brain hears about it afterward.

The reflex arc

A **reflex arc** is the nerve pathway that produces a reflex, an automatic and rapid response to a stimulus. It has five parts:

1. A **sensory receptor** detects the stimulus.
2. A **sensory neuron** carries the signal into the spinal cord.
3. An **integration center** in the spinal cord links input to output, either by a direct synapse or through interneurons.
4. A **motor neuron** carries the command out.
5. An **effector**, usually a muscle, responds.

Because the signal makes a short trip, a reflex is faster than a movement that goes up to the brain and back.

The stretch reflex and the knee-jerk test

The **stretch reflex** is the automatic contraction of a muscle when it is suddenly stretched. The sensors are **muscle spindles**, tiny stretch detectors inside the muscle. They are part of **proprioception**, your sense of body position, from Chapter 6.

When a doctor taps the tendon below your kneecap:

1. The tap stretches the quadriceps, the big muscle on the front of the thigh.
2. Muscle spindles in the quadriceps fire.
3. Their sensory neurons enter the spinal cord and synapse **directly** on quadriceps motor neurons. With only one synapse, this is a **monosynaptic** reflex.
4. The quadriceps contracts, and the lower leg kicks forward.
5. A branch of the sensory neuron also excites an inhibitory interneuron that relaxes the hamstrings on the back of the thigh, so they don't fight the kick. This is **reciprocal inhibition**.

The knee-jerk (patellar) reflex tests spinal cord segments L2 to L4 (Wikipedia: Patellar reflex). A missing reflex can point to damage in that loop. A much-too-strong reflex can point to a problem *above* the loop, as Section 7.6 explains. In daily life, the stretch reflex helps keep a buckling knee from collapsing when Maya lands awkwardly.

Reflexes are not fully separate from the brain. Signals from the brain constantly turn them up or down. When that control is cut off, for example after a spinal cord injury, reflexes below the injury often become exaggerated (OpenStax, Section 10.2).

Reflexes can even learn. Eric Kandel studied a protective reflex in the sea slug *Aplysia*, which has only about 20,000 nerve cells: touch it, and it pulls in its gill. He showed that this reflex could be strengthened for days or weeks by changes at the synapse between sensory and motor neurons, work that earned a share of the 2000 Nobel Prize in Physiology or Medicine (Nobel Prize press release, 2000). You'll see more in Chapter 9.

7.5 From Command to Muscle: The Motor Cortex and the Corticospinal Tract

Reflexes are automatic. Maya's penalty kick is not. A voluntary movement starts in the brain.

The primary motor cortex

The **primary motor cortex** is a strip of the frontal lobe, on the **precentral gyrus** just in front of the central sulcus, that sends the main commands for voluntary movement. It lies right in front of the somatosensory cortex from Chapter 6.

The motor cortex holds a body map, the **motor homunculus**. Neighboring body parts are controlled by neighboring strips of cortex, and parts that need fine control, like the hands, lips, and tongue, get far more cortex than the trunk or legs (OpenStax, Section 10.3). That's why you can thread a needle with your fingers but not your toes.

The real map is less tidy than the classic drawing of a little person stretched along the cortex. A 2023 brain-imaging study in humans found that the foot, hand, and mouth areas are not one continuous strip. They alternate with zones that don't control any single body part. Those zones are wired to a brain network involved in planning actions and in body control such as arousal, and they became active when people planned coordinated hand and foot movements or moved the trunk or face. The researchers named this system the **somato-cognitive action network (SCAN)**: the motor strip mixes areas for fine control of one body part with areas for whole-body action planning (Gordon and colleagues, 2023, *Nature*). The homunculus is still a useful first picture, as long as you remember it is a simplification.

Control of the limbs is **contralateral**: each side of the motor cortex controls the opposite side of the body. Maya's right-legged kick came mainly from her *left* motor cortex.

The corticospinal tract

A command reaches motor neurons in the spinal cord through the **corticospinal tract**, a long bundle of axons running from the cortex (*cortico*) to the spinal cord (*spinal*). The axons start in the motor cortex and nearby areas, descend through the deep white matter and the brainstem, and most of them cross to the other side in the lowest part of the brainstem, the medulla. That crossing is why the left brain controls the right body. The crossed fibers form the **lateral corticospinal tract**, which mainly controls the limbs, especially fine finger movements. A smaller set controls trunk muscles (OpenStax, Section 10.3; Wikipedia: Corticospinal tract). In the spinal cord, these axons connect to motor neurons and to the reflex circuits you just learned about.

7.6 Upper vs. Lower Motor Neurons: A Doctor's Shortcut

The command chain uses two kinds of neurons, and doctors care a lot about which one is damaged.

- An **upper motor neuron** starts in the brain, such as in the motor cortex, and carries commands down to the brainstem or spinal cord. It never touches a muscle.
- A **lower motor neuron** has its cell body in the brainstem or the front (ventral) part of the spinal cord, and its axon runs out to a muscle. Every command, from the brain or from a reflex, must pass through lower motor neurons.

Upper motor neurons don't just say "go." They also hold spinal reflex circuits in check. So the two kinds of damage look different:

- **Lower** motor neuron damage cuts the muscle's only connection. The muscle becomes weak and floppy, its reflexes shrink or vanish, it wastes away over time, and it may show small twitches called fasciculations (Wikipedia: Lower motor neuron lesion).
- **Upper** motor neuron damage leaves the reflex loops working but unsupervised. The muscle is weak, reflexes are exaggerated, and muscles become stiff in a way that increases with fast stretching, called **spasticity**. Stroking the sole makes the big toe

point up instead of curling down: the **Babinski sign**, which is abnormal after about 12 months of age (Wikipedia: Upper motor neuron lesion).

The table below organizes the comparison you just read.

Finding	Upper motor neuron damage	Lower motor neuron damage
Muscle tone	Increased (spastic)	Decreased (floppy)
Reflexes	Exaggerated	Reduced or absent
Babinski sign	Present (toe goes up)	Absent
Muscle wasting	Little	Marked
Fasciculations	No	Yes
Example	Stroke in the motor cortex	Injury to a nerve

Some diseases damage both. Amyotrophic lateral sclerosis (ALS), covered in Chapter 13, attacks upper and lower motor neurons, so patients can show both sets of signs.

A quick way to remember



Think "**U**pper = **U**p." With upper motor neuron damage, tone goes up, reflexes go up, and the big toe goes up.

7.7 The Basal Ganglia: Gas Pedal and Brake

We have a commander and a delivery route. But how does the brain choose *which* movement to send, and keep the others from slipping out? When Maya kicks, she must swing her right leg *and* hold back every competing movement.

The analogy: a car with the parking brake on

Picture a car parked on a hill with the parking brake pulled tight. To drive, you release the brake for the movement you want and keep it on for everything else. Your brain works this way. At rest, a set of nuclei holds a steady brake on movement. To move, the brain releases that brake for one chosen action. Releasing a brake is a "double negative": you create movement by *stopping* something that was stopping you.

This part has a lot of names



The basal ganglia circuit is famous for being confusing, so it's fine if it takes two reads. Keep the car in mind: one pathway releases the brake, one presses it, and dopamine tips the balance.

Meet the players

The **basal ganglia** are a group of nuclei deep in the brain that help select wanted movements, suppress unwanted ones, and form habits. They work in a loop with the cortex and thalamus. The main motor parts are:

- The **striatum** (the caudate and putamen), the input station. It receives excitatory input from the cortex, and its output neurons are inhibitory (they use GABA).
- The **globus pallidus**, with an external part (**GPe**) and an internal part (**GPi**).
- The **subthalamic nucleus (STN)**, the only basal ganglia nucleus whose output is excitatory (glutamate).
- The **substantia nigra**, a midbrain nucleus named "black substance" for its dark color. Its **pars compacta (SNc)** contains dopamine-making neurons that send dopamine to the striatum. Its **pars reticulata (SNr)** works with the GPi as an output station.

GPi and SNr are the brake. Their inhibitory neurons fire at a high rate all the time, holding back the thalamus, which would otherwise excite the motor cortex (Wikipedia: Basal ganglia).

The direct and indirect pathways

From the striatum, signals reach the brake by two routes, called the **direct and indirect pathways**.

Direct pathway ("GO"): Cortex excites striatal neurons that carry D1 dopamine receptors. These neurons inhibit GPi/SNr. Inhibiting the brake releases the thalamus, which excites the motor cortex, and the chosen movement goes ahead.

Indirect pathway ("NO-GO"): Cortex excites a different set of striatal neurons that carry D2 receptors. These inhibit GPe. Because GPe normally inhibits the STN, quieting GPe releases the STN. The STN then excites GPi/SNr, pressing the brake harder, and competing movements are held back.

The table lists every connection in this classic model and its sign. If you keep track of the signs, the rest of the circuit makes sense.

Connection	Transmitter	Effect
Cortex → striatum	Glutamate	Excites (+)
Striatum (D1) → GPi/SNr	GABA	Inhibits (−)
Striatum (D2) → GPe	GABA	Inhibits (−)
GPe → STN	GABA	Inhibits (−)
STN → GPi/SNr	Glutamate	Excites (+)
GPi/SNr → thalamus	GABA	Inhibits (−)
Thalamus → cortex	Glutamate	Excites (+)
SNc → striatal D1 neurons	Dopamine	Excites (+)
SNc → striatal D2 neurons	Dopamine	Inhibits (−)

Dopamine tips the balance

Look at the last two rows. Dopamine excites the D1 (GO) neurons and inhibits the D2 (NO-GO) neurons (Wikipedia: Basal ganglia; OpenStax, Section 10.3). Both effects push the same way: **more dopamine means a weaker brake and more movement.**

This two-pathway picture is the classic model of the basal ganglia, laid out in the late 1980s, including in a widely cited 1989 review by Albin, Young, and Penney (*Trends in Neurosciences*, 1989). It explains movement disorders as two opposite kinds of imbalance:

- **Hypokinetic disorders** ("too little movement") happen when the brake is too strong. Parkinson's disease is the main example.
- **Hyperkinetic disorders** ("too much movement") happen when the brake is too weak. Examples include the dance-like movements called **chorea** in Huntington's disease, in which striatal neurons break down and die (NINDS: Huntington's Disease), and the extra movements (dyskinesia) some people with Parkinson's develop after years of dopamine-boosting medicine.

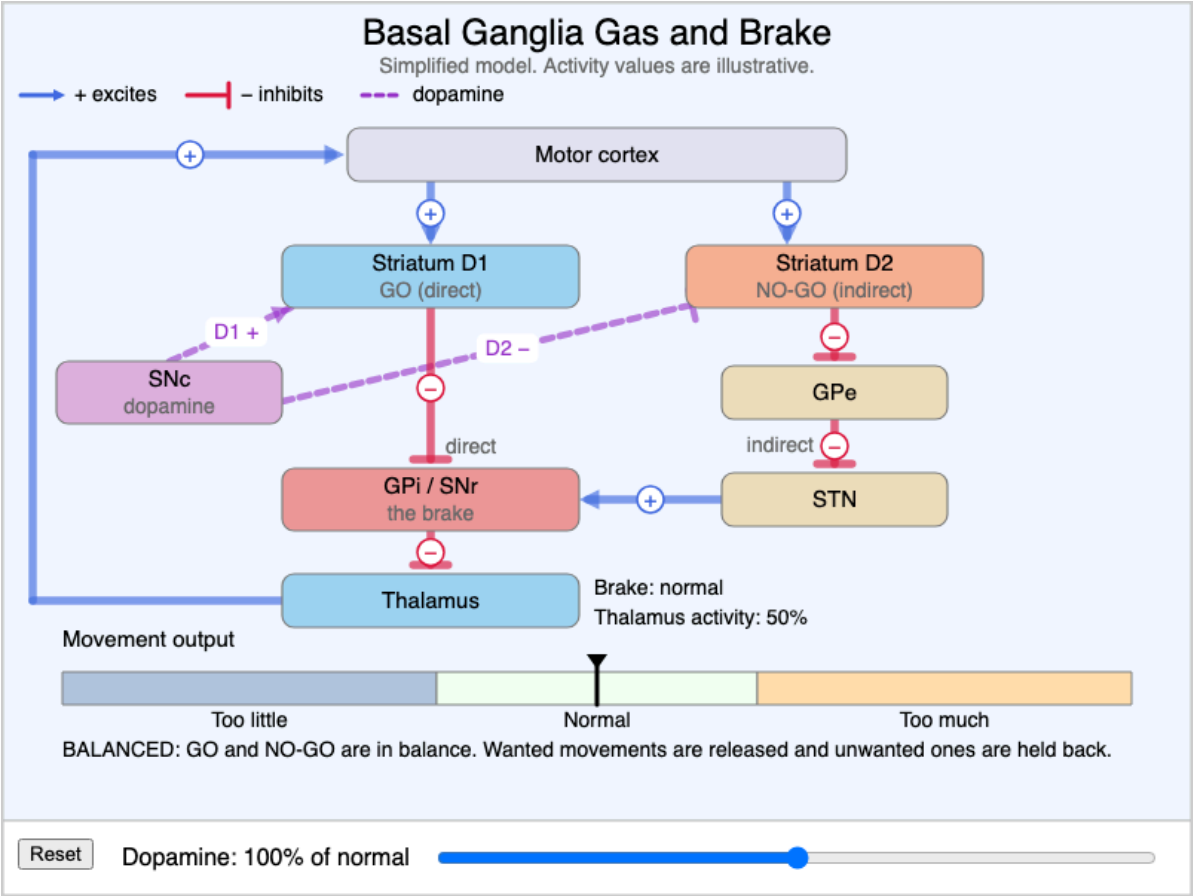
A useful model, not the whole brain



The two-pathway model is a simplified map. Real basal ganglia have extra routes, such as a "hyperdirect" pathway from cortex straight to the STN, and scientists still debate how cleanly the two pathways separate. In mice, for example, neurons of both pathways become active together just as a movement starts, which challenges the simple idea that one pathway only means "go" and the other only means "stop" (Cui and colleagues, 2013).

Now try the circuit yourself. Every label in the simulation (striatum, GPe, GPi/SNr, STN, SNc, thalamus, direct and indirect pathways) was defined above.

Diagram: Basal Ganglia Gas and Brake



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch07-basal-ganglia/

Open the Basal Ganglia Gas and Brake fullscreen

MicroSim specification: Basal Ganglia Gas and Brake

Type: microsim **sim-id:** ch07-basal-ganglia
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: explain
Learning Objective: The learner will explain how lowering or raising dopamine shifts the balance between the direct and indirect pathways, and predict whether movement output will be too little, normal, or too much.

Canvas: width-responsive; 550 px drawing area plus 50 px control area (iframe 602 px).

Controls: dopamine slider, 0% to 200% of normal (step 10%, default 100%); Reset button.

Behavior: nodes and connection signs match the table in Section 7.7 (arrows with + are excitatory, flat bars with − are inhibitory, dashed lines are dopamine). Line thickness scales with the sending node's activity. Illustrative model with dopamine d (1 = normal): D1 = 0.5 + 0.35(d − 1); D2 = 0.5 − 0.35(d − 1); GPe = 1 − D2; STN = 1 − GPe; GPi/SNr = 0.5 − 0.5(D1 − 0.5) + 0.5(STN − 0.5); movement output = thalamus = 1 − GPi/SNr. The meter reads "Too little" when output < 0.35 (dopamine 50% or less), "Normal" from 0.35 to 0.65, and "Too much" when output > 0.65 (dopamine 150% or more). The sim is labeled as a simplified model with illustrative values.

Start at 100% dopamine, where every pathway is medium thickness and the meter reads "Normal." **Before you touch the slider, predict:** if dopamine drops, which pathway gets thinner and which gets thicker? Then drag the slider to 30%. The direct pathway fades, the indirect pathway thickens, the GPi/SNr brake strengthens, the thalamus goes quiet, and the meter slides into "Too little." That is the basal ganglia in Parkinson's disease.

Now drag the slider to 170%. The direct pathway dominates, the brake weakens, and the meter moves into "Too much," like the extra movements that can appear when dopamine signaling is pushed too high. Find the settings where the meter changes zones, and notice that "normal" is a balance, not a maximum.

7.8 The Cerebellum: The Coordination Coach

The basal ganglia help choose *which* movement happens. The cerebellum helps make it *smooth and accurate*.

A navigation app constantly compares where you *are* with where you *should be*, and recalculates when you drift. The **cerebellum**, the wrinkled structure under the back of the brain, does this for movement.

Cerebellar coordination is the cerebellum's job of timing and smoothing movements by comparing the intended movement with the actual one and sending corrections. It receives a copy of the **plan** from the cortex (through the brainstem) and **feedback** about the actual movement, mostly from muscle spindles and other proprioceptors. When the two don't match, it sends corrections through the thalamus to the motor cortex (OpenStax, Section 10.3). If Maya's planted foot slips, her cerebellum helps adjust the swing.

The cerebellum is small but packed. It is only about 10% of the brain's mass, yet it holds about 69 billion of the brain's roughly 86 billion neurons, about four out of five (Herculano-Houzel, 2009).

Cerebellar damage doesn't paralyze anyone. Instead, movements become clumsy and poorly timed, a condition called **ataxia**. Signs include **dysmetria** (overshooting or undershooting a target), an **intention tremor** that gets worse as the hand nears a target, and a wide, unsteady walk. Damage to one side of the cerebellum affects the **same** side of the body (Wikipedia: Cerebellum), unlike the motor cortex. Doctors use this difference to locate a problem.

Question	Basal ganglia	Cerebellum
Main job	Select and start wanted movements; suppress others	Coordinate, time, and correct movements
Analogy	Gas pedal and brake	Navigation app that recalculates
Damage causes	Too little movement (Parkinson's) or too much (chorea)	Clumsy, inaccurate movement (ataxia)
Typical tremor	At rest (in Parkinson's disease)	During movement, worse near the target

7.9 Motor Learning: Practice Makes Automatic

The first time Maya tried to curve a ball around a wall of defenders, she had to think about every detail. Now she does it without thinking. What changed?

Motor learning is the process by which practice turns a clumsy, effortful movement into a smooth, accurate, and largely automatic skill. It leans on two structures you just met (OpenStax, Section 10.3):

- The **cerebellum** uses the errors from each attempt to fine-tune the next. Slow, careful practice gives it time to notice and fix errors.
- The **basal ganglia**, working with the cortex, help "package" a sequence of movements into a habit that runs with little conscious attention.

As a skill moves from early (slow, many errors) to late (fast, automatic), attention is freed for the game, like watching the goalkeeper instead of your own foot. OpenStax also notes that imagined practice, rehearsing a movement in your mind, can improve performance because it uses some of the same circuits. It adds to real practice but doesn't replace it.

7.10 When the Brake Is Stuck: Parkinson's Disease, Levodopa, and DBS

Now we can put the chapter together to understand one of the most common movement disorders.

What goes wrong

Parkinson's disease is a nervous system disorder that affects movement and gets worse over time. It happens mainly because dopamine-making neurons in the substantia nigra pars compacta weaken and die. By the time symptoms appear, most people have lost about 60 to 80% or more of these cells (NINDS: Parkinson's Disease). Damaged cells in most people with Parkinson's contain **Lewy bodies**, clumps of a protein called **alpha-synuclein**.

The average age when symptoms start is in the early to mid-60s. In most people the cause is unknown, and both genes and environment are thought to contribute (NINDS). Because the risk rises with age, the number of people living with Parkinson's is growing as populations get older. A 2025 study based on Global Burden of Disease data projected that the number of people with Parkinson's worldwide will more than double between 2021 and

2050, to about 25 million, with population aging as the main driver (Su and colleagues, 2025, *BMJ*).

Your simulation shows why losing dopamine slows movement. The direct pathway weakens, the indirect pathway strengthens, and both changes tighten the brake on the thalamus. NINDS lists four common motor signs:

- **Tremor** most obvious when the hand is at rest, often a "pill-rolling" rub of thumb and finger. Some people never develop a tremor.
- **Rigidity**, stiffness a doctor feels when moving the person's arm, sometimes with small catches ("cogwheel" rigidity).
- **Bradykinesia**, slowness of movement, including fewer facial expressions.
- **Postural instability**, balance problems that raise the risk of falls, often with a stooped, shuffling walk.

Many people also have sleep problems, constipation, or loss of smell before movement symptoms begin (NIA: Parkinson's Disease).

Levodopa: refilling the tank

Why not just give dopamine? Because dopamine in the blood can't easily cross the **blood-brain barrier**, the tightly sealed lining of the brain's blood vessels. Its precursor can. **Levodopa** (L-dopa) is a medicine that the brain converts into dopamine, and it is the main treatment for Parkinson's disease. Levodopa is almost always combined with **carbidopa**, which blocks levodopa's breakdown in the rest of the body so more reaches the brain (NINDS).

The story connects back to Ply. Arvid Carlsson showed that dopamine is a neurotransmitter that matters for movement: animals given a drug that depleted their transmitter stores stopped moving on their own, and recovered after receiving L-dopa. His work led to the realization that Parkinson's is caused by too little dopamine and could be treated with L-dopa. Carlsson shared the 2000 Nobel Prize with Paul Greengard and with Eric Kandel, the *Aplysia* scientist (Nobel Prize press release, 2000).

Levodopa eases symptoms, but it does not replace lost neurons or stop the disease from progressing. After years of treatment, its effect may wear off between doses ("off" periods),

and some people develop **dyskinesia**, extra twisting or writhing movements (NINDS). In the simulation, that is like overshooting from "Too little" into "Too much."

Deep brain stimulation

Deep brain stimulation (DBS) is a treatment in which a neurosurgeon implants a thin wire electrode deep in the brain, connected to a battery-powered pulse generator under the skin of the chest, like a heart pacemaker. The electrical pulses change abnormal activity in the circuit. DBS does not cure Parkinson's and does not help every symptom (NINDS).

The targets come straight from the basal ganglia circuit: the **subthalamic nucleus (STN)** or the **internal globus pallidus (GPi)**. The FDA approved DBS at these targets for Parkinson's disease in 2002, after approving DBS in the thalamus for essential tremor and Parkinson's tremor in 1997 (NINDS: DBS history). A newer version, **adaptive DBS**, senses brain signals and adjusts stimulation automatically. The FDA approved the first adaptive DBS system for Parkinson's disease in February 2025 (Medtronic press release, February 24, 2025).

At the Bedside: The Slowing Teacher

Meet the patient

Mr. Alvarez is a 62-year-old retired history teacher. For about a year, his right hand has shaken while it rests in his lap. The shaking fades when he reaches for his coffee. His wife says he walks more slowly, with short shuffling steps, and his right arm no longer swings. His handwriting has become small and cramped, and his voice is softer. Looking back, he lost much of his sense of smell several years ago, and his wife says he sometimes seems to act out his dreams.

What the doctor checks: The neurologist watches him sit, stand, and walk. His right hand shows a pill-rolling tremor at rest that lessens when he moves on purpose. Moving his right wrist, she feels stiffness with small catches (cogwheel rigidity). When he taps finger and thumb quickly, the taps get smaller and slower (bradykinesia). He takes several small steps to turn. Just as important, his strength is normal, his reflexes are normal, there is no Babinski sign, and his finger-to-nose test is accurate.

Where is the problem? (localization): Normal strength, normal reflexes, and no Babinski sign argue against upper or lower motor neuron damage. An accurate finger-to-nose test with no intention tremor argues against the cerebellum. A resting tremor, rigidity, and

slowness that began on one side point to the **basal ganglia**, specifically to lost dopamine input from the **substantia nigra pars compacta**. The early loss of smell and dream-enacting behavior fit the same disease.

Diagnosis: Parkinson's disease. No single test proves it. Doctors diagnose it mainly from the history and exam. Blood tests and MRI help rule out other conditions, and a dopamine transporter (DaT) scan can help, though it can't tell Parkinson's apart from some related disorders (NINDS).

Why it happens: Most of his dopamine neurons in the SNc have been lost. With less dopamine in the striatum, the direct (GO) pathway weakens and the indirect (NO-GO) pathway strengthens. The GPi/SNr brake on the thalamus becomes too strong, so the motor cortex gets too little "go" signal: the "Too little" zone in the simulation.

Treatment today: Standard care starts with medicine that raises dopamine signaling, most often carbidopa-levodopa. Other options include dopamine agonists, which act like dopamine, and MAO-B inhibitors, which slow dopamine breakdown. Exercise, physical therapy, and speech therapy help with movement, balance, and voice. If medicines later stop working smoothly, his neurologist may discuss DBS of the STN or GPi (NINDS). Newer options, as of 2026, include a small pump that delivers a levodopa-based medicine under the skin around the clock, which the FDA approved in October 2024 for advanced Parkinson's with "off" periods (AbbVie, 2024). In September 2026 the FDA approved tavapadon, the first approved dopamine agonist designed to act selectively on D1-type receptors (D1 and D5), the kind found on direct (GO) pathway neurons (NeurologyLive, 2026). Like levodopa, these treat symptoms. None has been shown to slow the disease.

What's new in research: The **alpha-synuclein seed amplification assay (SAA)** is a lab test that checks spinal fluid for misfolded alpha-synuclein "seeds" that can make normal alpha-synuclein misfold and clump. In a study of 1,123 people, it was positive in 87.7% of people with Parkinson's disease and negative in 96.3% of healthy controls, and it was also positive in many people who had early warning signs like loss of smell or dream-enacting behavior but no movement symptoms yet (Siderowf et al., 2023, *Lancet Neurology*). In 2024 the FDA issued a **Letter of Support** encouraging its use in research and clinical trials (Michael J. Fox Foundation, 2024). That is **not** FDA approval of a diagnostic test.

A version is offered by a commercial lab, and NINDS notes that such tests can help diagnose Parkinson's but cannot tell it apart from some similar disorders, such as multiple

system atrophy and Lewy body dementia (NINDS). Researchers hope it will help find people early enough to test treatments that might slow the disease.

Your turn: diagnose a variation

Eight years later, Mr. Alvarez still takes carbidopa-levodopa. About an hour after each dose, he develops twisting, writhing movements of his arms and trunk that he can't control. Before his next dose, he becomes slow and stiff again. What is happening, and how does the basal ganglia model explain it?

Answer: These are **levodopa-induced dyskinesias** plus **"off" periods**. At the dose's peak, dopamine signaling overshoots: the direct pathway dominates, the indirect pathway is suppressed, and the GPi/SNr brake becomes too weak, so unwanted movements slip through (the "Too much" zone). As the dose wears off, he slides back into "Too little." Swings like this are one reason doctors may adjust medicines or consider DBS.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Muscles decide for themselves how hard to contract.
Reality: A muscle fiber contracts only when its motor neuron fires. The nervous system sets force by choosing how many motor units to recruit and how fast each one fires.

Myth: Parkinson's disease is just shaking.
Reality: Slowness (bradykinesia) and rigidity are core features, and some people with Parkinson's never develop a tremor. Many also have non-movement symptoms, like loss of smell or sleep problems, sometimes years before movement symptoms.

Myth: Every reflex goes up to the brain before you react.
Reality: Reflexes like the knee-jerk are handled by spinal cord circuits. The brain finds out afterward, though it does adjust how strong reflexes are.

Myth: Levodopa is dopamine, and it cures Parkinson's.
Reality: Levodopa is the raw material the brain turns into dopamine, used because dopamine can't easily cross the blood-brain barrier. It eases symptoms but doesn't restore lost neurons or stop progression.

Brain Bee Practice

1. What is a motor unit?

A single motor neuron together with all of the muscle fibers it controls. When the neuron fires, all of those fibers contract together.

2. Name the parts of a reflex arc in order.

Sensory receptor, sensory neuron, integration center in the spinal cord, motor neuron, and effector (usually a muscle).

3. A patient has weakness in one arm, exaggerated reflexes, and an upgoing big toe when the sole is stroked. Upper or lower motor neuron damage?

Upper motor neuron damage. Brisk reflexes, spasticity, and a Babinski sign mean the lower motor neurons and reflex loops work but have lost control from above.

4. Which neurons die in Parkinson's disease, and which neurotransmitter do they make?

Neurons in the substantia nigra pars compacta, in the midbrain. They make dopamine and send it to the striatum.

5. Damage to the right side of the cerebellum causes clumsiness on which side of the body?

The right side. Cerebellar damage affects the same side of the body, unlike motor cortex damage, which affects the opposite side.

Exercises

Remember

1. List the two ways the nervous system increases the force of a muscle contraction.

2. Name the two pathways from the striatum to GPi/SNr, and say which is "GO" and which is "NO-GO."

Answer

1. Firing motor neurons faster, and recruiting more motor units.
2. The direct pathway is "GO"; the indirect pathway is "NO-GO."

Understand

1. Explain why ATP is needed for a muscle to *relax*, not just to contract.
2. Explain why dopamine, which excites D1 neurons but inhibits D2 neurons, pushes both pathways toward more movement.

Answer

1. ATP lets each myosin head release actin and reset. Without ATP, myosin stays locked on, which is why muscles stiffen after death (rigor mortis).
2. Exciting the direct pathway inhibits the GPi/SNr brake. Inhibiting the indirect pathway weakens a route that would press the brake harder. Both weaken the brake and favor movement.

Apply

1. A doctor taps a patient's patellar tendon and gets no response on either side. Using the reflex arc, list three different places where the problem could be.
2. In the Basal Ganglia Gas and Brake simulation, find the lowest dopamine setting that still reads "Normal." Describe how the direct pathway, indirect pathway, and GPi/SNr compare with 100%.

Analyze

1. Compare a patient with a stroke in the left motor cortex to a patient with damage to the left side of the cerebellum. Which side of the body is affected in each, and how would the movement problems look different?

2. Huntington's disease damages striatal neurons. The classic model proposes that chorea comes from early loss of the striatal neurons that form the indirect pathway. Use the circuit signs to explain why losing a NO-GO pathway would cause *extra* movement.

Evaluate

1. A website claims, "Parkinson's is caused by low dopamine, so the best treatment is the highest possible dose of levodopa." Evaluate this claim using the direct and indirect pathways and dyskinesia.
2. The alpha-synuclein seed amplification assay has an FDA Letter of Support for clinical trials but is not an FDA-approved diagnostic. Weigh the benefits and risks of using it to tell people without symptoms that they may develop Parkinson's disease.

Create

1. Design a classroom demonstration (no animals or medicines) that shows the difference between small and large motor units, or between a reflex and a voluntary movement. Describe materials, steps, and what students should observe.
2. Write a short fictional case of a patient with a cerebellar problem. Include at least three findings and a localization paragraph explaining why the cerebellum, not the basal ganglia or motor neurons, is the likely site.

Key Takeaways

- Muscles only pull. A motor neuron's signal releases calcium in a muscle fiber, letting myosin pull on actin; ATP lets myosin let go and reset.
- A motor unit is one motor neuron and all its fibers. The brain sets force by recruiting small motor units first, then larger ones, and by firing them faster.
- Reflex arcs, like the monosynaptic stretch reflex tested by the knee-jerk, run through the spinal cord, though the brain sets their strength.
- The primary motor cortex sends commands down the corticospinal tract, which mostly crosses in the medulla, so each side of the brain controls the opposite side of the body.

- Upper motor neuron damage causes spasticity, brisk reflexes, and a Babinski sign. Lower motor neuron damage causes floppy weakness, weak reflexes, wasting, and fasciculations.
- The basal ganglia act as a gas pedal and brake. Dopamine from the substantia nigra strengthens the direct (GO) pathway and weakens the indirect (NO-GO) pathway. The cerebellum corrects errors, and both help motor learning.
- In Parkinson's disease, lost dopamine neurons make the brake too strong. Levodopa, other medicines, exercise, and DBS of the STN or GPi treat symptoms but don't cure the disease.

You followed a movement from neuron to bedside!



You can now trace a kick from a decision in the cortex to myosin pulling on actin, and explain why a missing brain chemical can freeze a person in place. Next, in Chapter 8, we'll see how these circuits are built, and why the teenage brain is still under construction.

Chapter 8: The Developing and Teenage Brain

Summary

Your brain was not built all at once. It started as a tiny folded tube, filled with new neurons that crawled to their places, and made far more connections than it would keep. During childhood and the teen years, the brain prunes the connections it doesn't use and insulates the ones it does, with the prefrontal cortex finishing last. This chapter follows that journey to the mid-twenties, explains why teens are drawn to rewards and peers, and shows what happens when alcohol interferes before birth.

Concepts Covered

1. Neural Tube
2. Neurogenesis
3. Neuronal Migration
4. Synaptogenesis
5. Synaptic Pruning
6. Myelination Over Time
7. Critical Period
8. Adolescent Brain
9. Prefrontal Maturation
10. Reward Sensitivity in Teens
11. Teratogen
12. Fetal Alcohol Spectrum
13. Nature and Nurture

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System (neurons, glia, myelin)
- Chapter 2: The Action Potential (how signals travel along axons)
- Chapter 3: Synapses and Neurotransmitters (synapses, dopamine, glutamate, GABA)
- Chapter 4: A Tour of the Brain: Neuroanatomy (cerebral cortex, frontal lobe, prefrontal cortex)

A Brain Under Construction



I'm Ply, a sea slug with only about 20,000 neurons, so I got built pretty fast. Your brain took much longer, and parts of it are still being remodeled as you read this. This chapter is about you: how your brain got built, why the teen years are a special construction phase, and what can go wrong before birth.

8.1 Why Do Teenagers Take More Risks?

Maya is 16. After a Saturday soccer game, a teammate with a brand-new license offers her a ride home. Three other friends pile in. Someone turns the music up and dares the driver to "see what this car can do." Maya knows the road curves ahead. She aced a reaction-time quiz last week while studying for the Brain Bee. Yet with friends cheering in the back seat, the dare doesn't sound as dumb as it would if she were alone.

That night, Maya scrolls past a headline: "Teen brains aren't finished until 25!" Is her brain "half-built"? And if she knew the risk, why did the dare feel so tempting? This chapter answers with what scientists have actually measured. The short answer: the teenage brain isn't broken. It is in a very active phase of construction, and the timing of that construction helps explain both the risks teens take and how quickly they learn.

8.2 Building a Brain: The Big Picture

Before we name any structures, picture how a new city might be built.

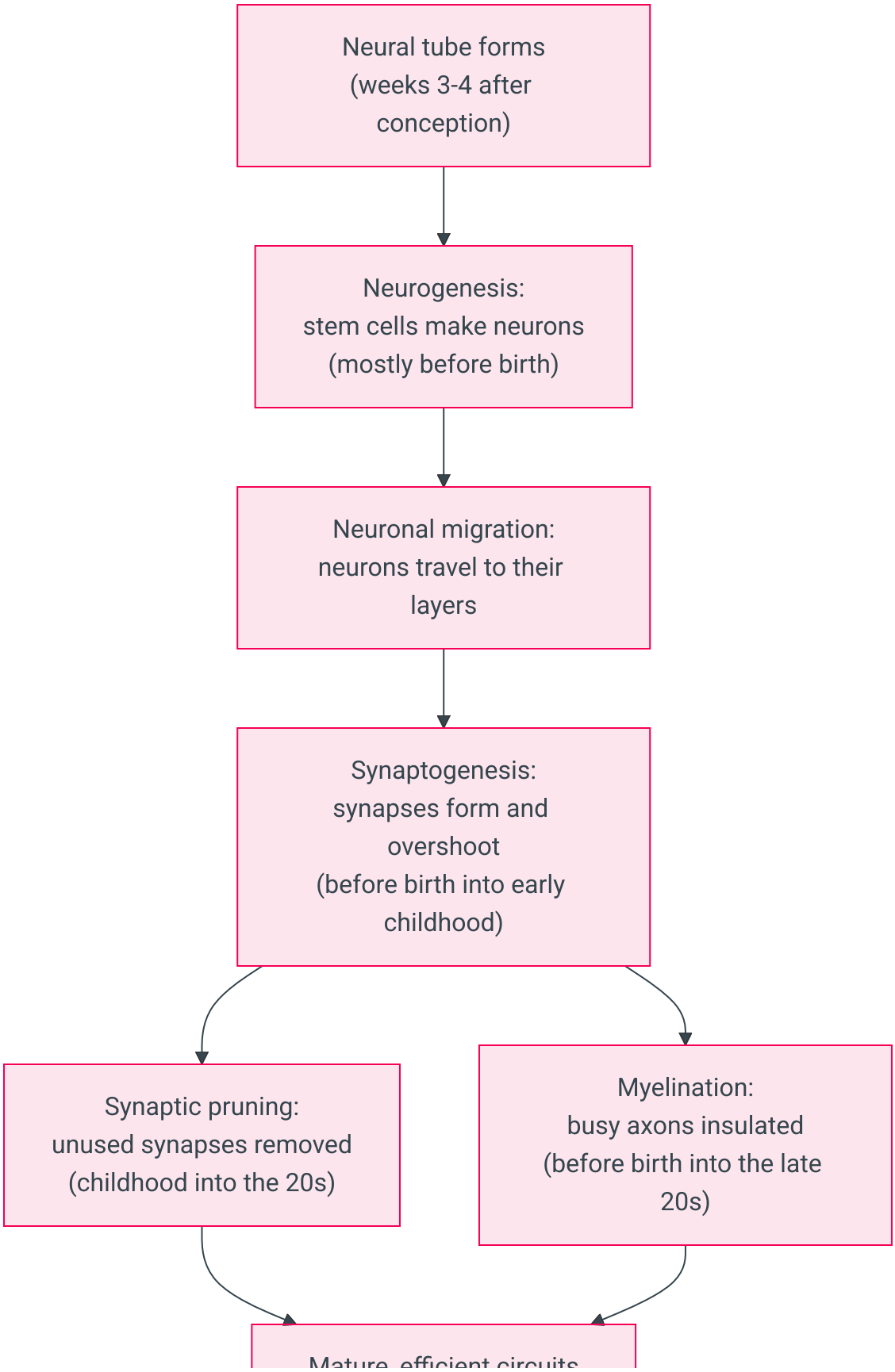
First, builders lay down the outline. Next, factories make lots of workers, who travel along scaffolding to their job sites. Then they build roads between every building they can reach,

far more than the city needs. For years, the city watches traffic. Busy roads are kept and paved into highways. Unused roads are closed. The city ends up with fewer roads, but a much more efficient network.

Your brain was built in almost exactly that order:

1. A flat sheet of cells folds into a tube that sets the basic outline (the **neural tube**).
2. Stem cells divide to make enormous numbers of new neurons (**neurogenesis**).
3. The new neurons travel to their final positions (**neuronal migration**).
4. Neurons connect to each other by forming synapses, overshooting what an adult brain keeps (**synaptogenesis**).
5. Unused synapses are removed (**synaptic pruning**), and busy pathways are insulated with myelin (**myelination**).

The first three steps happen mostly before birth. The last two continue into the twenties. The flowchart below summarizes the sequence.


Neural tube forms (weeks 3-4 after conception)
Neurogenesis: stem cells make neurons (mostly before birth)
Neuronal migration: neurons travel to their layers
Synaptogenesis: synapses form and overshoot (before birth into early childhood)
Synaptic pruning: unused synapses removed (childhood into the 20s)
Myelination: busy axons insulated (before birth into the late 20s)
Mature, efficient circuits

Mature, efficient circuits
that keep adapting for life

8.3 The Neural Tube: Where It All Starts

Early in pregnancy, part of the embryo's outer cell layer (the ectoderm) forms a flat strip called the neural plate. Its edges rise like two walls, curl toward each other, and zip together into a hollow tube. This is the **neural tube**, which becomes the entire central nervous system. The upper end becomes the brain and the rest becomes the spinal cord. The hollow inside remains as the brain's fluid-filled ventricles and the spinal cord's central canal (OpenStax, Section 5.1; NINDS).

According to the National Institute of Neurological Disorders and Stroke (NINDS), the neural tube typically folds and closes during the third and fourth weeks of development, about a month after conception, often before a person knows they are pregnant.

When the tube does not close properly, the result is a **neural tube defect**. If the back end fails to close, part of the spinal cord can be left exposed, a condition called spina bifida. If the front end fails to close, the forebrain does not develop, a condition called anencephaly (NINDS).

The CDC reports that folic acid, a B vitamin, is the only form of folate shown to help prevent neural tube defects. Because the tube closes so early, the CDC recommends folic acid every day for anyone who could become pregnant, not just after a positive test (CDC). Keep this example in mind for Section 8.13.

8.4 Making Neurons and Moving Them Into Place

Neurogenesis

Cells lining the inner wall of the neural tube divide very fast. These are **neural stem cells**, which can copy themselves and also produce specialized cells. **Neurogenesis** is the creation of new neurons from stem cells. Later, stem cells switch to producing glia, the support cells from Chapter 1 (OpenStax, Section 5.2).

NINDS states that most of the brain's neurons have already been created by the time we're born. Whether adults make many new neurons is still debated. NINDS notes that

neuroscientists disagree about how many and how often (NINDS, Brain Basics). The big neuron-building phase happens before birth.

Neuronal migration

New neurons usually aren't born where they will work. **Neuronal migration** is the movement of new neurons from their birthplace to their final home. Many climb along long glial fibers called **radial glia**, which stretch like ropes from the inner wall of the neural tube to the outer surface (NINDS, Brain Basics). Radial glia are also neural stem cells, so they help make neurons and then guide them. The cortex is built "inside-out": the earliest-born neurons settle in the deepest layers, and later-born neurons crawl past them toward the surface (OpenStax, Section 5.2).

If migration goes wrong, neurons end up in the wrong place. In a rare condition called **lissencephaly** ("smooth brain"), the cortex develops without its normal folds. NINDS lists neuronal migration problems as the cause (NINDS).

Surprisingly, the developing brain also makes extra neurons, and large numbers die along the way. This is part of the plan. Neurons compete for survival signals called neurotrophins, and those that don't get enough self-destruct in an orderly process called apoptosis (OpenStax, Section 5.3).

8.5 Wiring Up: Synaptogenesis and Synaptic Pruning

Synaptogenesis: making too many connections

Once a neuron arrives, it grows dendrites and an axon and connects with other neurons. Recall from Chapter 3 that a synapse is the junction where one neuron passes a chemical message to another. **Synaptogenesis** is the formation of new synapses.

In a classic study, Peter Huttenlocher and Arun Dabholkar measured synapse density in human cortex at different ages, comparing an auditory (hearing) area with a prefrontal (planning) area. Synapse formation began in both before birth. But auditory cortex peaked around 3 months after birth, while the prefrontal area didn't peak until after 15 months (Huttenlocher and Dabholkar, 1997).

At their peaks, young brains are crowded with synapses. A later study of the human prefrontal cortex found that dendritic spines, the tiny bumps where most excitatory

synapses sit, are two to three times more dense in childhood than in adults (Petanjek and colleagues, 2011).

Synaptic pruning: use it or lose it

Why build extra connections? Your genes can't predict which language you'll hear or whether you'll play soccer or piano. So the brain overbuilds, then lets experience decide.

Synaptic pruning is the removal of weak or unused synapses during development. The rule is often summarized as "use it or lose it." Synapses that are active often get strengthened and kept. Synapses that are rarely used get removed (OpenStax, Section 5.3). Like closing unused roads, this makes traffic flow better.

Pruning, like synapse formation, follows a regional schedule. In Huttenlocher's data, net synapse loss in the auditory cortex was over by about age 12, while in the prefrontal cortex it extended to mid-adolescence (Huttenlocher and Dabholkar, 1997). Petanjek's team found that substantial pruning of prefrontal spines continues through the twenties before settling at adult levels (Petanjek and colleagues, 2011).

Who does the pruning? Partly microglia, the brain's resident immune cells. In young mice, microglia were caught "eating" synaptic inputs in the visual system during peak pruning, and this depended on how active those inputs were (Schafer and colleagues, 2012).

Less Can Be More



A mature brain has fewer synapses than a toddler's brain, and that's a good thing. Pruning turns a tangled thicket into tuned circuits shaped by what you actually do. Every big idea starts at a single synapse, but a good brain also knows which ones to let go!

8.6 Myelination Over Time

Pruning is half of the remodeling story. The other half is insulation. Recall from Chapters 1 and 2 that **myelin** is a fatty wrapping made by glial cells, and it lets action potentials jump from node to node, so signals travel much faster.

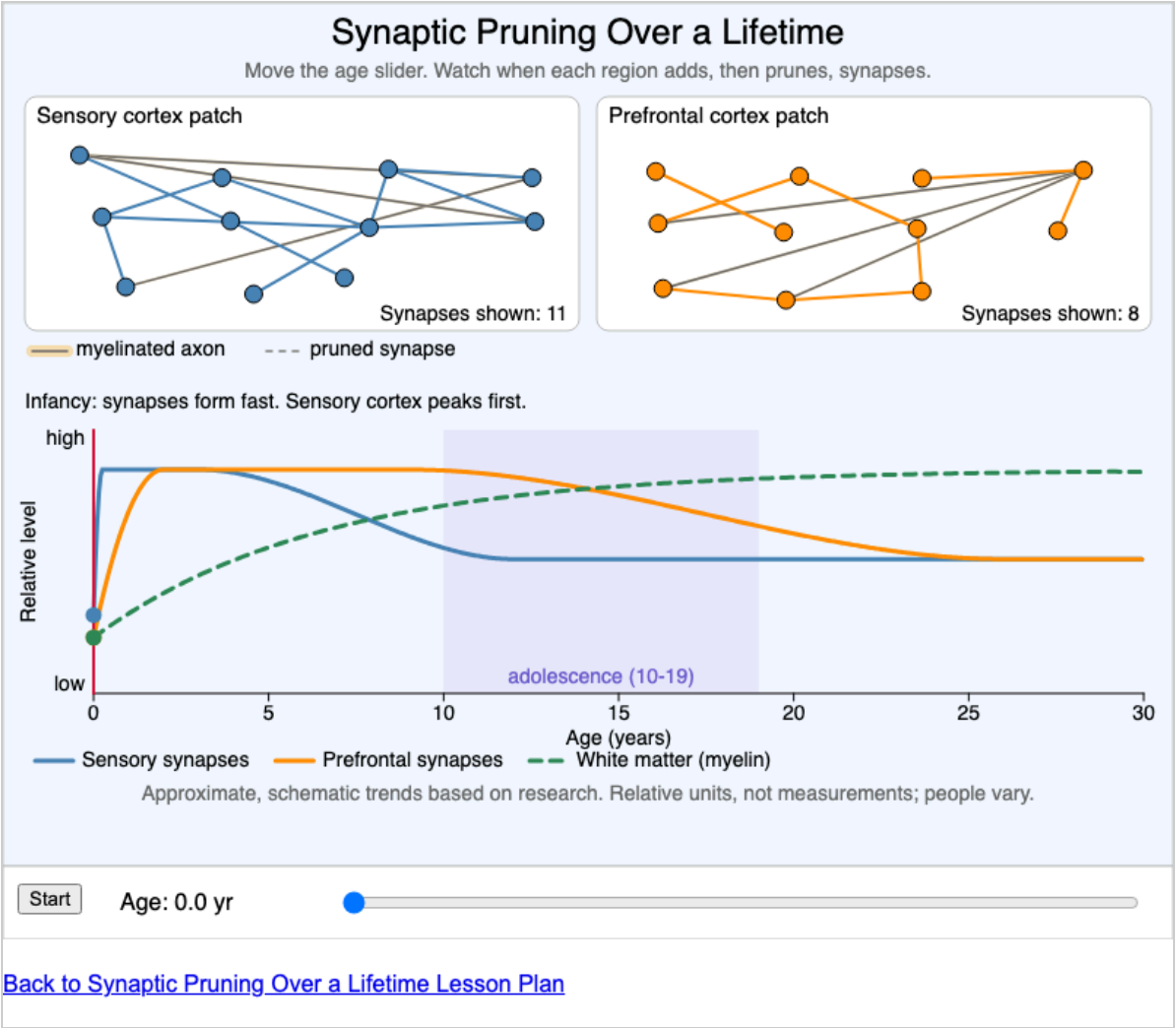
Myelin starts being laid down before birth. It appears first in peripheral nerves, then the spinal cord, then the brain. The busiest period is the first year after birth, and it continues in the front of the brain through childhood and adolescence (OpenStax, Section 5.3). We call this gradual, region-by-region process **myelination over time**.

How long does it continue? MRI can track **white matter**, the parts of the brain made mostly of myelinated axons. One team scanned 103 people aged 5 to 32, each at least twice. Many pathways finished maturing by late adolescence, but the long "association" pathways linking distant parts of the cortex kept maturing after adolescence (Lebel and Beaulieu, 2011).

A huge study combined 123,984 MRI scans from 101,457 people, from before birth to age 100. Total white matter volume rose quickly in early childhood, then kept rising slowly, peaking at about 29 years. Gray matter volume (cell bodies and synapses), by contrast, peaked at about 6 years and then slowly declined (Bethlehem and colleagues, 2022). Both changes are part of normal maturation.

The MicroSim below puts this together. Its curves follow the findings above: sensory cortex peaks and prunes early, prefrontal cortex peaks later and keeps pruning into the twenties, and white matter keeps rising for years.

Diagram: Synaptic Pruning Over a Lifetime



Back to Synaptic Pruning Over a Lifetime Lesson Plan

Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch08-synaptic-pruning/

Open the Synaptic Pruning Over a Lifetime fullscreen

MicroSim specification: Synaptic Pruning Over a Lifetime

Type: microsim **sim-id:** ch08-synaptic-pruning
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: compare
Learning Objective: The learner will compare the timing of synapse overproduction, synaptic pruning, and myelination in sensory cortex versus prefrontal cortex from birth to age 30.

Canvas: drawing area 590 px tall plus a 50 px control area; width responsive.

Controls: Start/Pause button (plays age forward from 0 to 30, then loops; starts paused) and an age slider (0 to 30 years, step 0.1).

Behavior: Top: sensory (blue) and prefrontal (orange) neuron patches; solid lines are synapses, dashed gray lines are pruned synapses, and three long axons gain thicker myelin with age. Bottom: schematic relative synapse density (sensory peaks near 3 months and prunes until about 12; prefrontal peaks near 2 years and prunes into the mid-20s) and relative white matter volume (peak near 29), with adolescence (10 to 19) shaded and a marker at the chosen age. Labeled "approximate, schematic trends based on research"; no numeric y-axis.

Sources: Huttenlocher and Dabholkar 1997; Petanjek and colleagues 2011; Bethlehem and colleagues 2022 (all cited in Sections 8.5 and 8.6).

What to try: Drag the slider slowly from birth to age 3. Which region peaks first? Keep going and watch dashed "pruned" lines appear in the sensory patch while the prefrontal patch stays crowded. Stop at 16, Maya's age, and read the note above the graph.

What to notice: At 16, sensory pruning is long finished, but prefrontal pruning is under way and white matter is still climbing. Notice what the sim does *not* show: a sudden "finish line." The curves are schematic, so focus on the order and shape of events, not exact heights.

8.7 Critical Periods: Windows for Experience

What happens if a young brain doesn't get the experience it expects? David Hubel and Torsten Wiesel answered this in kittens. They closed one eyelid for a time, then recorded from neurons in the visual cortex. If the eye was closed during a window in the first few months of life, the cortex rewired so that far fewer neurons responded to the closed eye. During the most sensitive weeks (the fourth and fifth weeks of life), closing an eye for as

little as 3 to 4 days caused a sharp change. Closing an adult cat's eye for over a year produced no detectable effect (Hubel and Wiesel, 1970).

Hubel and Wiesel shared the 1981 Nobel Prize in Physiology or Medicine for their discoveries about how the visual system processes information (NobelPrize.org).

A **critical period** is a window in development when a particular experience (or a harmful exposure) has an especially large and lasting effect on the brain.

This matters in the clinic. In **amblyopia** ("lazy eye"), the brain and one eye don't work together well, so the brain relies on the stronger eye and vision in the weaker eye worsens. Doctors cover the stronger eye with a patch, or blur it with eye drops, to force the brain to use the weaker eye. The National Eye Institute says early treatment works well, and treatment is usually less effective in adults than in children (NEI).

Critical periods don't mean the brain stops changing afterward. Plasticity, the brain's ability to change with experience, is highest early in life and declines with age, but it doesn't disappear (OpenStax, Section 5.4). Chapter 9 explores lifelong plasticity.

8.8 The Adolescent Brain: Remodeling, Not Broken

Adolescence is the phase of life between childhood and adulthood. The World Health Organization defines it as ages 10 to 19 (WHO). The **adolescent brain** is the brain during this phase. Surprisingly, the National Institute of Mental Health (NIMH) explains that the brain stops growing in size by early adolescence. The teen years are about fine-tuning how the brain works (NIMH), through the pruning and myelination you just explored. NIMH lists several features of the teen brain:

- **It is highly adaptable.** Challenging classes, exercise, and creative activities like music or art can help strengthen brain circuits.
- **Sleep timing shifts.** The sleep hormone melatonin stays high later at night and drops later in the morning, which may explain why teens stay up late and struggle to wake early.
- **It may respond to stress differently,** which may raise the risk of anxiety and depression.
- **Many mental illnesses first appear in adolescence,** including anxiety, depression, bipolar disorder, eating disorders, and schizophrenia (see Chapters 11 and 15).

- **Most teens become healthy adults,** and some adolescent brain changes may support long-term resilience.

None of these points says the teen brain is "defective." It is specialized for a stage of life where learning fast, exploring, and building social connections really matter.

8.9 Prefrontal Maturation: The Last Region to Finish

Recall from Chapter 4 that the **prefrontal cortex**, at the front of the frontal lobe, handles executive functions: planning, prioritizing, resisting impulses, and weighing long-term consequences. NIMH describes it as one of the last brain regions to mature (NIMH).

Prefrontal maturation is the slow refinement of this region and its connections. It includes pruning of extra synapses, myelination of the long pathways linking the prefrontal cortex to the rest of the brain, and strengthening of the circuits that get used.

A well-known study scanned 13 healthy children every two years for 8 to 10 years (ages 4 to 21). Time-lapse "movies" of gray matter showed that higher-order association areas, which combine information, matured only after the sensory and motor areas that feed them (Gogtay and colleagues, 2004). A 2021 review calls this a "sensorimotor-to-association axis" of development (Sydnor and colleagues, 2021). It's the same pattern you saw in the MicroSim: sensory first, prefrontal last.

So is the brain "finished" at 25?

You have probably heard that "the brain isn't done developing until 25." Here is what the research shows:

- **Development continues into the twenties.** NIMH states that the brain finishes developing and maturing in the mid-to-late 20s (NIMH). Prefrontal pruning continues through the twenties (Petanjek and colleagues, 2011), and total white matter volume peaks at about 29 (Bethlehem and colleagues, 2022).
- **There is no single finish line.** Different measures level off at different ages. Gray matter volume peaks in childhood, while white matter keeps growing into the late twenties. Neuroscientists themselves have urged the field to work out how "brain maturity" should even be defined and measured (Somerville, 2016).

- **People vary a lot.** The brain-chart study found large differences between individuals of the same age (Bethlehem and colleagues, 2022). No one's brain flips a switch on their 25th birthday.
- **Different abilities mature at different ages.** A study of 5,227 people aged 10 to 30 in 11 countries found that cognitive capacity, the ability to reason logically in calm conditions, reached adult levels around age 16. Psychosocial maturity, the ability to restrain yourself in emotional, exciting, or risky moments, didn't reach adult levels until after 18 (Icenogle and colleagues, 2019).

So "25" is rough shorthand, not a hard cutoff. Brain development continues gradually into the mid-to-late twenties, with large individual differences, and the brain keeps changing with experience for life.

Careful With the Number 25



Don't say "the brain is finished at 25" on a Brain Bee answer or anywhere else. Say "brain development, especially in the prefrontal cortex, continues into the mid-to-late twenties, and the timing varies from person to person." That's accurate, and it shows you know the science behind the slogan.

8.10 Reward Sensitivity in Teens

Back to Maya in the car: she understood the danger, so why did the dare feel tempting? The answer involves two brain systems that mature on different schedules.

The first is the reward system. Dopamine neurons (Chapter 3) signal to a deep region called the **ventral striatum**, which includes the **nucleus accumbens**. This circuit becomes active when we expect something good, like praise or the thrill of winning. The second is the control system centered on the prefrontal cortex, which can put the brakes on impulses.

Psychologist Laurence Steinberg proposed that around puberty, the brain's reward-related and social-emotional system is remodeled, driven mainly by big changes in the dopamine system. This increases **reward sensitivity**, the tendency to be strongly motivated by possible rewards, especially in the presence of peers. Meanwhile, the control system matures gradually through adolescence and young adulthood. The gap between the two

makes mid-adolescence a time of heightened vulnerability to risky choices (Steinberg, 2008).

In one fMRI study of 37 people aged 7 to 29, teens showed exaggerated activity in the nucleus accumbens when they received rewards, compared with both children and adults. Meanwhile, a prefrontal area involved in evaluating rewards looked more like a child's than an adult's (Galvan and colleagues, 2006).

The peer effect

In one experiment, 306 adolescents (13 to 16), young adults (18 to 22), and adults (24 and older) completed questionnaires and a risk-taking task, either alone or with two same-age peers present. Everyone took more risks with friends, but the peer effect was much stronger for adolescents and young adults than for adults (Gardner and Steinberg, 2005).

A later study put teens, young adults, and adults in an fMRI scanner during a simulated driving task. When teens knew peers were watching, reward-related regions, including the ventral striatum, became more active, and that activity predicted their risky choices. Adults didn't show this peer boost (Chein and colleagues, 2011). So friends do more than "pressure" teens. Just having them around seems to make the reward of a risky choice feel bigger.

According to the CDC (in a fact page updated in 2025), drivers aged 16 to 19 have a fatal crash rate almost three times as high as drivers aged 20 and older per mile driven, and the presence of teen or young adult passengers increases the crash risk of unsupervised teen drivers (CDC). That is one reason the graduated driver licensing systems recommended by the CDC limit teen passengers and nighttime driving while new drivers gain experience (CDC).

Reward sensitivity isn't all bad. The same drive also pushes teens to try new things, make friends, and learn skills, which are important jobs of adolescence. The goal is to point that energy toward healthy challenges.

Use Your Brain's Schedule



Knowing about the peer effect is a tool. Decide on your rules (like "I don't ride with a driver who's showing off") when you're calm and alone, because your in-the-moment judgment will be under the most pressure exactly when friends are cheering.

8.11 Teratogens: When the Environment Interferes

A **teratogen** is something in the environment that can cause, or raise the risk of, a birth defect by interfering with an embryo's or fetus's development. Examples include some medicines, street drugs, alcohol, tobacco and nicotine, toxic chemicals, and some viruses and bacteria (Nationwide Children's Hospital). Because the brain and spinal cord keep developing throughout pregnancy, they stay sensitive to teratogens the whole time.

Timing matters. Critical periods work in both directions: the brain's sensitivity during these windows can be beneficial or damaging (OpenStax, Section 5.4). An exposure while the neural tube is closing can affect different structures than the same exposure while synapses are forming.

Alcohol in a pregnant person's blood passes to the developing baby through the umbilical cord (CDC). In a widely cited study in young rats, alcohol triggered the death of large numbers of developing neurons by blocking a type of glutamate receptor and over-activating a type of GABA receptor (Chapter 3). The researchers found that the most vulnerable period lined up with the period of rapid synapse formation, which in humans runs from about the sixth month of pregnancy to several years after birth (Ikonomidou and colleagues, 2000). Animal studies can't tell us everything about people, but they help explain why prenatal alcohol exposure is linked to a smaller brain.

8.12 Fetal Alcohol Spectrum Disorders

Fetal alcohol spectrum disorders (FASDs) are a group of conditions that can occur in a person who was exposed to alcohol before birth. The word "spectrum" means the effects range from mild to severe and differ from person to person. FASDs can affect behavior, learning, and physical health for life (CDC).

FASD is an umbrella term, not a single diagnosis. The CDC describes several diagnoses under it:

Diagnosis	What it involves (simplified)
Fetal alcohol syndrome (FAS)	The most involved end of the spectrum: central nervous system problems, specific facial features, and growth problems
Partial fetal alcohol syndrome (pFAS)	Prenatal alcohol exposure, some of the facial features, and either growth problems or central nervous system problems
Alcohol-related neurodevelopmental disorder (ARND)	Problems with learning and behavior, and sometimes intellectual disability, without the full set of physical features
Alcohol-related birth defects (ARBD)	Problems with organs such as the heart, kidneys, bones, or hearing
Neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE)	Problems with thinking and memory, behavior, and daily living skills

Source: CDC, About FASDs.

Signs and how common it is

Common signs include trouble paying attention, hyperactivity, poor memory, learning disabilities (especially in math), poor judgment, poor coordination, small head size, and short height or low weight. Some people also have distinctive facial features, such as a smooth ridge between the nose and upper lip, called a smooth philtrum (CDC). But many people with an FASD, such as those with ARND, don't have these features, and NIAAA notes that FASDs are often undiagnosed or misdiagnosed (NIAAA).

FASDs are more common than many people think. A study that examined first graders in four U.S. communities between 2010 and 2016 estimated that 1.1% to 5.0% had an FASD (May and colleagues, 2018). The authors note that four communities may not represent every part of the country, but this study is still the source of the "1% to 5% of U.S. first

graders" estimate in NIAAA's fact sheet, updated in December 2025 (NIAAA). NIAAA calls prenatal alcohol exposure a leading preventable cause of birth defects and neurodevelopmental disorders in the United States (NIAAA).

What happens in the brain

Brain scans of people exposed to alcohol before birth most often show a smaller overall brain volume and abnormalities of the corpus callosum, the thick bundle of axons connecting the two hemispheres. A review of imaging studies concluded that alcohol's effects appear widespread, affecting almost the entire brain (Lebel, Roussotte, and Sowell, 2011). That fits this chapter: alcohol can disrupt several steps of the building plan.

Prevention

The CDC is clear: there is no known safe amount of alcohol during pregnancy or while trying to get pregnant, no safe time, and no safe type (wine and beer included). It's also never too late to stop, because the baby's brain keeps growing throughout pregnancy (CDC). FASDs are completely preventable if a developing baby is not exposed to alcohol.

8.13 Nature and Nurture: Both, Always

Is the brain shaped by **nature** (genes) or **nurture** (environment and experience)? This chapter's honest answer: both, working together.

- **Genes set up the plan.** Genes guide the folding of the neural tube, the birth of neurons, and the paths they migrate along. OpenStax estimates that about 70% of neural tube defects are due to genetic factors.
- **The environment can change the outcome.** Yet many of those same defects can be prevented when the mother gets enough folic acid (OpenStax, Section 5.1). A genetic risk plus a nutritional factor together determine what happens.
- **Experience tunes the wiring.** Hubel and Wiesel's kittens had normal genes for vision, but without visual experience in one eye during the critical period, their visual cortex wired up differently.
- **Harmful exposures and supportive environments both matter.** Alcohol before birth can alter brain development. After birth, the CDC lists early diagnosis, special education and

social services, and a stable, loving home free of violence as protective factors that can reduce later problems for people with FASDs (CDC, FASD Treatment).

So **nature and nurture** don't compete. They work together: genes build a brain designed to be shaped by experience, and experience works on the brain genes have built. The teen years are one of the most important stages of that back-and-forth.

At the Bedside: A Second Grader Who Can't Keep Up

Meet the patient

Jordan is 7 and in second grade. His teacher reports that he has trouble sitting still, loses track of directions halfway through, and is falling behind in math even with extra help. His foster mother adds that he forgets things he learned the week before, gets frustrated easily, and is the shortest child in his class. His records note that his birth mother drank alcohol regularly during her pregnancy.

What the doctor checks: The pediatrician measures Jordan's height, weight, and head circumference and plots them on growth charts. All three are below the 10th percentile for his age. She examines his face closely and notes short eye openings, a thin upper lip, and a smooth philtrum (the ridge between the nose and upper lip). His neurological exam shows mild clumsiness but no weakness. A team evaluation, including a psychologist, finds below-average memory and executive function (attention, planning, and impulse control). There is no blood test for FASDs. The diagnosis is made from history, physical findings, growth, and neurodevelopmental testing (CDC; Hoyme and colleagues, 2016).

Where is the problem? (localization): Unlike a stroke, which damages one spot, Jordan's symptoms point to many systems at once: attention and impulse problems suggest prefrontal circuits, memory problems suggest circuits including the hippocampus, clumsiness suggests motor networks, and a small head suggests the brain grew less than expected. Imaging studies of people with prenatal alcohol exposure fit this picture: reduced overall brain volume, frequent abnormalities of the corpus callosum, and widespread changes in many regions (Lebel, Roussotte, and Sowell, 2011). This is a **diffuse developmental** problem, not a focal lesion.

Diagnosis: Fetal alcohol syndrome, the most involved condition on the fetal alcohol spectrum. Jordan has all four key elements: characteristic facial features, growth problems,

signs of reduced brain growth (small head size), and neurobehavioral impairment, along with documented prenatal alcohol exposure (Hoyme and colleagues, 2016).

Why it happens: Alcohol reached Jordan through the umbilical cord while his brain was being built. It acted as a teratogen during critical windows. Animal research suggests it can kill large numbers of developing neurons during the period of rapid synapse formation, partly by disrupting glutamate and GABA signaling (Ikonomidou and colleagues, 2000). Fewer neurons, altered wiring, and a smaller brain help explain his trouble with attention, memory, and learning.

Treatment today: There is no cure for FASDs, but early help makes a real difference. Care includes special education matched to the child's needs, behavioral support, social services for the family, medicines for some symptoms, and case management (CDC, FASD Treatment; NIAAA). A stable, loving home, early diagnosis, and freedom from violence are protective factors that reduce later problems.

What's new in research: Researchers are testing whether the nutrient **choline** helps young children with FASDs. A combined report of three small randomized, placebo-controlled trials in children aged 2.5 to 5.9 found a modest benefit of choline on a memory task compared with placebo (partly only a trend, and larger in the youngest children), but no effect on IQ or executive functioning (Wozniak and colleagues, 2025). Choline is still being studied for FASDs. It is not an established standard treatment, and families should not start supplements without talking to a doctor.

Your turn: diagnose a variation

Suppose a different second grader, Sam, has the same attention and impulse-control problems as Jordan. But Sam's height, weight, and head size are all normal, his face has none of the features listed above, and his birth mother is known not to have drunk alcohol during pregnancy. What condition should the doctor think about first, and why can't the doctor diagnose an FASD?

Answer: Without prenatal alcohol exposure, an FASD isn't the right diagnosis. Attention and impulse problems with normal growth and features could instead suggest attention-deficit/hyperactivity disorder (ADHD), which the CDC notes shares some symptoms with FAS (CDC). This shows why the history (including prenatal exposures) and the physical exam matter: similar behaviors can come from different causes.

Part 2: Not a disease, a developmental stage

Nothing is medically wrong with Maya. Her brain is doing what a typical 16-year-old brain does. Her reward system is highly responsive, especially with friends watching (Chein and colleagues, 2011), and her prefrontal control circuits are still being refined (Steinberg, 2008). Her logical knowledge of the danger is adult-level, but her self-control in an exciting, emotional moment may not be yet (Icenogle and colleagues, 2019).

What helps: Planning ahead when calm, graduated licensing rules that limit teen passengers and night driving, and a parent-teen driving agreement (CDC) work *with* the teen brain. Next time, Maya rides home with a teammate's parent.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: "The teenage brain is just a broken or unfinished adult brain."
Reality: The teen brain is in a normal, active remodeling phase. It is highly adaptable, and NIMH notes that most teens become healthy adults.

Myth: "Brain development is over by 18."
Reality: Prefrontal pruning continues through the twenties, long association pathways keep maturing after adolescence, and white matter volume peaks at about 29. Development continues into the mid-to-late twenties.

Myth: "The brain is finished at exactly 25."
Reality: "25" is rough shorthand. Different measures level off at different ages, people vary widely, and scientists are still working out how to define and measure "brain maturity."

Myth: "More synapses always means a smarter brain."
Reality: Toddlers have far more synapses than adults. Pruning away unused synapses makes circuits more efficient. Mature brains are tuned, not crowded.

Myth: "A little alcohol late in pregnancy is safe for the baby."
Reality: The CDC states there is no known safe amount, time, or type of alcohol during pregnancy. The baby's brain grows throughout pregnancy.

Brain Bee Practice

1. What embryonic structure gives rise to the brain and spinal cord, and when does it normally close?

The neural tube. According to NINDS, it typically folds and closes in the third to fourth week after conception, often before a person knows they are pregnant.

2. What type of glial cell acts as a guide rope for migrating neurons in the developing cortex?

Radial glia. New neurons climb along their long fibers from the inner wall of the neural tube toward the brain's surface. Radial glia also act as neural stem cells.

3. Define synaptic pruning, and name a region that finishes pruning early and one that finishes late.

Synaptic pruning is the removal of weak or unused synapses during development ("use it or lose it"). Sensory cortex, such as auditory cortex, finishes early (by about age 12), while prefrontal cortex continues pruning through adolescence and into the twenties.

4. What did Hubel and Wiesel's kitten experiments show about critical periods?

Closing one eye during a window early in life caused far fewer visual cortex neurons to respond to the closed eye, and the effect lasted, while closing an adult cat's eye had no detectable effect. This showed a critical period for visual cortex wiring. Hubel and Wiesel shared the 1981 Nobel Prize.

5. Name the umbrella term for conditions caused by prenatal alcohol exposure, and name its most involved diagnosis.

Fetal alcohol spectrum disorders (FASDs). The most involved diagnosis is fetal alcohol syndrome (FAS), which includes central nervous system problems, characteristic facial features, and growth problems.

Exercises

Remember

1. List the five main steps of brain construction in order, starting with the neural tube.
2. What is a teratogen? Give one example from this chapter.

Answer

1. Neural tube formation, neurogenesis, neuronal migration, synaptogenesis, then synaptic pruning together with myelination.
2. A teratogen is something in the environment that can interfere with development before birth and cause a birth defect. Alcohol is the main example in this chapter.

Understand

1. Explain, using the "city roads" analogy, why the brain makes more synapses than it keeps.
2. Explain why the CDC recommends folic acid for anyone who could become pregnant, not just people who already know they are pregnant.

Answer

1. The brain can't know in advance which connections will be useful, just as a city can't predict which roads will carry traffic. It builds extra connections, then keeps and strengthens the busy ones and removes the unused ones, which makes the remaining circuits more efficient.
2. The neural tube closes about three to four weeks after conception, often before someone knows they are pregnant. Folic acid has to already be in the body during that window to help prevent neural tube defects.

Apply

1. A 9-year-old has amblyopia in her left eye. Using the idea of a critical period, explain why her eye doctor wants to start patching her right eye now rather than waiting until she is an adult.
2. Maya's younger brother is about to get his driver's license. Using what you learned about reward sensitivity and peers, design two rules for his first six months of driving

and explain the brain science behind each.

Analyze

1. In the MicroSim, compare the sensory and prefrontal synapse curves at ages 2, 12, and 22. What pattern do you see, and how does it match Gogtay's finding about the order of cortical maturation?
2. Jordan (the Bedside case) and a child with a stroke might both have trouble with attention. Analyze why the doctor localizes Jordan's problem as "diffuse" but a stroke as "focal."

Evaluate

1. A news headline says: "Science proves teens can't make good decisions until 25." Evaluate this claim using at least three pieces of evidence from Section 8.9. What would a more accurate headline say?
2. Some say a developing brain means teens have no responsibility for their choices; others say the brain science is irrelevant. Evaluate both views using the "maturity gap" study.

Create

1. Design a one-page poster explaining synaptic pruning and myelination to 9th graders, with an analogy, a sketch graph labeled as schematic, and one healthy-habit takeaway.
2. Write a short public-awareness message (about 100 words) about preventing fetal alcohol spectrum disorders. It must be accurate, non-blaming, and include at least two facts from the CDC.

Key Takeaways

- The nervous system starts as a **neural tube** that closes about three to four weeks after conception. Folic acid helps prevent neural tube defects.
- Most neurons are made before birth (**neurogenesis**) and then travel to their places, often along radial glia (**neuronal migration**).

- The brain overproduces synapses (**synaptogenesis**) and then removes unused ones (**synaptic pruning**). Sensory cortex peaks and prunes early, while prefrontal cortex peaks later and keeps pruning into the twenties.
- **Myelination** continues for decades, and total white matter volume peaks at about age 29. Experience during **critical periods** has an especially strong effect on wiring.
- The **adolescent brain** is remodeling, not broken. Development continues into the mid-to-late twenties with large individual variation. "25" is shorthand, not a finish line.
- Teens show heightened **reward sensitivity**, especially around peers, while prefrontal control circuits are still maturing. This helps explain risk-taking, and it can be managed with smart planning.
- Alcohol is a **teratogen**. Prenatal exposure can cause **fetal alcohol spectrum disorders**, which are lifelong but completely preventable. Brain development always reflects **nature and nurture** working together.

You Followed a Brain From Tube to Twenties!



You just traced how a brain builds, trims, and insulates itself, and why your own brain is in one of its most exciting construction phases right now. Next up, in Chapter 9, we'll see how all those carefully kept synapses store memories, and meet the famous patient H.M., who taught scientists where memories are made.

Chapter 9: Learning, Memory, and Neuroplasticity

Summary

Every time you learn something, your brain physically changes. This chapter explains what memory is, how short-term, working, and long-term memory differ, and why the hippocampus is needed to form new memories of facts and events but not new skills. You will see how synapses grow stronger through Hebbian learning and long-term potentiation, and how Eric Kandel used the sea slug *Aplysia* to watch learning happen at a single synapse. The chapter ends with Patient H.M., the man whose surgery in 1953 taught science that memory is not one thing.

Concepts Covered

1. Learning
2. Memory
3. Short-Term Memory
4. Working Memory
5. Long-Term Memory
6. Declarative Memory
7. Procedural Memory
8. Hippocampus
9. Memory Consolidation
10. Neuroplasticity
11. Hebbian Learning
12. Long-Term Potentiation
13. Habituation and Sensitization

14. Aplysia Model
15. Amnesia
16. Patient H.M.

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters
- Chapter 4: A Tour of the Brain: Neuroanatomy

Welcome to my favorite chapter



This is the chapter where my family gets famous! Scientists used sea slugs like me to discover how a memory is stored at a synapse. By the end, you'll know why your brain is never quite the same after you learn something, and you'll have better ways to study for your next test.

9.1 Maya's Two-Week Problem

Maya's Brain Bee competition is two weeks away. She has a thick stack of flashcards on neuroanatomy, and soccer practice takes up most of her afternoons. Her plan is simple: relax for twelve days, then cram everything into the last two nights. Her older cousin, a nursing student, shakes her head. "Do twenty minutes a day instead," she says. "Same total time. You'll remember way more."

Maya isn't convinced. The total hours are the same, so why would the schedule matter?

Her cousin is right, and the reasons go all the way down to the synapse. In the 1880s, Hermann Ebbinghaus memorized lists of nonsense syllables and tested himself after different delays. He found that forgetting is fast at first and then slows down, a pattern now called the **forgetting curve**. A 2015 study repeated his experiment and got similar results (Murre & Dros, 2015).

Ebbinghaus also noticed that spreading repetitions out in time works better than bunching them together. A large 2006 review pooled 839 tests of this idea from 317 experiments and confirmed the **spacing effect**: spaced study usually beats cramming for long-term recall (Cepeda et al., 2006).

By the end of this chapter, you'll be able to explain a leading idea about *why* spacing works, using what happens inside neurons. First, though, we need to pin down what learning and memory are.

9.2 Intuition First: Paths Through a Field

Imagine a grassy field between your school and a bus stop. The first person who walks across leaves almost no mark. But if people keep taking the same route, the grass gets trampled, and a path appears. Soon the path is the easiest way across, and people follow it without thinking. If everyone stops using it, the grass slowly grows back.

Your brain works in a similar way. Your neurons are linked by an enormous number of synapses. When a pattern of activity runs through the same connections again and again, those connections change so the pattern is easier to repeat. That's the core idea of this whole chapter.

Now for the scientific words.

- **Learning** is the process by which experience changes the nervous system, and therefore changes later behavior. It includes studying vocabulary, getting used to a noisy room, and practicing a soccer move.
- **Memory** is the information that learning leaves behind, along with the brain's ability to store it and get it back later. Learning is the *walking*; memory is the *path*.

Memory has three basic steps. First, **encoding** turns an experience into a pattern of neural activity. Second, **storage** keeps that information over time. Third, **retrieval** brings it back when you need it. A failure at any step feels like "forgetting," but the cause can be very different.

9.3 Memory Comes in Stages

Not all memories last the same amount of time. Psychologists and neuroscientists sort them by how long they last.

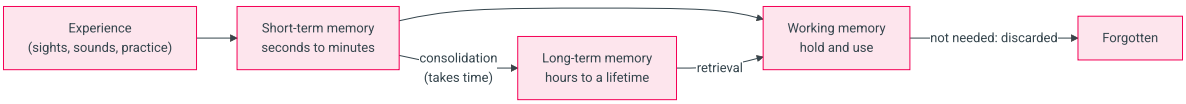
Short-term memory holds a small amount of information for seconds to a few minutes. When a friend tells you a phone code and you repeat it until you type it in, you are using short-term memory. If you get distracted, it's usually gone.

Working memory is a special kind of short-term memory that you actively *use*, not just hold. Think of it as the brain's mental whiteboard. When Maya does a math problem in her head, she keeps the numbers on the whiteboard, works with them, and erases them when she's done. Working memory depends on networks in the cerebral cortex, including the frontal and parietal lobes (OpenStax, Section 18.1). What sets it apart is that information is thrown away once it's no longer needed. You don't need to remember where you parked last Tuesday, only where you parked today.

Long-term memory stores information for hours, days, or a lifetime. Your first day of high school, the rules of soccer, and how to ride a bike are all long-term memories.

How does a fragile short-term memory become a lasting long-term one? Through **memory consolidation**: the gradual process that turns new, easily disrupted memories into stable, long-lasting ones. Consolidation takes time. Right after learning, a memory can be weakened or lost. As consolidation goes on, the memory becomes much harder to disrupt. Emotion matters too. Stress hormones released right after an event can strengthen consolidation, which is one reason emotional moments are often remembered vividly (OpenStax, Section 18.1).

The flowchart below shows how information moves through these stages. Every term in it has already been defined above.



Notice the arrow from long-term memory back to working memory. When you remember something, you pull it out of storage and into your mental whiteboard so you can use it.

9.4 Two Big Families of Long-Term Memory

Long-term memory is not one single system. It splits into two big families that depend on different brain regions.

Declarative memory is memory you can consciously bring to mind and *declare*, or put into words. It answers "what" questions. It has two types:

- **Episodic memory** holds personal events tied to a time and place, like Maya's last birthday party.
- **Semantic memory** holds facts and general knowledge, like "the hippocampus is in the temporal lobe."

Procedural memory is memory for skills and habits. It answers "how" questions: how to dribble a ball, type on a keyboard, or tie your shoes. It builds up slowly with practice, and it's hard to explain in words. Try describing exactly how you keep your balance on a bike. You can do it, but you can't easily *say* it.

Procedural memory is the best-known member of a wider family that scientists call **nondeclarative memory**: memory that shows up in what you *do* rather than in what you can report. Besides skills and habits, this family includes simple conditioning, emotional learning, and *priming*, where seeing something once makes it easier to recognize later even if you don't remember seeing it (Squire, 2009). This chapter focuses on procedural memory because it gives the clearest contrast with declarative memory.

The table below summarizes the two families you just met.

Feature	Declarative memory	Procedural memory
Question it answers	"What?" (facts and events)	"How?" (skills and habits)
Can you put it into words?	Yes	Not easily
How it's learned	Can form after a single experience	Usually needs repeated practice
Example	Remembering that dopamine is a neurotransmitter	Getting faster at a video game

Feature	Declarative memory	Procedural memory
Key brain regions	Hippocampus and nearby medial temporal lobe, plus cortex for long-term storage	Basal ganglia and cerebellum, among others

The brain-region row comes from decades of patient and animal studies, summarized in Squire (2009). You'll see where that evidence came from in Section 9.6.

9.5 The Hippocampus: Memory's Librarian

The **hippocampus** is a curved structure tucked inside the medial (inner) part of each temporal lobe. You have two, one on each side of the brain. Its name comes from the Greek word for "seahorse," because of its curled shape. It was one of the deep structures on the brain tour in Chapter 4.

The hippocampus is essential for *forming* new declarative memories. Think of it as a librarian who receives a new book (an experience), catalogs it, and links it to related books on shelves all over the library (the cortex). Over months and years, those links in the cortex become strong enough to stand on their own. That's why damage to the hippocampus mostly harms *new* memories while many old memories survive. This slow handoff from the hippocampus to the cortex is one form of memory consolidation.

The hippocampus also helps with spatial memory, meaning memory for places and routes. A famous study used MRI to compare licensed London taxi drivers, who must learn the city's tangled streets, with people who didn't drive taxis. The back (posterior) part of the hippocampus was larger in the taxi drivers, and its size was related to how long they had been driving (Maguire et al., 2000). At the same time, a front part of the hippocampus was *smaller* in the drivers. The study suggests that adult brains can change their structure in response to what we ask them to do. Because it compares groups at one point in time, though, it can't prove by itself that driving *caused* the change.

The hippocampus is not a hard drive



A common mistake is saying "memories are stored in the hippocampus." The hippocampus is needed to *form* new memories of facts and events, but long-term declarative memories end up spread across the cortex. Skills rely mostly on other regions, like the basal ganglia and cerebellum.

9.6 Amnesia and the Lessons of Patient H.M.

Amnesia is a serious loss of memory caused by brain injury, disease, or (rarely) psychological trauma. Doctors describe two main kinds, based on time:

- **Anterograde amnesia** is trouble forming *new* memories after the injury. ("Antero" means forward.)
- **Retrograde amnesia** is loss of memories from *before* the injury. ("Retro" means backward.)

Many people with amnesia have some of both. Unlike in movies, a person with amnesia usually still knows who they are and can hold a conversation.

The most famous case of amnesia in history is **Patient H.M.**, whose real name, Henry Molaison, was made public after he died in 2008. In 1953, at age 27, Henry had severe epilepsy that high doses of medication could not control. His seizures made it impossible for him to work. A neurosurgeon named William Scoville, in Hartford, Connecticut, removed the medial part of the temporal lobe on *both* sides of his brain. This is called a bilateral medial temporal lobe resection. By the surgeon's description, it included much of the hippocampus, the amygdala, and nearby cortex (Squire, 2009).

The operation helped control his seizures, but it left him with severe anterograde amnesia. The psychologist **Brenda Milner** traveled from Montreal to test him. She and Scoville published the results in 1957 (Scoville & Milner, 1957). H.M. was studied by Milner, her student Suzanne Corkin, and many others for about five decades. What they found reshaped neuroscience:

1. **Memory is its own brain function.** H.M.'s intelligence, personality, language, and perception seemed largely intact. Before his case, many scientists thought memory

was spread evenly through the cortex and mixed in with other abilities. H.M. showed that forming new memories depends on specific structures.

2. **Short-term memory is separate from long-term memory.** H.M. could repeat back a string of six or seven digits, a normal score. He could keep a number in mind for a while by rehearsing it over and over. But once his attention moved to something else, the information was gone (Squire, 2009).
3. **Old memories can survive.** H.M. recognized famous people who were in the news before his surgery much better than those who became famous after it. Some memories from the years just before surgery were lost, so he also had some retrograde amnesia.
4. **Procedural memory is separate from declarative memory.** This was the most surprising finding. Milner asked H.M. to trace a star while seeing his hand and the paper only in a mirror. That is hard for anyone at first, because the mirror flips every movement. Over three days of practice, H.M. got steadily better, just like healthy people do. Yet each day he had no memory of ever doing the task before (Squire, 2009).

That mirror-drawing result showed that a person can learn a skill without remembering the learning. The brain has more than one memory system.

One man, two memory systems



H.M. got better and better at mirror drawing but couldn't remember practicing it. His procedural memory worked while his declarative memory for new events did not. That's strong evidence that the brain uses separate systems for "knowing that" and "knowing how."

One more point keeps the story accurate. Because H.M.'s surgery removed several structures, his case alone could not show that the hippocampus *by itself* is the key. Later studies of patients and animals with smaller lesions showed that the hippocampus and the cortex around it form a medial temporal lobe memory system. Damage limited to the hippocampus causes real but milder memory loss than H.M. had (Squire, 2009). You'll see H.M. again at the bedside at the end of this chapter.

9.7 Neuroplasticity: The Brain That Changes

So far, we've talked about *where* memories form. Now we ask *how*. The answer is neuroplasticity.

Neuroplasticity (or just "plasticity") is the nervous system's ability to change its structure and function in response to experience. "Plastic" here means moldable, like clay, not the material water bottles are made of. Plasticity happens at several levels:

- **Synapses** can become stronger or weaker.
- **Neurons** can grow new branches and new synapses, or lose old ones.
- **Brain regions** can change size or take on new jobs, as in the taxi-driver study.

Plasticity is strongest early in life (you read about synaptic pruning in Chapter 8), but it continues throughout adulthood. Every new memory is a small act of plasticity.

9.8 Hebbian Learning: Firing Together

In 1949, the psychologist Donald Hebb proposed an idea in his book *The Organization of Behavior*. If neuron A repeatedly helps make neuron B fire, he suggested, the connection from A to B should grow stronger. This rule is called **Hebbian learning**. It's often summed up as "neurons that fire together, wire together." That catchy phrase came later from other scientists, not from Hebb himself, but it captures his idea.

In the field analogy, each time two connected neurons are active together, the path between them gets a little more worn in. Hebbian learning explains how memories can link things together. If you always hear a song during summer road trips, the neurons that represent the song and the neurons that represent the trips are active at the same time. Their connections strengthen. Later, the song alone can bring back the memories of the trips.

Hebb's rule was a smart guess. For about 25 years, nobody had direct proof that real synapses behave this way.

9.9 Long-Term Potentiation: Hebb's Idea in a Real Brain

In 1973, Timothy Bliss and Terje Lømo reported the evidence. Working with anesthetized rabbits, they stimulated a bundle of axons, called the perforant path, that carries signals into a part of the hippocampus called the dentate gyrus. Then they gave a burst of high-frequency stimulation. Afterward, the same single test pulse produced a bigger response in

the dentate gyrus than before. In most of their animals, the boost lasted from 30 minutes to 10 hours (Bliss & Lømo, 1973). Later experiments showed that it can last for weeks.

This lasting boost in synaptic strength after intense activity is called **long-term potentiation (LTP)**. "Potentiation" just means "made stronger." The opposite process, a long-lasting *weakening* of a synapse, is called **long-term depression (LTD)**. Both are needed: a brain that could only strengthen synapses would eventually fill up and lose flexibility (OpenStax, Section 18.4).

How LTP works: a lock that needs two keys

To understand LTP, recall from Chapter 3 that **glutamate** is the brain's main excitatory neurotransmitter. At many synapses in the hippocampus, glutamate acts on two kinds of receptors on the receiving (postsynaptic) neuron:

- **AMPA receptors** are channels that open when glutamate binds. They let in sodium ions and depolarize (excite) the cell. They do most of the everyday signaling.
- **NMDA receptors** are channels that also bind glutamate, but at resting voltage their pore is plugged by a magnesium ion. The plug only pops out when the cell is *already* strongly depolarized. When NMDA receptors do open, they let in calcium ions as well as sodium.

That means an NMDA receptor is like a lock that needs two keys at the same time: glutamate from the sending neuron *and* strong depolarization of the receiving neuron. Scientists call this a **coincidence detector**. It's Hebb's rule built out of a protein: the synapse is strengthened only when the sending neuron fires *and* the receiving neuron is strongly active at the same time.

Here is the sequence, step by step:

1. A strong burst of activity releases lots of glutamate.
2. Many AMPA receptors open, and the postsynaptic neuron depolarizes strongly.
3. The depolarization pops the magnesium plug out of the NMDA receptors.
4. Calcium flows in through the NMDA receptors.
5. Calcium switches on enzymes, including one called CaMKII. These enzymes make existing AMPA receptors work better and add new AMPA receptors to the membrane.

6. With more and better AMPA receptors, the same amount of glutamate now produces a bigger response. The synapse has been potentiated.

This first stage is called **early LTP**. It lasts a few hours and uses proteins already present in the synapse. A longer-lasting stage, **late LTP**, needs the neuron to make *new* proteins, and it can involve growing new synaptic connections, such as new dendritic spines (OpenStax, Section 18.4). Hold on to that idea. You'll see it again in the sea slug.

This part is dense, and that's okay



If the NMDA receptor feels confusing, just remember the two-key lock: glutamate *and* a strongly excited receiving cell. Everything else in LTP follows from that one clever trick.

Does LTP really underlie memory? The evidence is strong but still being tested. In rats, drugs that block NMDA receptors interfere with some kinds of learning. In 2006, researchers also showed that a single learning experience (rats learning to avoid a mild shock) produced the same synaptic changes in the hippocampus as LTP made in the lab (Whitlock et al., 2006). Most neuroscientists think changes in synaptic strength like LTP and LTD are a central mechanism of memory, but the full link is still an active research question (OpenStax, Section 18.4).

9.10 The Aplysia Model: Learning in a Sea Slug

The human brain has billions of neurons, far too many to track the change behind a single memory. The neuroscientist **Eric Kandel** decided to study learning in a much simpler animal: the sea slug *Aplysia*. According to the Nobel committee, *Aplysia* has only around 20,000 nerve cells, many of them unusually large and easy to record from (Nobel Prize press release, 2000). (Some textbooks give a lower estimate, about 10,000.) Using a simple animal to discover rules that also apply to humans is called the **Aplysia model**, and it's a classic example of how basic research works.

Aplysia breathes through a delicate **gill**. Behind the gill is a fleshy spout called the **siphon**. If you gently touch the siphon, the slug quickly pulls its gill in for protection. This is the **gill-withdrawal reflex**. The circuit behind it is small enough to map neuron by neuron:

- A **sensory neuron** in the siphon detects the touch.
- It connects directly to a **motor neuron** that makes the gill muscle contract.
- A shock to the tail activates other sensory neurons, which drive **facilitating interneurons**. The most important of these release the neurotransmitter **serotonin** (5-HT) onto the terminal of the siphon sensory neuron (Kandel, 2012).

Two simple kinds of learning

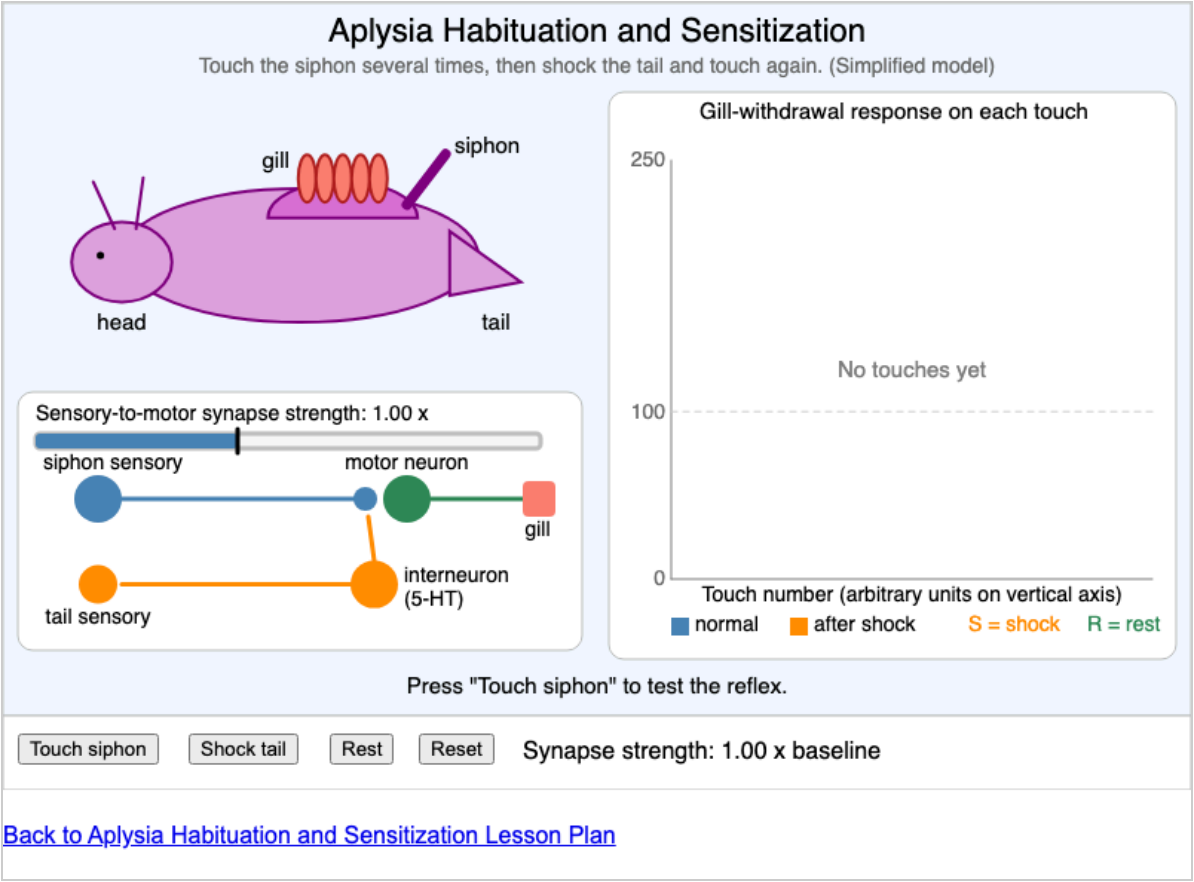
With this reflex, Kandel's team studied two of the simplest forms of learning. Neither one links two different things together; both simply change how strongly an animal responds. Together they are called **habituation and sensitization**.

Habituation is a decrease in response to a harmless stimulus that is repeated over and over. You do this all the time. When you first sit near a loud air conditioner, you notice it. After a while, you stop hearing it. When the siphon is touched again and again, the slug's gill withdrawal gets smaller and smaller. Kandel's group showed that the cause is not a tired muscle or a worn-out sense organ. Instead, the siphon sensory neuron releases *less neurotransmitter* onto the motor neuron with each touch. The synapse itself weakens (Kandel, 2012). After a rest, a habituated response gradually comes back.

Sensitization is an *increase* in response to many stimuli after a strong or unpleasant one. After a scary movie, you might jump at the smallest creak in the house. In *Aplysia*, a shock to the tail makes the gill pull in harder when the siphon is touched later, even though the siphon touch hasn't changed. It works like this. The tail shock activates the facilitating interneurons, which release serotonin onto the siphon sensory neuron's terminal. Serotonin triggers a chain of chemical signals inside that terminal, using a messenger called cAMP and an enzyme called protein kinase A. The result is that the sensory neuron releases *more* transmitter with each action potential, so the motor neuron gets a bigger signal (Kandel, 2012). When sensitization restores a response that had been habituated, it's called **dishabituation**.

Notice that the same synapse can be weakened by one kind of experience and strengthened by another. The synapse is where the learning lives.

Diagram: Aplysia Habituation and Sensitization



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch09-aplysia-learning/

Open the Aplysia Habituation and Sensitization MicroSim fullscreen

MicroSim specification: Aplysia Habituation and Sensitization

sim-id: ch09-aplysia-learning
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: explain
Learning Objective: The learner will explain how repeated siphon touches and a tail shock change the strength of the sensory-to-motor synapse, producing habituation or sensitization of the gill-withdrawal reflex.

Canvas: responsive width; 480 px drawing area plus 50 px control area.

Controls: buttons for Touch siphon, Shock tail, Rest, and Reset.

Behavior: Each siphon touch records a response bar equal to 100 times the current synaptic strength (arbitrary units) and then depresses the synapse (habituation). A tail shock raises a serotonin facilitation factor and partly restores a depressed synapse, so later touches give larger, orange bars (sensitization and dishabituation). Rest recovers half of the remaining habituation and removes half of the remaining facilitation. The side view shows the gill pulling in by an amount that matches the response. The circuit panel shows the siphon sensory neuron, motor neuron, tail sensory neuron, and serotonin interneuron, with a synaptic-strength meter. Labeled as a simplified, qualitative model.

Try this in the sim. Touch the siphon six or seven times and watch the bars shrink while the synapse-strength meter falls below 1.0. That's habituation. Now shock the tail and touch again. The next bar jumps up and turns orange, because serotonin has boosted transmitter release from the sensory neuron. Press **Rest**, test again, and see the partial recovery.

Then press **Reset** and shock the tail *before* any touches. The first response is bigger than the baseline of 100. In each case, ask yourself: did the siphon touch change, or did the synapse change? The numbers are arbitrary and show direction only.

From short-term to long-term memory in a slug

Kandel's team found that *Aplysia* has both short-term and long-term memory, just like we do.

- A **single** tail shock produces sensitization that lasts minutes. This short-term memory uses chemical changes to proteins that are already in the synapse.

- **Repeated, spaced** shocks produce sensitization that lasts days to weeks. This long-term memory needs the neuron to switch on genes and build *new proteins*. If protein synthesis is blocked, the long-term change fails, but the short-term change still works (Kandel, 2012; Nobel press release, 2000).

Long-term memory also changes the *structure* of the synapse. After long-term habituation, sensory neurons had about 35 percent fewer connections onto their target cells than in untrained animals. After long-term sensitization, the number of sensory-neuron terminals more than doubled (Kandel, 2012). Learning literally rewires the circuit.

This should sound familiar. Short-term memory in the slug works like early LTP (modify existing proteins). Long-term memory in the slug works like late LTP (make new proteins, grow new connections). The same basic rules show up in sea slugs and in the mammalian hippocampus.

For this work, Eric Kandel shared the **2000 Nobel Prize in Physiology or Medicine** with Arvid Carlsson and Paul Greengard "for their discoveries concerning signal transduction in the nervous system." The Nobel committee credited Kandel with showing how the strength of synapses can be changed and which molecules are involved, using the sea slug's nervous system (Nobel Prize press release, 2000). Kandel's Nobel lecture was titled "The Molecular Biology of Memory Storage: A Dialog between Genes and Synapses" (Nobel lecture page).

9.11 Back to Maya: Why Spacing Beats Cramming

Now we can answer Maya's question. Remember the key finding from the sea slug: a single training session produces a short-term change, but **repeated, spaced** sessions switch on new protein synthesis and the growth of new connections. The same holds for many animals. A 2016 review found that spaced training produces stronger long-term memory than massed (crammed) training in *Aplysia*, fruit flies, bees, rodents, and monkeys, as well as people (Smolen, Zhang & Byrne, 2016). Researchers are still working out exactly why, but one idea is that the molecular steps that build long-term memory need time between sessions to finish and reset.

Cramming feels effective because the information is fresh the next morning, but much of it slides down the steep early part of the forgetting curve. Spaced study gives your synapses repeated chances to consolidate. Here's Maya's new plan:

Study habit	What it does in the brain	Maya's version
Space it out	Gives consolidation time between sessions	20 minutes of flashcards every day for two weeks
Test yourself	Practices retrieval. On tests given days later, it beat re-reading, even though re-reading looked better on a test given 5 minutes later (Roediger & Karpicke, 2006)	Says answers out loud before flipping the card
Mix in meaning	Links new facts to existing memories (Hebbian connections)	Connects "hippocampus" to H.M.'s story instead of just the word
Practice skills often	Builds procedural memory through repetition	Uses short daily sessions to label brain diagrams

Study like a sea slug



Five short sessions spread over a week usually beat one five-hour marathon. In sea slugs like me, spacing gives synapses time to build the new proteins that long-term memory needs, and scientists think something similar may happen in you.

At the Bedside: Patient H.M. and Anterograde Amnesia

This bedside case is different from the others in this book. It describes a real, well-documented historical patient. The clinical reasoning below is written for teaching. It shows how the case would be understood with today's knowledge.

Meet the patient

In 1953, Henry Molaison is 27 years old and lives in Connecticut. He has had seizures since childhood, and they have become so frequent and severe that he can't hold a job, even on high doses of anti-seizure medicine. After an experimental operation on both sides of his brain, his seizures are much better controlled. But his family and the hospital staff notice something alarming. He doesn't recognize hospital staff he has seen many times. He apologizes for forgetting the names of people he was introduced to minutes ago, and he forgets each day's events almost as fast as they happen. Yet he can chat normally, his personality seems unchanged, and he does well on intelligence tests.

What the doctor checks: A neurologist or neuropsychologist would test several kinds of memory separately. A digit-span test (repeating back a list of numbers) checks short-term memory; H.M. did normally. Delayed recall, such as remembering a short story or a list of words after 20 minutes of distraction, checks the formation of new declarative memories; H.M. failed. Questions about public events and famous faces from different decades check older memories. Skill-learning tasks like mirror drawing check procedural memory; H.M. improved normally. Today, an MRI scan would show exactly which structures were missing. Doctors evaluating memory loss also commonly use cognitive testing, blood tests, and brain imaging to look for causes (MedlinePlus).

Where is the problem? (localization): The pattern points to a specific system. Attention, language, and short-term memory work, so the cortex as a whole is functioning. Skill learning works, so the basal ganglia and cerebellum are fine. Older memories are mostly present, so long-term storage in the cortex is largely intact. What's broken is the step that turns new experiences into lasting declarative memories. That step depends on the hippocampus and the surrounding medial temporal lobe on *both* sides. The surgery removed exactly that region.

Diagnosis: Severe anterograde amnesia, with some retrograde amnesia for the years just before the operation, caused by bilateral medial temporal lobe resection.

Why it happens: Without the hippocampus and nearby cortex on both sides, new information can stay in short-term or working memory but can't be consolidated into long-term declarative memory. Because procedural memory relies on different circuits, H.M. could still learn new motor skills without remembering that he had practiced them.

Treatment today: There is no treatment that can regrow a removed hippocampus. Care for memory loss depends on the cause, and support focuses on daily life: written reminders for

important tasks, familiar objects and photos, and help from family and caregivers (MedlinePlus).

H.M.'s case showed how much memory can be lost when the medial temporal lobes are removed on both sides, and epilepsy surgery is planned very differently today. According to the National Institute of Neurological Disorders and Stroke (NINDS), surgery is usually considered only after at least two seizure medicines have failed, surgeons try to avoid brain areas needed for memory, speech, and movement, and less invasive options now include laser ablation and implanted responsive-stimulation devices (NINDS: Epilepsy and Seizures).

What's new in research: After Henry Molaison died on December 2, 2008, his brain was preserved and sliced into thin sections for study. In 2014, a team led by Jacopo Annese published a detailed 3D digital reconstruction built from 2,401 images collected during a 53-hour sectioning procedure. They found that a sizable piece of the back part of his hippocampus had actually survived the operation, while most of the entorhinal cortex, which feeds information into the hippocampus, had been removed. They also found a small lesion in the left orbitofrontal cortex and changes in the white matter (Annese et al., 2014). These details help scientists interpret five decades of testing.

Your turn: diagnose a variation

A 60-year-old woman has a stroke that damages her cerebellum. Months later, she can tell you what she had for breakfast and describe the details of her hospital stay. But in physical therapy, she improves much more slowly than expected at a new balance exercise, even after weeks of practice. Which memory system is most affected, and how is she the "opposite" of H.M.?

Answer: Her declarative memory (remembering events and facts) works, so her hippocampus is doing its job. Her trouble is learning a new motor skill, which is procedural memory. The cerebellum is one of the structures important for procedural learning. She is roughly the reverse of H.M., who could learn skills but couldn't remember new events. Comparing patients like this is how neuroscientists show that two brain systems are truly separate.

H.M. was a real, historical patient whose case is documented in the published scientific literature; the "Your turn" variation is a fictional teaching case. This is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Memory works like a video recording that plays back exactly what happened.
Reality: Remembering is an active rebuilding process. Each time you recall a memory, it can be changed and then stored again, a process called reconsolidation (OpenStax, Section 18.1). That's why two people can honestly remember the same event differently, and why confident memories can still be wrong.

Myth: Everyone has a learning style (visual, auditory, or kinesthetic), and you learn best when teaching matches your style.
Reality: People do have preferences, but a major 2008 review found virtually no evidence that matching teaching to a person's "style" improves learning (Pashler et al., 2008). Strategies like spacing and self-testing help nearly everyone.

Myth: Cramming works just as well as spacing if the total study time is the same.
Reality: Cramming can get you through tomorrow's quiz, but spaced practice leads to much better long-term memory. The spacing effect holds across hundreds of experiments (Cepeda et al., 2006).

Myth: The adult brain is fixed, and only children's brains can change.
Reality: Plasticity is strongest early in life, but it continues in adults. Every new long-term memory changes synapses, and adult brain structure can differ with experience, as in London taxi drivers (Maguire et al., 2000).

Myth: H.M. couldn't learn anything after his surgery.
Reality: H.M. could not form new declarative memories, but he learned new motor skills such as mirror drawing at a normal rate. He just couldn't remember the practice sessions.

Brain Bee Practice

1. What is the difference between anterograde and retrograde amnesia?

Anterograde amnesia is an inability to form new memories after a brain injury. Retrograde amnesia is the loss of memories formed before the injury. Patient H.M. had severe anterograde amnesia and some retrograde amnesia.

2. Which receptor acts as a coincidence detector during long-term potentiation, and why?

The NMDA glutamate receptor. It opens only when glutamate is bound *and* the postsynaptic cell is strongly depolarized, which removes the magnesium block from its pore. Calcium then enters and triggers the strengthening of the synapse.

3. In Aplysia, which neurotransmitter released by facilitating interneurons produces sensitization of the gill-withdrawal reflex?

Serotonin (5-HT). A tail shock activates interneurons that release serotonin onto the siphon sensory neuron's terminal. This increases transmitter release onto the gill motor neuron.

4. What task showed that Patient H.M. could still form procedural memories?

Mirror drawing. Brenda Milner had him trace a star while seeing only its reflection in a mirror. He improved over three days of practice but did not remember having done the task before.

5. Who shared the 2000 Nobel Prize in Physiology or Medicine with Eric Kandel?

Arvid Carlsson and Paul Greengard. The prize recognized their discoveries about signal transduction in the nervous system. Kandel's part was showing how synapses change during learning and memory, using *Aplysia*.

Exercises

Remember

1. Define *memory consolidation* in one sentence.
2. Name the two main types of declarative memory and give an example of each.

Answer

1. Memory consolidation is the gradual process that turns new, fragile memories into stable long-term memories.
2. Episodic memory (a personal event, like your last birthday) and semantic memory (a fact, like "glutamate is excitatory").

Understand

1. Explain why habituation in *Aplysia* is considered learning and not just muscle fatigue.
2. Explain, in your own words, how Hebbian learning could make a song remind you of a summer trip.

Answer

1. Kandel's group showed the change happens at the synapse between the sensory neuron and the motor neuron, which releases less transmitter with each touch. The muscle and sense organ still work, and a tail shock can bring the response right back (dishabituation), which fatigue would not explain.
2. During the trip, neurons representing the song and neurons representing the trip are active at the same time, so the connections between them strengthen. Later, activating the "song" neurons is enough to activate the "trip" neurons.

Apply

1. A new student moves next to a train track. At first, every train wakes her up. After two weeks, she sleeps through them. One night a smoke alarm goes off, and afterward she wakes up at the next train. Name the type of learning shown in each part of this story.
2. Using what you learned about the spacing effect and late LTP, design a two-week study schedule for a 40-word vocabulary list. Explain why your schedule should work better than studying the night before.

Analyze

1. Compare early LTP in the hippocampus with short-term sensitization in *Aplysia*. What is similar, and what is different?
2. H.M. could not form new declarative memories, but many of his older memories survived. What does this tell you about where long-term declarative memories are stored, compared with where they are formed?

Evaluate

1. A company advertises an app that "identifies your learning style so you can study the way your brain prefers." Using evidence from this chapter, judge whether a student should pay for it.
2. H.M.'s surgery was an experiment that caused permanent harm, yet it led to major discoveries. Today, surgeons would not do this operation. Evaluate how modern epilepsy surgery has changed because of what was learned.

Create

1. Design a simple experiment, using classmates as volunteers, to test whether spaced study beats cramming. Name your two groups, what they study, how you will measure memory, and what result would support the spacing effect.
2. Create a one-page comic strip in which a single synapse "narrates" what happens to it during habituation, sensitization, and long-term memory formation in *Aplysia*. Include serotonin, transmitter release, and new protein synthesis.

Key Takeaways

- **Learning** changes the nervous system; **memory** is what that change stores. Memories move from short-term and working memory into long-term memory through **consolidation**.
- Long-term memory has separate systems: **declarative memory** (facts and events) depends on the **hippocampus** and medial temporal lobe to form, while **procedural memory** (skills) relies on other circuits like the basal ganglia and cerebellum.
- **Patient H.M.** lost the ability to form new declarative memories after both medial temporal lobes were removed in 1953, but he could still learn motor skills. His case

showed that memory is a distinct brain function with several systems.

- **Neuroplasticity** means the brain changes with experience at every age. **Hebbian learning** proposes that connections strengthen when neurons are active together.
- **Long-term potentiation** is a lasting increase in synaptic strength. NMDA receptors act as coincidence detectors, letting in calcium that adds and boosts AMPA receptors.
- In the **Aplysia model**, **habituation** weakens and **sensitization** strengthens the same sensory-to-motor synapse. Long-term memory there needs new proteins and new synaptic connections, work recognized with Kandel's 2000 Nobel Prize.
- Spaced practice usually beats cramming for long-term memory. A leading explanation, best shown in animals like *Aplysia*, is that lasting synaptic changes need time and repeated activation to build.

You just rewired your brain!



Every big idea starts at a single synapse, and reading this chapter changed some of yours! Come back in a few days to make those changes last. Next, in Chapter 10, we'll look at sleep and how it connects to memory.

Chapter 10: Sleep and Brain States

Summary

Every night your brain moves through a predictable series of states, from relaxed waking to light sleep, deep slow-wave sleep, and dreaming REM sleep. This chapter explains how scientists read those states with the EEG, how a master clock in the hypothalamus times them, and why sleep matters for memory, mood, and safety. You'll see why teenagers need 8 to 10 hours of sleep and why so few get it. Finally, you'll meet a teen with narcolepsy and learn how the loss of a small group of orexin neurons can make the boundary between waking and sleep fall apart.

Concepts Covered

1. Consciousness
2. Circadian Rhythm
3. Suprachiasmatic Nucleus
4. Melatonin
5. Sleep Stages
6. NREM Sleep
7. REM Sleep
8. Electroencephalogram (EEG)
9. Brain Waves
10. Sleep and Memory
11. Teen Sleep Needs
12. Sleep Deprivation
13. Narcolepsy
14. Orexin (Hypocretin)

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters
- Chapter 4: A Tour of the Brain: Neuroanatomy
- Chapter 9: Learning, Memory, and Neuroplasticity

Welcome to the night shift



I'm a sea slug, and even I have daily rhythms of rest and activity. You'll spend about a third of your life asleep, yet most people have no idea what their brain is doing during those hours. By the end of this chapter, you'll be able to read a night of sleep like a doctor reads a chart, and you'll know why your own sleep is worth protecting.

10.1 Maya's Six-Hour Nights

It's the middle of Brain Bee season, and Maya has a system. Soccer practice ends at 6, homework fills the evening, and after that she studies neuroanatomy flashcards until about 12:30 a.m. Her alarm goes off at 6:30. That's six hours of sleep on school nights. On Saturdays she sleeps until almost noon, and she figures that evens things out.

Lately, though, something is off. Facts she studied on Tuesday seem to have vanished by Thursday. She snapped at her younger brother over nothing. During a free period she put her head down "for a second" and woke up 20 minutes later. Maya is a smart, careful student, so she asks a fair question: *Is six hours actually a problem, and if so, what exactly is her brain missing?*

To answer her, we need to see what the brain does at night. Sleep is not one thing. It's a sequence of very different brain states, and the last hours before the alarm are not like the first.

10.2 Is the Brain Off When You Sleep? Consciousness and Brain States

Think about your school building at night. The halls are dark, but the custodians are cleaning and the computers are backing up. The building isn't off. It's in a different *mode*, doing work that can't happen during class. Your brain at night is a lot like that.

Consciousness is your state of awareness of yourself and your surroundings. In medicine, doctors often think about two parts: *arousal* (how awake you are) and *awareness* (what you are experiencing). In deep sleep, both drop. During dreaming (REM sleep), you are asleep and mostly cut off from the outside world, but you can still have vivid experiences inside your head.

A **brain state** is an overall pattern of activity across the brain that goes along with a certain level of consciousness. Waking, light sleep, deep sleep, and dreaming sleep are all different brain states. Each has its own electrical signature and chemistry.

The key idea for this chapter: **the brain never shuts off during sleep.** Neurons keep firing action potentials (you met these in Chapter 2). What changes is the *pattern* of firing, which neurons are active, and which neurotransmitters are being released.

10.3 Listening to the Brain: The EEG and Brain Waves

The stadium analogy

Imagine standing outside a packed football stadium with a microphone. If 70,000 fans are all chatting in small groups, your microphone picks up a low, fuzzy hum. You can't make out any single voice, and the sound is small. But if the whole crowd starts chanting together, slowly and in rhythm, your microphone picks up big, rolling waves of sound.

That is almost exactly how a brain recording works. Each neuron is one fan. When millions of cortical neurons are busy with different jobs, their electrical signals partly cancel out, and the recording looks small and fast. When large groups of neurons fire together in a slow rhythm, their signals add up into tall, slow waves.

What an EEG measures

An **electroencephalogram (EEG)** is a recording of the brain's electrical activity made with small metal disks (electrodes) placed on the scalp. The electrodes don't record single action potentials. Instead, they pick up the combined, mostly synaptic electrical activity of huge numbers of cortical neurons lined up near the surface. (Those synaptic currents come from the receptor channels you studied in Chapter 3.)

The German psychiatrist Hans Berger recorded the first human EEG in 1924 and published his results in 1929. One of the first patterns he described was a rhythm of about 10 waves per second over the back of the head when a person relaxed with eyes closed. We now call it the alpha rhythm.

In a sleep study, the EEG is combined with sensors for eye movements, muscle tone, and breathing. That full overnight recording is called a **polysomnogram**.

Brain waves

Brain waves are the repeating rhythms that show up in an EEG. Scientists describe them with two measurements:

- **Frequency:** how many waves happen each second, measured in hertz (Hz). Ten waves per second is 10 Hz.
- **Amplitude:** how tall the waves are, measured in microvolts (μV), or millionths of a volt.

Fast, small waves usually mean many neurons are doing different jobs. Slow, tall waves usually mean large groups of neurons are firing together in sync, like the chanting crowd. Now that both terms are defined, here is a summary of the main rhythms you'll meet in this chapter.

Brain wave	Frequency (approx.)	When you see it
Beta	faster than about 13 Hz	Alert, eyes open, thinking hard
Alpha	about 8 to 13 Hz	Awake and relaxed with eyes closed
Theta	about 4 to 7 Hz	Drowsy; N1 sleep

Brain wave	Frequency (approx.)	When you see it
Delta (slow waves)	below about 4 Hz; the slow waves that define N3 are 0.5 to 2 Hz and tall (over 75 µV)	Deep N3 sleep

Slow and tall means in sync



Remember this one rule: tall, slow EEG waves mean lots of neurons are firing *together*. That's why deep sleep has the biggest waves of the night, even though you are the least aware you'll ever be.

10.4 The Clock Inside: Circadian Rhythms, the SCN, and Melatonin

A rhythm that keeps time on its own

Most people get sleepy around the same time each night, even without a bedtime rule. That's because your body runs on an internal clock.

A **circadian rhythm** is a cycle in the body or behavior that repeats about once every 24 hours. The word comes from Latin: *circa* ("about") and *dies* ("day"). Body temperature, hormone levels, alertness, and the timing of sleep all follow circadian rhythms.

The "about" matters. When people live in carefully controlled labs with no clues about the time of day, their clocks keep running, but not at exactly 24 hours. A well-known 1999 study found that the human circadian clock runs on an average cycle of about 24.18 hours (Czeisler and colleagues, *Science*, 1999). Each day, morning light nudges the clock back into step with the real day. Resetting a biological clock to match the outside world is called *entrainment*.

The master clock: the suprachiasmatic nucleus

The brain's master clock is the **suprachiasmatic nucleus (SCN)**, a pair of tiny clusters of neurons in the hypothalamus. The name tells you where it sits: *supra* means "above," and

the *chiasm* is the optic chiasm, where the two optic nerves cross. (You toured the hypothalamus in Chapter 4.)

That location is not an accident. The SCN needs to know when it's light outside. A special group of cells in the retina, called *intrinsically photosensitive retinal ganglion cells*, contain a light-sensitive pigment called melanopsin. These cells send signals straight to the SCN along a pathway called the retinohypothalamic tract. Melanopsin is most sensitive to blue light, at about 480 nanometers (OpenStax, *Introduction to Behavioral Neuroscience*, section 15.2).

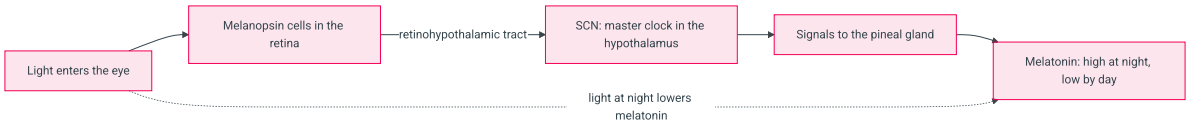
Inside each SCN neuron, "clock genes" keep time with a feedback loop: the proteins CLOCK and BMAL1 turn on the *Per* and *Cry* genes, and the PER and CRY proteins slowly build up and switch CLOCK and BMAL1 back off. One full loop takes about a day.

Melatonin: the darkness signal

The SCN controls many body rhythms, including the release of a hormone that signals "it's night." **Melatonin** is a hormone made by the pineal gland, a small gland deep in the brain. Melatonin levels are high at night and low during the day. Rising melatonin in the evening helps you feel sleepy as it gets dark (NINDS, *Brain Basics: Understanding Sleep*).

Bright light, especially at night, quickly lowers melatonin. That's one reason doctors and scientists talk so much about evening light from rooms and screens.

The flowchart below traces the pathway from light to melatonin that we just described.



Two forces that time your sleep

The clock is only half the story. Scientists often describe sleep timing with a **two-process model** (OpenStax, section 15.3):

- **Process S (sleep pressure):** the longer you stay awake, the stronger your need for sleep becomes. One chemical that builds up during waking is adenosine, which makes you feel sleepy. Caffeine works by blocking adenosine's effects, which is why coffee delays sleepiness without removing the need for sleep.

- **Process C (the circadian clock):** the SCN pushes you toward alertness at some times of day and toward sleep at others, no matter how long you've been awake.

When both forces line up at night, falling asleep is easy. When they fight, as after flying across time zones, sleep gets harder.

10.5 A Night in Stages: NREM and REM Sleep

Sleep is a staircase, not a light switch

Falling asleep is less like flipping a switch and more like walking down a staircase into a basement, then climbing back up to a strange, busy attic, several times a night.

These steps are called **sleep stages**: distinct phases of sleep identified from the EEG, eye movements, and muscle tone. Under the scoring rules of the American Academy of Sleep Medicine (AASM), there are three stages of NREM sleep (N1, N2, and N3) and one stage of REM sleep. (Older books split deep sleep into "stage 3" and "stage 4." The current rules combine them into N3.)

NREM sleep

NREM sleep (non-rapid eye movement sleep) is the part of sleep in which the eyes are mostly still and the EEG slows down step by step. It includes three stages.

- **N1 (falling asleep).** This is the lightest stage and the doorway into sleep. It usually lasts only several minutes. The relaxed alpha rhythm fades and is replaced by slower theta waves of about 4 to 7 Hz.
- **N2 (light sleep).** Two new EEG features appear. **Sleep spindles** are short bursts of fast waves, roughly 12 to 14 Hz, lasting at least half a second. **K-complexes** are single large waves: a sharp swing one way followed by a slower swing the other way. N2 takes up more of the night than any other stage (NINDS).
- **N3 (deep or slow-wave sleep).** The EEG fills with tall, slow delta waves of about 0.5 to 2 Hz, over 75 μV in amplitude (Watson and colleagues, 2013). This is the deepest stage of sleep, and it's the hardest one to wake someone from. Most N3 happens in the first half of the night.

REM sleep

REM sleep (rapid eye movement sleep) is the stage in which the eyes dart back and forth under closed lids, the EEG looks surprisingly like waking, and most of the body's muscles are temporarily paralyzed. It was first described by Eugene Aserinsky and Nathaniel Kleitman in a short 1953 paper in *Science*, after Aserinsky noticed bursts of rapid eye movements in sleeping people.

REM has three features worth remembering:

1. **An "awake-looking" EEG.** The waves are low in amplitude and mixed in frequency. REM often includes runs of *sawtooth waves* (about 2 to 6 Hz), which look like the teeth of a saw.
2. **Rapid eye movements** in bursts.
3. **Muscle atonia**, a near-total loss of muscle tone in the arms and legs. The brainstem actively blocks movement signals so that you don't act out your dreams. Breathing muscles and eye muscles keep working.

Dreams are most vivid in REM, though people can dream in other stages too. Across a night, a person spends about two hours dreaming, even if they remember little of it (NINDS).

Four stages, one trick



That's a lot of vocabulary, so tie each stage to one picture: N1 is "drifting," N2 is "spindles," N3 is "big slow waves," and REM is "busy brain, frozen body." If you can sketch one wave for each, you're ready for the Brain Bee.

Cycles across the night

A healthy sleeper goes N1 → N2 → N3 → back up to N2 → REM. That loop is one **sleep cycle**, and it takes about 90 minutes. The first REM period usually begins about 90 minutes after you fall asleep and lasts only about 10 minutes. Later REM periods get longer and can reach about an hour near morning (OpenStax, section 15.3).

So the night is lopsided:

- **Early night:** mostly N2 and N3, with short REM periods.
- **Late night:** little or no N3, with mostly N2 and long REM periods.

The table below sums up the four stages you just read about.

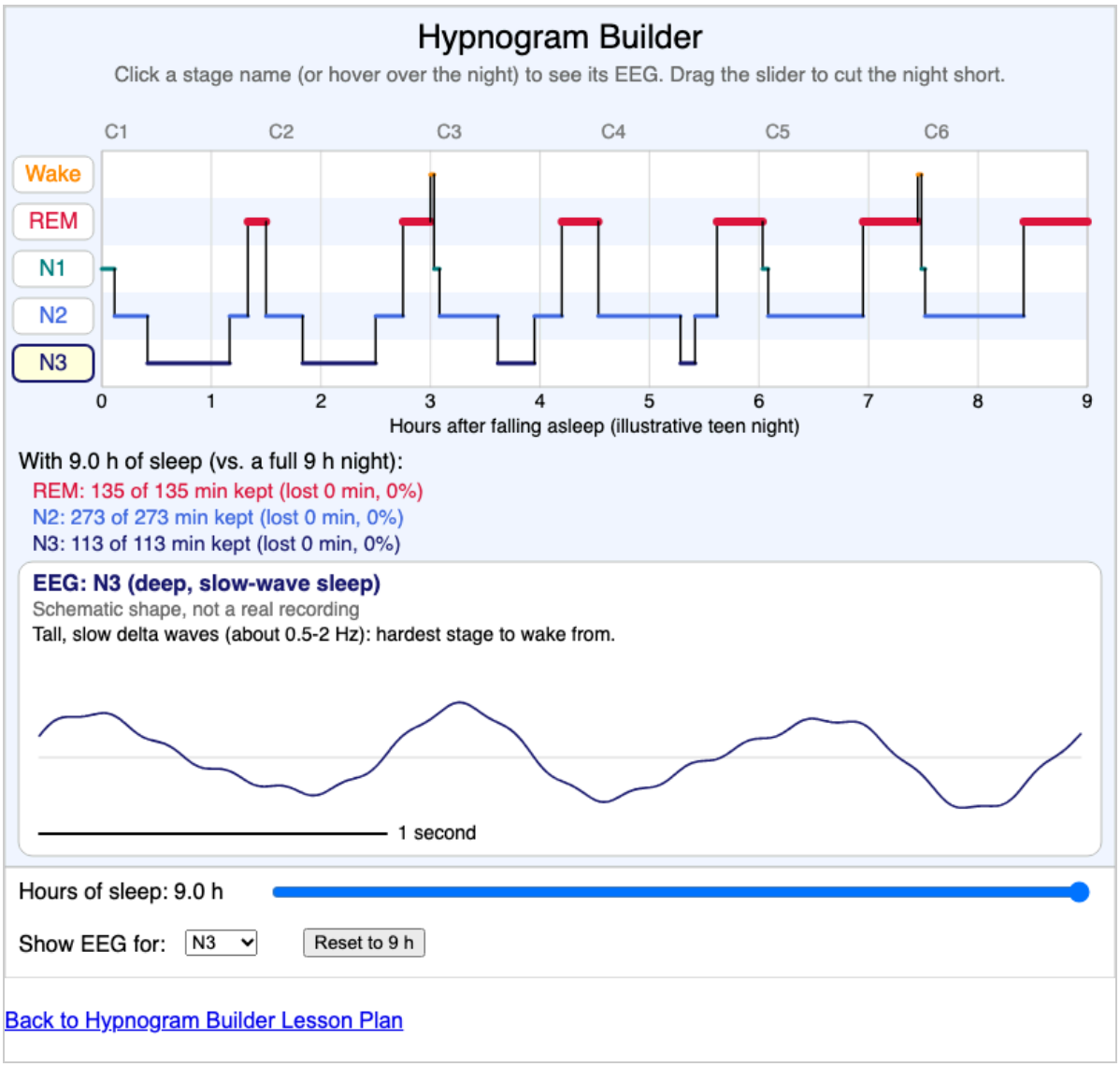
Stage	Type	EEG signature	Body and experience
N1	NREM	Theta waves (about 4 to 7 Hz)	Drifting off; easy to wake
N2	NREM	Sleep spindles and K-complexes	Light sleep; largest share of the night
N3	NREM	Tall delta waves (about 0.5 to 2 Hz)	Deep sleep; hard to wake; mostly early in the night
REM	REM	Low-voltage, mixed, "awake-looking"	Rapid eye movements, vivid dreams, limb muscles paralyzed; longer toward morning

10.6 Building a Hypnogram

A **hypnogram** is a graph of sleep stages across a night. Time runs left to right, and each stage gets its own row, with Wake at the top and N3 at the bottom. Sleep doctors make hypnograms from a polysomnogram.

The MicroSim below shows an illustrative hypnogram for a healthy teenager who sleeps 9 hours. With cycles of about 90 minutes, 9 hours holds roughly five or six cycles. The data are made up to show the typical pattern, not taken from a real person.

Diagram: Hypnogram Builder



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch10-hypnogram/

Open the Hypnogram Builder fullscreen

MicroSim specification: Hypnogram Builder

Type: microsim **sim-id:** ch10-hypnogram
Library: p5.js
Status: Implemented
Bloom Level: Analyze
Bloom Verb: interpret
Learning Objective: The learner will interpret a hypnogram to identify each sleep stage by its EEG signature and explain which stages are lost when a 9-hour night is cut to 6 hours.

Content: Illustrative (not real) 540-minute teen night, six cycles of about 90 minutes. Totals: REM 135, N2 273, N3 113, N1 15, Wake 4 minutes. N3 only in the first four cycles; REM periods grow from 10 to 35 minutes. Schematic 3-second EEG per stage (alpha 8 to 13 Hz; theta 4 to 7 Hz; spindle about 12 to 14 Hz and K-complex; delta 0.5 to 2 Hz; low-voltage mixed waves with sawtooth waves), labeled "Schematic shape, not a real recording."

Controls: "Hours of sleep" slider (4 to 9 h, step 0.5, default 9). "Show EEG for" menu (default N3). "Reset to 9 h" button. Clicking a stage label or hovering over the night also selects a stage.

Behavior: Time after the "Alarm" line is grayed out; a readout lists minutes of REM, N2 and N3 kept and lost. At 6.0 h: REM 68 of 135 kept (lost 67, 50%), N2 167 of 273 (lost 106, 39%), N3 113 of 113 (lost 0). Not animated.

Chapter Anchors: cycles of about 90 minutes; most N3 in the first half of the night; REM periods longer toward morning; cutting 9 h to 6 h loses about half of REM and almost no N3.

Try this:

1. Click each stage name on the left (or use the menu) and compare the EEG traces. Which stage has the tallest, slowest waves? Where do you see a spindle and a K-complex?
2. Hover across the night from left to right. Notice where the N3 "valleys" are and how the red REM bars get longer as morning approaches.
3. Now be Maya. Drag the **Hours of sleep** slider down to **6.0 h**, which is like setting the alarm three hours early.

When you cut the night to 6 hours, almost all of the N3 survives, because deep sleep is packed into the early cycles. But you lose about half of the night's REM sleep (67 of 135 minutes in this example) and more than a third of N2. Short sleep doesn't shave a little off

every stage evenly. It chops off the end of the night, where the longest REM periods live. Going to bed later with the same alarm has a similar effect.

10.7 Why Sleep? Sleep and Memory

The librarian analogy

Picture a library. All day, returned books pile up on a small cart by the front desk. After closing, the librarian shelves each book where it belongs, next to related books. By morning the cart is empty and ready for a new day.

In Chapter 9, you learned that the hippocampus helps form new memories, while long-term storage depends heavily on the cortex. The hippocampus is like the cart, and the cortex is like the shelves. A lot of the sorting happens while you sleep.

What sleep does for memory

Sleep and memory is the research area that studies how sleep strengthens and reorganizes what we learned while awake, a process called *memory consolidation*. Here's what researchers have found so far (Diekelmann and Born, *Nature Reviews Neuroscience*, 2010; Rasch and Born, *Physiological Reviews*, 2013):

- **During slow-wave (N3) sleep,** slow oscillations in the cortex, sleep spindles, and fast bursts in the hippocampus appear to work together. They help *replay* new memories and move them from the hippocampus toward long-term storage in the cortex.
- **During REM sleep,** brain activity and gene activity related to synaptic plasticity may help strengthen and stabilize those memories in cortical circuits.
- **Both kinds of sleep likely matter.** The NINDS notes that memory consolidation most likely requires both NREM and REM sleep.

Sleep may also help the brain take out the trash. In a 2013 study in mice, the space between brain cells grew by about 60% during sleep, and a waste protein called beta-amyloid was cleared faster (Xie and colleagues, *Science*, 2013). This was a mouse study, and the idea is now debated. In 2024, a different team measured how fast a dye left the brains of mice and found that clearance was about 30% *lower* during sleep than during waking, and about 50% lower under anesthesia (Miao and colleagues, *Nature Neuroscience*, 2024; UK Dementia Research Institute summary). Other researchers have questioned that study's methods, and

neither result has been settled in humans. As of 2026, "sleep washes waste out of the brain" is an exciting hypothesis, not an established fact.

10.8 Teen Sleep Needs and the Shifted Teen Clock

How much sleep do teens need?

Teen sleep needs refers to how much sleep adolescents require for good health, and it's more than most people think. The American Academy of Sleep Medicine recommends that teenagers 13 to 18 years old sleep **8 to 10 hours per 24 hours** on a regular basis (Paruthi and colleagues, *Journal of Clinical Sleep Medicine*, 2016). The CDC uses the same range of 8 to 10 hours for teens (CDC, *About Sleep*). Adults 18 and older need 7 or more hours.

Very few teens reach that target. In the 2025 national Youth Risk Behavior Survey, only 24% of U.S. high school students (about 1 in 4) reported getting at least 8 hours of sleep on an average school night. That share did not change from 2023 to 2025, and it was lower in 2025 than in 2015 (CDC, YRBS: Sleep, 2026).

The teen clock runs late

Part of the problem is biology. During puberty, circadian rhythms commonly shift later. Teens tend to feel sleepy later at night and need to sleep later in the morning (CDC, *MMWR*, 2015). This is not laziness. It's a real change in the timing of the clock.

Now add an early school bell. In 2014 the American Academy of Pediatrics recommended that middle and high schools start no earlier than 8:30 a.m. But a CDC analysis of the 2011-12 school year found that the average start time for U.S. public middle and high schools was 8:03 a.m., and only 17.7% of these schools started at 8:30 or later (CDC, *MMWR*, 2015).

If your clock makes it hard to fall asleep before 11:30 p.m. and you must wake at 6:30 a.m., the most you can get is 7 hours.

Work with your clock, not against it



Your SCN listens to light. Bright light in the morning helps set your clock earlier, while bright light late at night pushes it later and lowers melatonin. A regular wake time, even on weekends, gives your clock a steady anchor.

10.9 Sleep Deprivation: What Short Sleep Costs

Sleep deprivation means getting less sleep than your body needs. It can be *acute* (one all-nighter) or *chronic* (too little sleep night after night, like Maya's six-hour routine).

The 6-hour experiment

One of the most important studies on chronic short sleep was done in a lab with 48 healthy adults (Van Dongen and colleagues, *Sleep*, 2003). Participants were assigned to spend 4, 6, or 8 hours in bed each night for 14 nights in a row (a fourth group stayed awake for three nights straight). The researchers tested their attention and thinking every day.

- People limited to 6 hours or less got steadily worse over the two weeks.
- By the end, their performance problems were as large as those seen after up to two full nights with no sleep at all.
- The surprising part was that their *ratings of their own sleepiness* barely changed after the first few days. They didn't realize how impaired they had become.

That matters for Maya. She feels "used to" six hours, but her brain may be paying a price she can't feel.

Effects across the body and mind

The National Heart, Lung, and Blood Institute lists many effects of sleep deficiency (NHLBI), which we can group like this:

Area	What short sleep can do
Learning and attention	Harder to learn, focus, and react quickly
Mood and social life	More frustration and worry; harder to read other people's emotions
Safety	Drowsy driving causes serious crashes, injuries, and deaths
Long-term health	Linked to high blood pressure, heart disease, diabetes, obesity, and depression

Can you catch up on weekends?

Sleeping in on Saturday does help you feel better, and it partly pays back some sleep debt. But it doesn't fully undo a week of short nights. In a 2019 lab study of adults, a pattern of short weeknight sleep followed by weekend "recovery" sleep still disrupted the body's metabolism (Depner and colleagues, *Current Biology*, 2019). Big swings between weekday and weekend sleep times also create what scientists call *social jet lag*: returning to the weekday schedule on Monday is like adjusting to a new time zone (OpenStax, section 15.5).

So, back to Maya's question. Her six-hour nights cut off the REM-rich end of every night, they keep her in the zone where performance slips without her noticing, and her Saturday sleep-ins can't fully fix it. The forgotten facts, the short temper, and the accidental nap in study hall all fit.

10.10 Orexin: The Brain's Wake Stabilizer

A light switch that needs a hand on it

Healthy people don't flicker in and out of sleep all day. Scientists describe this with a **flip-flop switch** model (OpenStax, section 15.3):

- A sleep-promoting group of neurons in the hypothalamus releases the inhibitory neurotransmitter GABA to quiet the wake centers.

- Wake-promoting groups in the brainstem and hypothalamus release norepinephrine, serotonin, histamine, and acetylcholine, and they quiet the sleep center in return.

Because each side shuts down the other, the system tends to snap firmly into one state. But a switch like that can be wobbly. It works best when something holds it steady in the "awake" position during the day.

Meet orexin

That stabilizer is **orexin**, also called **hypocretin**: a small signaling peptide made by a cluster of neurons in the lateral hypothalamus. It helps keep the brain awake and keeps the sleep-wake switch stable. Orexin neurons excite the wake-promoting centers, helping you stay awake through the day and preventing pieces of REM sleep from breaking into waking life.

Orexin has two names because two research teams discovered it at almost the same time in 1998. One team named the peptides "hypocretins" (de Lecea and colleagues, *PNAS*, 1998). The other named them "orexins," from the Greek word for appetite, because the team first studied their role in feeding (Sakurai and colleagues, *Cell*, 1998).

The link to sleep came from dogs. A research group had long studied a line of Doberman pinschers with inherited narcolepsy. In 1999 they showed that the dogs' disorder came from a mutation in the gene for orexin receptor 2 (Lin and colleagues, *Cell*, 1999). A year later, two groups studying human brains found that people with narcolepsy had lost most of their orexin. One reported an 85 to 95% reduction in the number of orexin neurons (Thannickal and colleagues, *Neuron*, 2000), and the other found a widespread absence of the orexin peptides themselves (Peyron and colleagues, *Nature Medicine*, 2000).

Missing orexin is not the same as being tired



Don't confuse narcolepsy with ordinary sleepiness from staying up late. A sleep-deprived teen has a working switch that's being pushed too hard. A person with narcolepsy type 1 has lost the hand that holds the switch steady, so even a full night's sleep doesn't fix the problem.

At the Bedside: The Student Who Collapsed When She Laughed

Meet the patient

Alex is a 17-year-old high school senior. For about a year she has been falling asleep in class, sometimes in the middle of a test, even after 9 hours of sleep. She takes naps after school and wakes up feeling refreshed for a short while. Her friends have noticed something stranger: when she laughs hard at a joke, her head drops, her knees buckle, and once she slid to the floor. She stayed fully aware the whole time and could hear everyone, and it was over in less than a minute. She also reports waking up unable to move for a few seconds, sometimes while "seeing" a person standing in her room. Her parents first wondered if she was just staying up too late.

What the doctor checks: The doctor takes a careful history and asks Alex to keep a sleep diary for one to two weeks to make sure she isn't simply short on sleep. A neurological exam is normal. Next comes a sleep study in two parts (NINDS).

First, an overnight **polysomnogram** records her EEG, eye movements, muscle tone, and breathing. The next day, a **multiple sleep latency test (MSLT)** gives her several scheduled nap chances and measures how fast she falls asleep and whether she goes straight into REM. Under current diagnostic criteria, narcolepsy is supported by an average time to fall asleep of 8 minutes or less across the naps, plus REM sleep appearing soon after sleep onset at least twice (in the naps, or in the naps plus the night before) (Reiter and colleagues, *Sleep*, 2015). Alex falls asleep in about 3 minutes on average and enters REM in three of five naps. Doctors can also measure orexin (hypocretin-1) in spinal fluid from a lumbar puncture; very low levels confirm type 1.

Where is the problem? (localization): Two clues point to the hypothalamus. First, Alex is sleepy all day despite enough sleep, so the system that *holds* wakefulness is failing. Second, pieces of REM sleep are breaking into waking life: losing muscle tone while awake is REM atonia at the wrong time, and "seeing" a figure while paralyzed on waking is a dream overlapping with waking. The neurons that keep the wake switch stable and keep REM in its place are the orexin neurons of the lateral hypothalamus.

Diagnosis: Narcolepsy type 1 (narcolepsy with cataplexy). Narcolepsy is a chronic neurological disorder in which the brain can't properly control the sleep-wake cycle. Type 1 is defined by excessive daytime sleepiness plus either very low orexin in spinal fluid or

cataplexy with a positive MSLT. **Cataplexy** is a sudden loss of muscle tone, often triggered by strong emotions like laughter, during which the person stays conscious. Narcolepsy type 1 affects an estimated 1 in 2,000 people in the U.S. (FDA, 2026), and symptoms usually begin between ages 7 and 25 (NINDS).

Why it happens: Nearly everyone with type 1 has extremely low orexin, mostly because the orexin-making neurons in the hypothalamus have been lost. Scientists think the most likely cause is an attack by the person's own immune system on these neurons, together with genetic and environmental factors. A gene variant called HLA-DQB1*06:02 raises the risk, and new cases have followed infections such as strep throat and the 2009 H1N1 flu (NINDS). Without orexin, the flip-flop switch from Section 10.10 becomes unstable, so Alex slips into sleep by day and REM features leak into wakefulness.

Treatment today: There's no cure, but treatment can control symptoms well, and it often takes time to find the right mix (NINDS). Care usually combines:

- **Healthy sleep habits:** a regular sleep schedule and short planned naps during the day.
- **Wake-promoting medicines and stimulants** for daytime sleepiness.
- **Sodium oxybate**, which is FDA-approved for cataplexy and daytime sleepiness and is distributed under tight restrictions.
- **Pitolisant**, a medicine that acts on histamine receptors and is approved for daytime sleepiness in adults and in children 6 and older.
- **Certain antidepressants**, which can reduce cataplexy.
- **Support at school and safety planning,** such as scheduled nap breaks during the day and talking with the doctor about when driving is safe.

What's new in research: On August 5, 2026, the FDA approved oveporexton (brand name Orzeyful), a twice-daily tablet that activates orexin receptor 2. According to the FDA, it directly activates the same brain receptor that the body's own orexin would normally stimulate, standing in for the missing signal rather than only treating individual symptoms (FDA press announcement, August 5, 2026). The approval is for **adults** with narcolepsy type 1. Its safety and effectiveness have not been established in people under 18, so for 17-year-old Alex it is not yet an approved option. The path to this drug ran straight from the orexin discoveries in Section 10.10.

Your turn: diagnose a variation

Jordan, 16, is also falling asleep in class. Jordan has never had sudden weakness when laughing or startled. A sleep diary shows Jordan sleeps about 5.5 hours on school nights (gaming until after 1 a.m., alarm at 6:45) and 11 hours on weekends. After two weeks of going to bed earlier and getting 9 hours a night, the daytime sleepiness mostly goes away. What is the most likely explanation, and why is it probably not narcolepsy type 1?

Answer: The most likely explanation is chronic insufficient sleep, or sleep deprivation. Jordan has no cataplexy, and the sleepiness improves once Jordan gets enough sleep. That points to a working sleep-wake switch that has simply been shortchanged, not lost orexin neurons. This is why doctors check a sleep diary before an MSLT: a person who is simply short on sleep can also fall asleep quickly during nap tests.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: "The brain shuts off when you sleep."
Reality: The brain stays active all night. It cycles through distinct states, and during REM sleep the EEG looks much like it does when you're awake. Sleep is a change in the *pattern* of activity, not an off switch.

Myth: "You can catch up on all your lost sleep on the weekend."
Reality: Sleeping in helps you feel better, but it doesn't fully undo a week of short nights. A lab study found that weekday short sleep plus weekend catch-up sleep still disrupted metabolism, and big weekend schedule swings cause social jet lag.

Myth: "After a while, your body gets used to six hours of sleep."
Reality: In the 14-day lab study, people on 6 hours a night kept getting worse at attention tasks, but they *felt* only a little sleepier. Feeling used to short sleep is not the same as performing well.

Myth: "Teens stay up late only because they're lazy or glued to their phones."
Reality: Screens and habits can make it worse, but puberty itself commonly shifts the circadian clock later. That's a big reason the American Academy of Pediatrics and the

American Academy of Sleep Medicine recommend middle and high school start times of 8:30 a.m. or later (AASM position statement, 2017).

Myth: "People with narcolepsy are just very tired."
Reality: Narcolepsy type 1 is a neurological disorder caused by the loss of orexin neurons. Its symptoms, like cataplexy and sleep paralysis, come from REM sleep breaking into waking. Ordinary sleep loss does not cause cataplexy.

Brain Bee Practice

1. Which brain structure is the body's master circadian clock, and where is it located?

The suprachiasmatic nucleus (SCN). It's in the hypothalamus, just above the optic chiasm, where it receives light information from the retina.

2. Name two EEG features that mark stage N2 sleep.

Sleep spindles (brief bursts of fast waves, roughly 12 to 14 Hz) and K-complexes (single large waves with a sharp swing followed by a slower swing in the opposite direction).

3. Why is REM sleep sometimes called 'paradoxical sleep'?

During REM sleep the EEG looks much like waking, with low-voltage, mixed fast activity, yet the person is deeply asleep and most body muscles are paralyzed. An awake-looking brain inside a sleeping, motionless body is the paradox.

4. A patient has sudden loss of muscle tone when laughing but stays fully conscious. What is this symptom called, and which neurons are usually lost?

Cataplexy. It's the hallmark of narcolepsy type 1, which is caused by the loss of orexin (hypocretin) neurons in the lateral hypothalamus.

5. Which hormone does the pineal gland release at night, and what does light do to it?

Melatonin. Bright light, especially at night, quickly lowers melatonin levels.

Exercises

Remember

1. List the four sleep stages used in current sleep scoring, and say which ones are NREM.
2. What does the abbreviation EEG stand for, and what does it measure?

Answer

1. N1, N2, N3, and REM. N1, N2, and N3 are NREM stages.
2. Electroencephalogram. It records the combined electrical activity of large groups of cortical neurons using electrodes on the scalp.

Understand

1. Explain in your own words why deep N3 sleep produces taller EEG waves than waking does.
2. Describe how light reaching the eye can change melatonin levels. Name the structures in the pathway.

Answer

1. In N3, large groups of cortical neurons fire together in a slow rhythm, so their electrical signals add up into tall, slow waves. When you're awake, neurons are doing many different jobs at different times, so their signals partly cancel out and the EEG looks small and fast.
2. Light activates melanopsin-containing retinal ganglion cells, which signal the SCN through the retinohypothalamic tract. The SCN controls the pineal gland, and light (especially at night) lowers the pineal gland's release of melatonin.

Apply

1. Using the Hypnogram Builder, set the slider to 7.5 hours. Record how many minutes of REM and N3 are kept, then explain why one stage loses more than the other.
2. A friend says, "I'll just drink an energy drink, so I don't need sleep." Use the idea of adenosine and sleep pressure to explain what caffeine does and doesn't do.

Analyze

1. Two hypnograms are shown to you. Night A has N3 in the first three cycles and REM periods that get longer through the night. Night B has REM appearing within a few minutes of falling asleep and several brief awakenings. Which night is more consistent with narcolepsy, and what evidence supports your answer?
2. Compare sleep deprivation and narcolepsy type 1. How are their causes different, even though both cause daytime sleepiness?

Evaluate

1. Your school board is debating whether to move the high school start time from 7:30 a.m. to 8:30 a.m. Using evidence from this chapter, write a short argument for or against the change. Include at least one possible drawback.
2. A sleep-tracking app claims it can tell you exactly how many minutes of REM you got last night using only your phone's motion sensor. Judge how trustworthy that number is, given how sleep stages are actually scored.

Create

1. Design a two-week experiment to test whether getting 9 hours of sleep instead of 6 improves vocabulary recall in high school students. Describe your groups, what you would measure, and how you would make the comparison fair.
2. Create a one-page poster for your school that explains teen sleep needs using accurate facts from this chapter and one hypnogram drawing.

Key Takeaways

- The brain never shuts off during sleep. It moves through distinct brain states that the EEG can tell apart by frequency and amplitude.
- Sleep has NREM stages (N1, N2, N3) and REM sleep. Cycles last about 90 minutes, with most deep N3 early in the night and the longest REM periods near morning.
- The suprachiasmatic nucleus in the hypothalamus is the master circadian clock. Light reaches it from the retina, and it controls the pineal gland's release of melatonin.

- Sleep helps consolidate memories, with slow-wave sleep and REM sleep likely playing complementary roles.
- Teens need 8 to 10 hours of sleep, but puberty shifts the clock later, and only about 1 in 4 U.S. high school students got 8 hours on school nights in the 2025 CDC survey.
- Cutting sleep short mostly removes late-night REM and N2, and chronic short sleep impairs performance even when people don't feel it.
- Narcolepsy type 1 is caused by the loss of orexin (hypocretin) neurons, which destabilizes the sleep-wake switch and lets REM features like cataplexy intrude into waking.

You made it through the night!



You can now read a hypnogram, name every sleep stage by its brain waves, and explain why a missing peptide can make someone collapse with laughter. Next, in Chapter 11, we'll look at emotion and stress, and how the brain and body react when life gets intense.

Chapter 11: Emotion, Stress, and the Body

Summary

Emotions are more than feelings. They are whole-body responses run by a network of brain regions, with the amygdala as one key hub. In this chapter you'll learn how the brain learns what to fear and how it triggers two stress systems: a fast, nerve-based "fight-or-flight" response and a slower hormone chain called the HPA axis, which releases cortisol. You'll see why a short burst of stress is healthy, why stress that never switches off wears the body and brain down, and how people regulate their emotions. The chapter ends at the bedside with post-traumatic stress disorder (PTSD) after a car crash, and the treatments that help.

Concepts Covered

1. Emotion
2. Limbic System
3. Amygdala
4. Fear Conditioning
5. Stress Response
6. HPA Axis
7. Cortisol
8. Fight or Flight
9. Chronic Stress Effects
10. Emotion Regulation
11. Post-Traumatic Stress Disorder

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters
- Chapter 4: A Tour of the Brain: Neuroanatomy
- Chapter 9: Learning, Memory, and Neuroplasticity

Why your heart pounds



Even I pull my gill in fast when something pokes my tail, and I only have about 20,000 neurons! You have billions, and some of them are wired to keep you alive when danger shows up. In this chapter we'll follow a scare from your eyes to your hormones and back again. Once you understand your stress system, it gets a lot less mysterious.

11.1 Maya's Racing Heart

It's 7:55 a.m., five minutes before Maya's chemistry test. She studied. She knows the material. But her heart is pounding, her palms are damp, her mouth is dry, and her stomach feels like it's doing laps. When the teacher hands out the papers, Maya's mind goes blank for a second, and then, slowly, the answers come back.

Nothing in that classroom is dangerous. Nobody is chasing Maya. So why does her body act as if a bear just walked in? And why do the jitters fade after a few minutes of writing, while the tired, drained feeling sticks around for the rest of the morning?

The answers lie in two systems that run side by side: a fast one that uses nerves and a slow one that uses hormones in the blood. Both are steered by brain regions that decide what matters to you emotionally. By the end of this chapter, you'll be able to trace Maya's whole experience.

11.2 What Is an Emotion?

Think about a smoke alarm. It doesn't know whether the smoke is from burnt toast or a house fire. Its job is to notice a possible threat fast and get everyone moving. You can

decide afterward whether it was a false alarm. Your emotional brain works a lot like that, except it also comes with feelings, facial expressions, and changes all over your body.

An **emotion** is a brief, organized response to something that matters to you. It has three parts that usually happen together:

- **Body changes:** heart rate, breathing, sweating, muscle tension, and hormone levels shift.
- **Behavior:** you freeze, run, smile, frown, or speak in a shaky voice.
- **Feeling:** the private experience you put a name to, like "I'm scared" or "I'm excited."

Scientists have argued for more than a century about the order of these parts. In the 1880s, William James and Carl Lange proposed that the body reacts first and the feeling comes from noticing those body changes. In the 1920s, Walter Cannon and Philip Bard pushed back. They argued that the brain produces the feeling and the body changes at the same time, rather than one causing the other. Later theories added a third ingredient: how you *interpret* the situation. A racing heart can feel like terror on a turbulent airplane and like fun on a roller coaster.

The table below sums up these three classic ideas.

Theory	Main idea	Example: you see a growling dog
James-Lange	Body change comes first; the feeling is your brain reading that change	Your heart races, and noticing it makes you feel afraid
Cannon-Bard	Brain triggers the feeling and the body change at the same time	Fear and a racing heart start together
Two-factor (Schachter-Singer)	Feeling depends on body arousal *plus* how you label the situation	Your heart races, and because there's a growling dog, you call it fear

Modern neuroscience keeps a piece of each. The role of interpretation will come back when we get to emotion regulation.

11.3 The Limbic System: The Brain's Emotion Network

In Chapter 4 you toured the brain's major regions. Several of them sit in a ring along the inner edge of each hemisphere, wrapped around the brainstem. In 1878, the French physician Paul Broca named this border region the "great limbic lobe," from the Latin *limbus*, meaning "edge." In 1937, the American neuroanatomist James Papez proposed that a loop of these structures produces emotional experience. Around 1950, Paul MacLean grouped them under the name **limbic system**.

Today, the **limbic system** is a useful nickname for a set of connected structures, deep in the brain, that work together on emotion, motivation, and emotional memory. Here are the main members and what each one contributes.

Structure	Where it is	Role in emotion and stress
Amygdala	Deep in the front of each temporal lobe	Flags what is emotionally important, especially threats; triggers stress responses
Hippocampus	Just behind the amygdala, in the temporal lobe	Stores the context of events (where, when); helps turn the stress response off
Hypothalamus	Below the thalamus, at the base of the brain	Launches the hormone and nerve responses to stress
Cingulate cortex (front part)	Arches over the corpus callosum	Tracks body sensations and gives them emotional meaning
Prefrontal cortex (especially its middle and lower surfaces)	Front of the frontal lobe	Reins in the amygdala and helps regulate emotion
Thalamus	Center of the brain	Relays sensory signals, including a quick route to the amygdala

Scientists don't all agree on exactly which structures belong in the limbic system, and many argue the term is outdated. One reason is that its most famous member, the hippocampus,

turned out to be mainly about memory, not emotion. Another is that regions outside the old ring, like the prefrontal cortex in the table above, matter a lot for emotion. Some researchers now describe separate networks for emotion and for memory rather than one "limbic system" (Rolls, 2015). Emotion isn't "housed" in one place. Think of the limbic system as a loose nickname for a team, not a single room.

11.4 The Amygdala: More Than a "Fear Center"

The **amygdala** is an almond-shaped cluster of nuclei (groups of neuron cell bodies) deep in each temporal lobe. You have two, one per hemisphere. Its main job is to tag incoming information with emotional importance: *Does this matter to me? Is it dangerous? Is it rewarding?*

The amygdala gets sensory information from two routes. A quick route comes almost straight from the thalamus. It's rough, but fast, like a blurry photo. A slower route passes through the sensory cortex first and delivers a detailed picture. This is a popular explanation for why you can jump at a garden hose before you realize it isn't a snake. Keep in mind that the fast route was mapped mainly in rats. In humans, some researchers argue it plays only a small role and that the cortex does more of the work than the simple two-route story suggests (Pessoa and Adolphs, 2010). The amygdala also gets context from the hippocampus ("I'm at the zoo, behind glass") and guidance from the prefrontal cortex ("this is just a test").

When the amygdala detects a threat, it sends signals to two main targets:

1. The **hypothalamus**, which launches the hormone stress response, and
2. **Brainstem** areas that speed the heart, change breathing, and trigger freezing or a startle.

Evidence for the amygdala's role in fear comes from several directions:

- **Monkeys.** In the late 1930s, Heinrich Klüver and Paul Bucy removed large parts of the temporal lobes, including the amygdala, in monkeys. The animals became strangely calm and stopped showing normal fear of threats.
- **A rare patient.** A woman known in research as S.M. has a rare genetic condition, Urbach-Wiethe disease, that destroyed both of her amygdalae. In a 2011 study, researchers exposed her to live snakes and spiders, took her through a haunted house,

and showed her scary films. She showed no fear and reported almost none (Feinstein and colleagues, 2011).

- **Brain imaging.** fMRI studies show the amygdala becomes more active during emotional stress.

The amygdala does more than fear



Calling the amygdala the "fear center" is like calling your phone a "flashlight." The amygdala also responds to rewarding things, helps you recognize emotions in other people's faces, and makes emotional events easier to remember.

Emotional events tend to stick in memory because the amygdala boosts the hippocampus while a memory is being stored. And in a later study, S.M. and two other people with the same condition *did* feel intense panic when they breathed air with extra carbon dioxide. So even fear is not handled by the amygdala alone. Some internal alarms use other pathways.

11.5 Fear Conditioning: Learning What to Fear

In Chapter 9 you saw how experience strengthens synapses. One famous kind of learning built on this is **classical conditioning**, learning that one event predicts another. In Ivan Pavlov's classic experiments, dogs learned that a sound predicted food, so the sound alone made them drool. The same kind of learning happens with danger.

Fear conditioning is a form of classical conditioning in which a neutral cue becomes a trigger for fear because it was paired with something painful or frightening. In a typical lab experiment with rats:

1. A tone plays. The rat ignores it. (The tone is the *neutral* stimulus.)
2. The tone plays again, and this time it ends with a mild foot shock. (The shock is the *unconditioned* stimulus. It causes fear without any learning.)
3. After a few pairings, the tone alone makes the rat freeze, and its heart rate and stress hormones rise. (The tone is now a *conditioned* stimulus.)

Where is this learning stored? The tone and shock signals meet on the same neurons in the amygdala. Pairing them strengthens the synapses that carry the tone signal, using the same kind of synaptic strengthening you learned about in Chapter 9 (long-term potentiation). When parts of the amygdala are damaged or blocked in animals, fear conditioning fails.

This learning is ancient. Ply's relatives prove it. In 1983, Thomas Carew, Robert Hawkins, and Eric Kandel showed that *Aplysia* could be classically conditioned. A light touch to the siphon, paired with a strong shock to the tail, soon caused a much bigger defensive withdrawal on its own (Carew, Hawkins, and Kandel, 1983). Even a sea slug can learn that a harmless cue predicts trouble.

Extinction: unlearning fear

What happens if the tone keeps playing and the shock never comes again? The rat slowly stops freezing. This is called **extinction**. But extinction doesn't erase the old fear memory. It creates a *new* memory that says "this cue is safe now." The new safety memory depends heavily on the ventromedial prefrontal cortex (the lower middle part of the prefrontal cortex), which can quiet the amygdala's output. Because the old memory still exists, fear can come back after a long break, in a new place, or after a big stressor.

Extinction matters for medicine because some treatments for anxiety and PTSD work by building new safety learning, as you'll see in the Bedside case.

11.6 The Stress Response: Two Systems, Two Speeds

Back to Maya at 7:55 a.m. Her amygdala has flagged the test as a threat. What happens next?

A **stressor** is anything that challenges your body's balance, whether it's a real danger, an imagined one, or a demand like a deadline. The **stress response** is the set of changes your body makes to meet that challenge. The endocrinologist Hans Selye, who helped found the field of stress research in the 1930s, described stress as "the nonspecific response of the body to any demand made upon it." The key word is *any*: a test, a breakup, a soccer final, and a car crash all trigger the same basic machinery.

Think of a fire station. When an alarm sounds, a dispatcher *radios* the nearest truck, which pulls out within seconds. At the same time, the dispatcher *mails* a request for extra

supplies, which arrive later but last for days. Your stress response has the same two channels:

- **The fast channel (nerves):** the sympathetic nervous system, which acts in seconds.
- **The slow channel (hormones in the blood):** the HPA axis, which acts over minutes and can last for hours.

The fast channel: fight or flight

In Chapter 4 you learned that the autonomic nervous system has two branches. The parasympathetic branch handles "rest and digest." The sympathetic branch handles emergencies. In 1915, the American physiologist Walter Cannon described the body's emergency mode as preparing for "fighting or flight," and the name **fight or flight** stuck.

The **fight-or-flight response** is the fast, sympathetic part of the stress response. Signals travel from the hypothalamus down through the brainstem and spinal cord and out along sympathetic nerves. Within seconds, two things happen:

1. Sympathetic nerves release **norepinephrine** (noradrenaline) directly onto many organs, such as the heart, blood vessels, and liver.
2. Sympathetic nerves also reach the **adrenal medulla**, the inner core of each adrenal gland (the adrenal glands sit on top of the kidneys). The adrenal medulla releases **epinephrine**, also called **adrenaline**, into the blood.

Here is what that does, and why each change helps in a true emergency.

Body change	Why it helps in danger	What Maya noticed
Heart beats faster and harder; blood pressure rises	Delivers more oxygen and fuel to muscles	Pounding heart
Airways widen, breathing speeds up	More oxygen in	Quick, shallow breaths
Liver releases glucose into the blood	Instant fuel for muscles and brain	(Not felt directly)

Body change	Why it helps in danger	What Maya noticed
Blood shifts away from the gut and skin toward muscles	Muscles get priority; digestion can wait	"Butterflies," dry mouth
Pupils widen	Lets in more light	(Not felt directly)
Sweating increases	Cools the body during action	Damp palms

Animals and people also **freeze**, holding still to avoid being noticed.

11.7 The HPA Axis and Cortisol

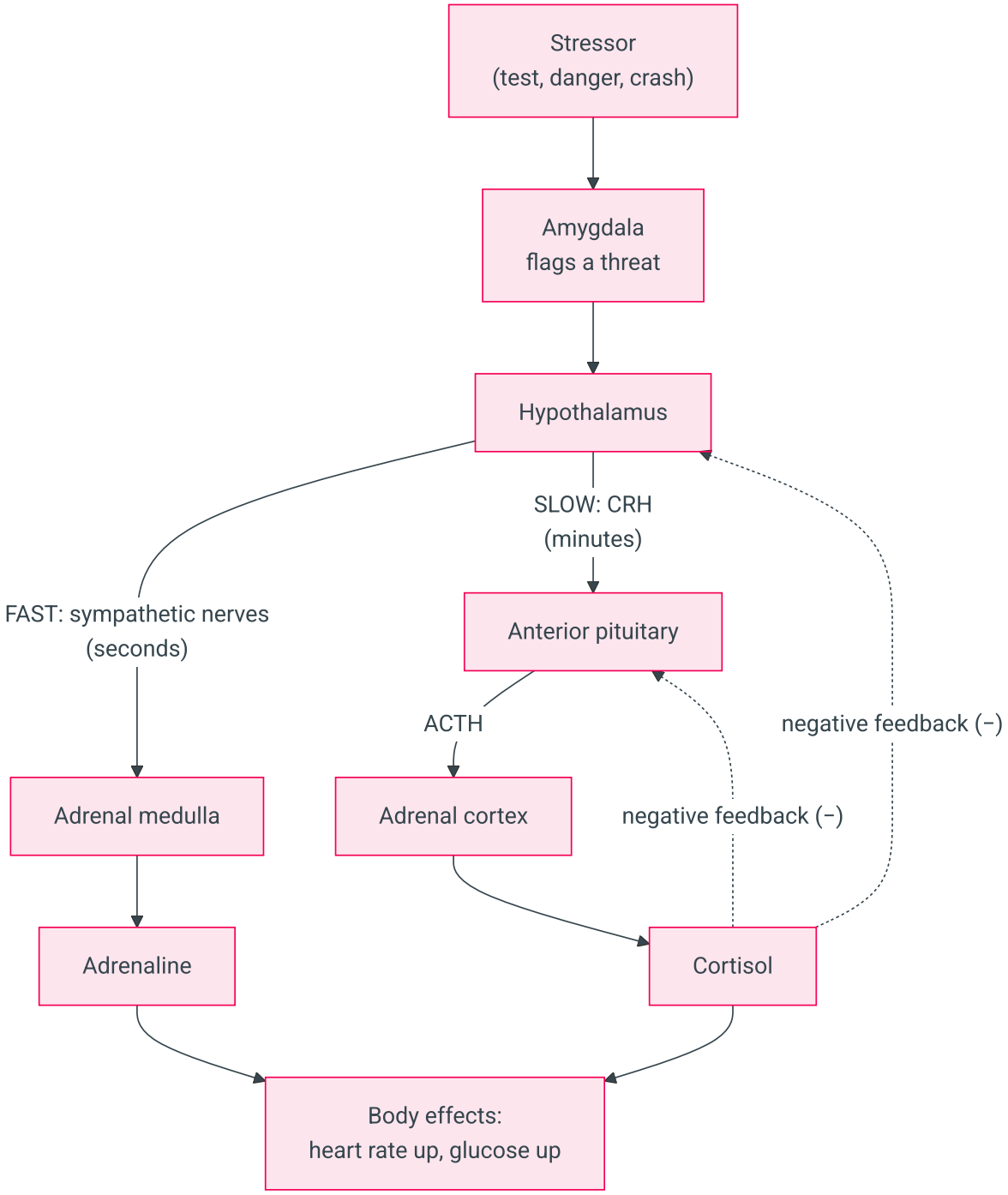
The slow channel is a relay race of three hormones passed between three organs: **h**ypothalamus, **p**ituitary, **a**drenal. Together they form the **HPA axis** (hypothalamic-pituitary-adrenal axis), the hormone chain that produces the stress hormone cortisol.

Here's how the relay runs:

1. **Hypothalamus → CRH.** When the amygdala signals a threat, neurons in the hypothalamus release **CRH** (corticotropin-releasing hormone) into a tiny network of blood vessels that leads straight to the pituitary gland just below.
2. **Pituitary → ACTH.** CRH tells the anterior (front) pituitary to release **ACTH** (adrenocorticotropic hormone) into the general bloodstream.
3. **Adrenal cortex → cortisol.** ACTH travels to the adrenal glands and tells the **adrenal cortex**, the outer layer of each gland, to make and release cortisol.

Notice that the same adrenal gland shows up in both channels. Its inner core (the medulla) answers the fast nerve signal with adrenaline. Its outer shell (the cortex) answers the slow hormone signal with cortisol.

The flowchart below puts both channels side by side.



What cortisol does

Cortisol is a steroid hormone, the body's main glucocorticoid ("glucose-related steroid"). During stress it:

- raises blood glucose, so the brain and muscles have fuel,

- helps keep blood pressure up,
- calms inflammation and changes how the immune system works,
- turns down "non-urgent" systems, such as reproduction,
- acts on the brain, including the hippocampus, amygdala, and prefrontal cortex.

Why is cortisol slow? Part of the reason is the relay itself: three hormones must be released in order. Another part is how cortisol works. As a steroid, it's a small, fat-based molecule. It slips through cell membranes and binds receptors *inside* the cell. Those receptors then travel to the nucleus and change which genes are turned on. Changing gene activity takes time, usually an hour or more, but it also means cortisol's effects last. These gene-driven effects can continue for hours, even after cortisol levels themselves have come back down (Joëls and Baram, 2009).

Cortisol isn't only about stress, though. It also follows a daily rhythm. Levels rise quickly after you wake up, peak within about 30 to 45 minutes, fall through the day, and reach their low point in the middle of the night. That's why doctors often measure cortisol in the morning.

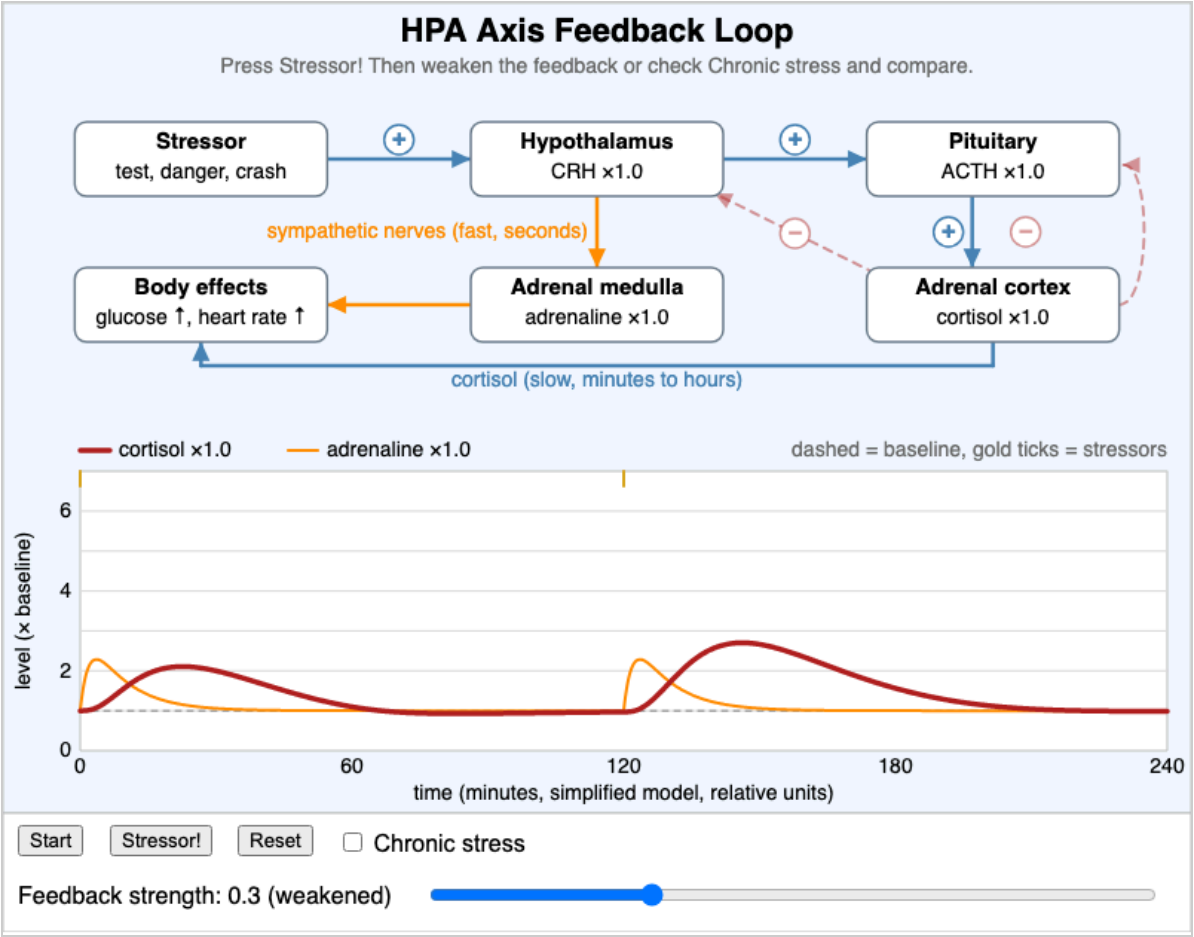
The brake: negative feedback

A system that only had an accelerator would be dangerous. The HPA axis also has a brake. When cortisol rises, it travels back to the brain and *slows its own production*. It tells the hypothalamus to release less CRH and the pituitary to release less ACTH. This is called **negative feedback**: a signal that turns down its own source.

A home thermostat is the classic example. When the room gets warm enough, the thermostat shuts off the furnace. The hippocampus helps with this brake too. It has many cortisol receptors, and when cortisol is high, it sends signals that help shut the hypothalamus down.

Because of this brake, a healthy stress response is **self-limiting**. Cortisol rises, does its job, and then returns to its resting level. Now try it yourself.

Diagram: HPA Axis Feedback Loop



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch11-hpa-axis/

Open the HPA Axis Feedback Loop fullscreen

MicroSim specification: HPA Axis Feedback Loop

Type: microsim **sim-id:** ch11-hpa-axis
Library: p5.js
Status: Implemented
Bloom Level: Analyze
Bloom Verb: differentiate
Learning Objective: The learner will differentiate a self-limiting acute stress response from a sustained cortisol elevation by predicting, then observing, how the cortisol curve changes when negative feedback is weakened or stressors repeat.

Canvas: width-responsive, 625 px tall (iframe 627 px).

Controls: Start/Pause (starts paused); Stressor! (one acute pulse); Reset; Chronic stress checkbox (a stressor every 30 simulated minutes); Feedback strength slider (0 to 1, step 0.1, default 1.0).

Diagram: Stressor → Hypothalamus (CRH) → Pituitary (ACTH) → Adrenal cortex (cortisol) → Body effects, with "+" links and dashed "−" feedback from cortisol to the hypothalamus and pituitary; a fast path runs through sympathetic nerves to the adrenal medulla (adrenaline).

Behavior: simplified model, relative units (1.0 = baseline). Adrenaline peaks within minutes; cortisol peaks about 20 to 30 minutes after a stressor and, with intact feedback, is near baseline in about an hour. Weaker feedback gives a higher, longer peak. Chronic stress keeps cortisol above baseline; chronic stress with feedback off reaches about 6 times baseline. The plot shows the last 240 simulated minutes.

Start with **Feedback strength** at 1.0 and press **Stressor!** Watch the orange adrenaline line jump almost at once, then fade. The red cortisol line rises more slowly, peaks later, and then glides back down to the dashed baseline. That delay is the HPA relay race at work, and the return to baseline is negative feedback doing its job.

Now predict before you test: what will happen if you drag the slider down to 0.3 and press **Stressor!** again? Then reset, check **Chronic stress**, and watch. With repeated stressors, cortisol never gets a chance to return to baseline, even with an intact brake. Finally, combine chronic stress with feedback set to 0. This is the model's picture of a stress system that can't switch off.

Read the two curves separately



When you describe the graph, talk about the two lines separately. Adrenaline answers "how fast?" and cortisol answers "how long?" Mixing them up is one of the most common mistakes on stress questions.

11.8 When Stress Doesn't Switch Off: Chronic Stress Effects

Is stress bad for you? It depends on how much, and for how long.

The good side of stress

Short bursts of stress are often helpful. Psychologists often describe this with an **inverted U** (the Yerkes-Dodson law): as stress rises from very low, performance improves, but past a sweet spot, more stress makes performance worse. Treat this as a rough rule of thumb, not a precise law. The original 1908 study tested how fast mice learned a black-or-white choice with electric shocks of different strengths, and later writers stretched it to cover stress and human performance in general. The helpful zone is called **eustress** ("good stress"), stress you feel you can handle. How you view a challenge matters. Seeing a pile of exams as a challenge you can meet, rather than a threat you can't, is linked to feeling the positive side of stress.

The costly side of stress

The stress response is built for short emergencies. Problems start when it is turned on too often, for too long, or when it fails to shut off. The scientist Bruce McEwen called this cumulative wear and tear **allostatic load**. (*Allostasis* means keeping the body stable by changing it, as the stress response does.) Ongoing stress can come from family conflict, money worries, bullying, or caring for a sick relative.

Chronic stress effects are the changes in the body and brain that can build up when stress lasts for weeks, months, or years. They include:

System	Possible effects of long-lasting stress
Sleep	Trouble falling or staying asleep
Heart and blood vessels	Higher blood pressure; added strain on the heart over time
Immune system	Short-term stress can boost some immune responses, but chronic stress tends to suppress them
Digestion	Stomachaches and other digestive problems
Mood	Higher risk of anxiety disorders and depression
Brain	Structural remodeling in the hippocampus, amygdala, and prefrontal cortex (best documented in animal studies)

The brain changes deserve a closer look, because they can create a vicious cycle. In animal studies, chronic stress shrinks the branching dendrites of some neurons in the hippocampus and prefrontal cortex. It also strongly suppresses the birth of new neurons in the hippocampus. Meanwhile, dendrites in part of the amygdala *expand*, and the amygdala can become more active. Put those together:

- The **hippocampus**, which normally helps shut off the HPA axis, works less well.
- The **prefrontal cortex**, which normally calms the amygdala, works less well.
- The **amygdala**, which turns the stress response on, gets louder.

The result can be a stress system that is quicker to turn on and slower to turn off. That's like turning the MicroSim's feedback slider down. Much of this evidence comes from rats and mice, and human brains are more complicated. The brain also stays plastic (able to change), so these patterns are not fixed destinies. Regular physical activity and social support are linked to a lower stress burden and better resilience.

Correlation is not causation



Most human stress research is correlational, which means it finds that two things go together. If people under chronic stress have more health problems, that's a strong clue, but other factors (like poverty or poor sleep) may also play a role. Animal experiments help scientists test cause and effect.

11.9 Emotion Regulation

Emotions are not pure reflexes. You can change them, and your brain has circuits for doing it.

Emotion regulation is the set of strategies people use to influence which emotions they have, how strong those emotions are, and how they express them. Some strategies change the situation (walking away from an argument) or your attention. One of the best studied is **cognitive reappraisal**: changing how you *think* about a situation to change how it *feels*.

Here's how Maya might use reappraisal. Before her next test, her heart starts pounding again. Instead of thinking "I'm panicking, I'm going to fail," she tells herself, "My heart is speeding up because my body is getting ready to focus. This is fuel." The situation hasn't changed, but her interpretation has, and that can change the feeling.

What happens in the brain during reappraisal? A 2014 analysis combined the results of 48 brain imaging studies. When people reappraised upsetting images, control regions in the prefrontal and parietal cortex became more active, and activity in the amygdala went down on both sides of the brain (Buhle and colleagues, 2014). In other words, the "thinking" brain can turn down the "alarm" brain.

Other strategies supported by health experts include:

- keeping a regular sleep routine,
- getting regular exercise and eating regular meals,
- trying relaxation methods, such as slow, deep breathing or mindfulness,
- writing in a journal,
- noticing and challenging unhelpful thoughts,

- leaning on supportive friends and family.

Slow breathing is interesting from a neuroscience point of view. It engages the parasympathetic "rest and digest" branch, partly through the vagus nerve, which helps counter the sympathetic surge.

Asking for help is a skill too



Regulating emotions doesn't mean handling everything alone. If stress or sadness keeps getting in the way of sleep, school, or friendships, talking to a trusted adult, school counselor, or doctor is a smart, strong move.

If you or someone you know is struggling, call or text **988** (the Suicide & Crisis Lifeline in the U.S.).

11.10 Post-Traumatic Stress Disorder

After something terrifying, such as a serious accident, an assault, a disaster, or combat, it is natural to have strong reactions like poor sleep, jumpiness, or replaying the event. Most people recover over time.

For some people, the reactions don't fade. **Post-traumatic stress disorder (PTSD)** is a mental health condition in which symptoms continue for more than a month after a traumatic event and are severe enough to interfere with daily life, such as relationships, school, or work. According to the National Institute of Mental Health (NIMH, 2023), about 6 of every 100 people will have PTSD at some point in their lives. A national survey of U.S. teens ages 13 to 18 (collected from 2001 to 2004) found that about 5% had had PTSD at some point, and it was more common in girls than boys.

NIMH groups PTSD symptoms into four types. To be diagnosed, an adult needs symptoms from all four groups for at least a month:

Symptom group	What it can look like
Re-experiencing	Flashbacks, nightmares, upsetting memories, a racing heart when reminded

Symptom group	What it can look like
Avoidance	Staying away from places, people, or thoughts linked to the event
Arousal and reactivity	Being easily startled, feeling on edge, trouble sleeping or concentrating, angry outbursts
Cognition and mood	Trouble remembering parts of the event, guilt or blame, ongoing fear or shame, losing interest in activities

Anyone can develop PTSD at any age, and it is not a sign of weakness. Risk factors include earlier trauma (especially in childhood), getting hurt during the event, and having little support afterward. Support from friends and family is linked to a lower chance of developing PTSD.

Researchers often describe PTSD as a problem of fear learning and recovery: a powerful fear memory forms during the trauma, and the brain struggles to learn that reminders are now safe. Imaging studies comparing groups of people have found stronger amygdala responses to emotional stress in people with PTSD.

At the Bedside: Nightmares After the Crash

Meet the patient

Jordan is a 22-year-old college student. Five months ago, Jordan was driving home at night when another car ran a red light and hit the passenger side. Jordan's friend in the passenger seat was badly hurt but survived. Jordan had only bruises. Since then, Jordan has had nightmares about headlights almost every week and sometimes "sees" the crash again while awake, heart pounding. Jordan now takes the bus or walks long distances to avoid driving, jumps at car horns, sleeps poorly, and has stopped going out with friends. Jordan feels guilty, thinking, "I should have seen that car coming." Grades are slipping, and Jordan's roommate encouraged a visit to the campus health center.

What the doctor checks: A careful history: what happened, when symptoms started, how long they've lasted, and how much they interfere with life. Because there was a crash, the doctor asks about head injury (a concussion can also cause sleep and concentration

problems) and does a brief neurological exam, which is normal. The doctor asks about mood, alcohol and drug use, and thoughts of self-harm, and uses a short PTSD screening questionnaire. A mental health clinician may confirm the diagnosis with a structured interview such as the Clinician-Administered PTSD Scale (CAPS-5).

Where is the problem? (localization): This is not a single damaged spot, like a stroke, but a *network* problem in this chapter's circuits. Re-experiencing and jumpiness fit an amygdala that responds too strongly to reminders like headlights and horns. Feeling unsafe in situations that are actually safe fits weak fear extinction, which depends on the prefrontal cortex's ability to calm the amygdala. Trouble placing the memory in the past and the right context fits the hippocampus, which stores context. The racing heart and sweating are the sympathetic fight-or-flight system firing on cue. Keep in mind that PTSD is diagnosed by a trained health professional from symptoms and history, not from a brain scan.

Diagnosis: Post-traumatic stress disorder (PTSD). Jordan has symptoms from all four groups (re-experiencing, avoidance, arousal and reactivity, and changes in thinking and mood), they've lasted much longer than a month, and they interfere with school and friendships.

Why it happens: During the crash, Jordan's amygdala and stress hormones were extremely active, which helped stamp in a powerful fear memory. Cues that were present (headlights, horns, being behind the wheel) became conditioned stimuli, just like the tone in a fear conditioning experiment. Normally, safe drives after a crash would build a new extinction memory: "driving is usually safe." But Jordan's avoidance means that new safety learning never gets a chance to happen, so the fear stays strong. PTSD is also not simply "too much cortisol." Some studies have even found lower-than-expected cortisol in people with PTSD, and scientists are still working out what that means.

Treatment today: PTSD is treatable. According to the U.S. Department of Veterans Affairs' National Center for PTSD and the 2023 VA/DoD clinical practice guideline (still the current version as of 2026), certain **trauma-focused talk therapies** work best, and they are recommended over medication as a first choice. These include:

- **Prolonged Exposure (PE):** gradually and safely approaching the memory and avoided situations (like driving), which builds new safety learning, much like extinction.
- **Cognitive Processing Therapy (CPT):** learning to notice and change stuck, unhelpful thoughts about the trauma, such as Jordan's self-blame.

- **Eye Movement Desensitization and Reprocessing (EMDR):** recalling the trauma while paying attention to a back-and-forth movement or sound.

Some medications also help. The FDA has approved two SSRI antidepressants for PTSD (sertraline and paroxetine), and the National Center for PTSD and the 2023 VA/DoD guideline list paroxetine, sertraline, and venlafaxine as the recommended medications. A doctor and patient choose treatment together. Support from friends and family also matters.

What's new in research: Traditional trauma-focused therapies often take about 12 weekly sessions, and many people drop out. In a 2018 randomized trial of 126 adults with PTSD, a five-session treatment called **Written Exposure Therapy (WET)**, in which patients write about the trauma during sessions, worked about as well as 12 sessions of Cognitive Processing Therapy, and far fewer people dropped out (Sloan, Marx, Lee, and Resick, *JAMA Psychiatry*, 2018). As of 2026, the National Center for PTSD lists WET among other supported therapies, and the 2023 VA/DoD guideline "suggests" it, a weaker endorsement than it gives PE, CPT, or EMDR, because there is less research behind it so far. Researchers are still studying who benefits most from shorter treatments.

Your turn: diagnose a variation

Sam, 17, was in a similar crash **two weeks ago**. Sam has had two nightmares, feels jumpy in cars, and is sleeping poorly. Does Sam have PTSD?

Answer: Not yet. Sam's reactions are common, natural responses to a frightening event, and PTSD requires symptoms lasting **more than a month** that interfere with daily life. Most people's symptoms fade over time, especially with support. A doctor would check in with Sam, watch how the symptoms change, check for injuries such as a concussion, and encourage Sam to keep up normal routines rather than avoid cars completely. If the symptoms last beyond a month and get in the way of life, Sam should be evaluated for PTSD.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Stress is always bad for you.
Reality: The stress response is a survival system. Short bursts of adrenaline and cortisol

supply fuel and can improve performance. Problems come from stress that is too intense, too frequent, or doesn't switch off.

Myth: The amygdala is the brain's "fear center" and does nothing else.
Reality: The amygdala flags anything emotionally important, including rewards, and strengthens emotional memories. Fear also involves the hypothalamus, brainstem, hippocampus, and prefrontal cortex.

Myth: Cortisol is a "bad" hormone that only shows up when you're stressed.
Reality: Cortisol follows a daily rhythm, peaking shortly after you wake up, and helps control blood glucose, blood pressure, and inflammation. Trouble comes when it stays high for long periods.

Myth: People with PTSD are weak, or they could get over it if they tried harder.
Reality: PTSD reflects real changes in how the brain's fear and stress circuits learn and recover. It can happen to anyone after trauma, and it's treatable with evidence-based therapies.

Myth: The best way to deal with a scary memory is to avoid every reminder of it.
Reality: Avoidance brings short-term relief, but it blocks the new safety learning (extinction) that helps fear fade. Gradual, supported exposure is a core part of several effective PTSD treatments.

Brain Bee Practice

1. Name the three structures of the HPA axis, in order, and the hormone each one releases.

Hypothalamus (CRH), anterior pituitary (ACTH), and adrenal cortex (cortisol).

2. What part of the adrenal gland releases adrenaline, and what controls it?

The adrenal medulla, the inner core of the adrenal gland. It is controlled directly by sympathetic nerves, which is why the adrenaline response is so fast.

3. What happened to patient S.M.'s amygdalae, and what did that reveal?

A rare genetic condition, Urbach-Wiethe disease, destroyed both of her amygdalae. She showed almost no fear of snakes, spiders, haunted houses, or scary films, which showed that the amygdala is needed for normal fear responses to outside threats.

4. In fear extinction, is the original fear memory erased? Explain.

No. Extinction creates a new "this is safe now" memory that competes with the old fear memory. It depends heavily on the ventromedial prefrontal cortex. Because the old memory remains, fear can return later.

5. How does cortisol limit its own release?

Through negative feedback. Cortisol acts on the hypothalamus and pituitary (with help from the hippocampus) to reduce the release of CRH and ACTH, so cortisol production slows down.

Exercises

Remember

1. Define *emotion* and list its three parts.
2. What does "HPA" stand for?

Answer

1. An emotion is a brief, organized response to something that matters to you. Its three parts are body changes, behavior, and feeling.
2. Hypothalamic-pituitary-adrenal.

Understand

1. Explain why the adrenaline response is faster than the cortisol response.
2. Explain, using the idea of a thermostat, what negative feedback does in the HPA axis.

Answer

1. Adrenaline release is triggered directly by sympathetic nerves within seconds. Cortisol requires a three-step hormone relay (CRH, then ACTH, then cortisol) through the bloodstream, and cortisol acts partly by changing gene activity, which takes longer.
2. Like a thermostat that shuts off the furnace when the room is warm, cortisol acts on the hypothalamus and pituitary to reduce CRH and ACTH. That lowers cortisol production and returns the system to baseline.

Apply

1. In the HPA Axis Feedback Loop MicroSim, set feedback to 1.0, check **Chronic stress**, and let the graph run for 240 minutes. Then do the same with feedback at 0. Record the approximate cortisol level at the end of each run, and explain the difference in terms of the hypothalamus and pituitary.
2. Maya's friend Leo feels his heart pounding before a soccer penalty kick and thinks, "I'm going to choke." Write two sentences Leo could say to himself using cognitive reappraisal, and explain which brain region this strategy is thought to engage.

Analyze

1. A rat is fear conditioned to a tone. Researchers then block activity in its ventromedial prefrontal cortex during extinction training. Predict what will happen to the rat's freezing over the next several days, and explain why.
2. Compare the amygdala, hippocampus, and prefrontal cortex in terms of how each one affects the stress response. Which one turns it up, and which ones help turn it down? How might chronic stress shift the balance?

Evaluate

1. A wellness app claims, "Cortisol is toxic. Our program will drive your cortisol to zero!" Evaluate this claim using what you learned about cortisol's normal functions and daily rhythm.
2. A news headline reads, "Stress shrinks your brain." Judge how accurate this is. In your answer, consider the kind of evidence (animal or human, correlational or experimental)

and whether the changes can reverse.

Create

1. Design a one-week "stress plan" for a student facing three exams. Include four strategies from this chapter and name the system or brain circuit each one targets.
2. Design an experiment testing whether extinction training reduces a conditioned fear response (a mild, harmless startle cue) in volunteers. Describe your groups, what you would measure (such as heart rate), and one ethical safeguard.

Key Takeaways

- An **emotion** is a whole-body response that combines body changes, behavior, and feeling, and is shaped by how you interpret a situation.
- The **limbic system** is a loose, debated label for a network of deep brain structures, including the amygdala, hippocampus, and hypothalamus, that works with the prefrontal cortex on emotion and stress.
- The **amygdala** tags what is emotionally important, triggers stress responses, and stores **fear conditioning**. Extinction is new safety learning, not erasing the old fear memory.
- The **stress response** has a fast nerve-based channel (**fight or flight**, adrenaline from the adrenal medulla) and a slow hormone channel (the **HPA axis**: CRH, then ACTH, then **cortisol** from the adrenal cortex).
- Cortisol raises blood glucose and blood pressure, calms inflammation, follows a daily rhythm, and shuts off its own production through **negative feedback**.
- Short-term stress can be helpful, but **chronic stress** can disrupt sleep, mood, immunity, and heart health and can remodel the hippocampus, amygdala, and prefrontal cortex.
- **Emotion regulation** strategies like reappraisal engage prefrontal control over the amygdala, and **PTSD** is a treatable condition, with trauma-focused talk therapies as the most effective treatments.

You traced a scare from start to finish!



You can now follow a stressor from the amygdala all the way to cortisol and back through the feedback loop. Next, in Chapter 12, we'll explore how the brain produces language, focuses attention, and makes decisions, and what happens when a stroke disrupts them.

Chapter 12: Language, Attention, and Decision-Making

Summary

Talking, paying attention, and making choices feel effortless, but each depends on networks of brain areas working together. This chapter covers the classic language areas, the modern network view of language, and the kinds of aphasia that strokes cause. It then explains why language usually leans on the left hemisphere, what split-brain patients revealed, how attention works and fails (as in neglect), and how executive function and a dopamine prediction-error signal guide decisions. It ends at the bedside with two stroke patients who lost language in very different ways.

Concepts Covered

1. Language Areas
2. Broca's Area
3. Wernicke's Area
4. Aphasia
5. Hemispheric Lateralization
6. Split-Brain Studies
7. Attention
8. Executive Function
9. Decision-Making
10. Reward Prediction Error
11. Neglect Syndrome

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters (especially dopamine)
- Chapter 4: A Tour of the Brain: Neuroanatomy (lobes, corpus callosum, prefrontal cortex)
- Chapter 9: Learning, Memory, and Neuroplasticity (working memory and plasticity)

Welcome to the talking, thinking, choosing brain



I'm a sea slug with about 20,000 neurons, and I can't say a single word. You, on the other hand, are reading this sentence, deciding whether it's worth your attention, and choosing whether to keep going. In this chapter you'll learn which brain networks make that possible, and how doctors use a patient's speech to find exactly where a stroke happened.

12.1 Two Ways to Lose Your Words

Maya, 16, volunteers on Saturday mornings at a rehabilitation hospital, partly to see real neurology while she studies for the Brain Bee. This week she meets two patients who both had a stroke in the past month.

The first, a retired bus driver, seems to understand almost everything Maya says. He laughs at her jokes and nods when she offers water. But when he tries to tell her about his grandson, the words come out one at a time, with long, painful pauses: "Grandson... soccer... goal. Good." He knows what he wants to say. He just can't get it out.

The second, a retired librarian, is the opposite. She talks easily, in long sentences with normal rhythm. But the sentences don't make sense: "Oh, the tarvels came by this morning, and I told them the window was very orange about it." When Maya asks her to point to the door, she smiles and points at the ceiling. She doesn't seem to notice anything is wrong.

How can one person understand every word but be unable to speak, while another speaks fluently but makes no sense? By the end of this chapter, you'll answer that the way a neurologist would: by listening carefully and working out *where* in the brain each problem lives.

12.2 Intuition First: Language Is a Team Sport

Before naming any brain areas, picture a busy restaurant.

- A **server** listens to each customer's order and figures out what they actually want, even if they mumble or use odd words.
- A **kitchen line** takes the order and builds the meal step by step, in the right sequence.
- A **pass-through window** connects the two, so orders can go back and forth quickly.
- A **manager** watches the whole room, decides which tables need attention first, and keeps the plan on track when something goes wrong.

Now break one piece. Damage the kitchen line, and the server still understands orders, but meals come out slowly with pieces missing. Damage the server, and the kitchen keeps cooking at full speed, but cooks the wrong things, and nobody notices. Block the window, and both sides work, but passing an order through exactly as given becomes hard.

That's surprisingly close to how language works in the brain. Maya's two patients have damage to different parts of the "restaurant." The manager stands for attention and executive function, which come later in the chapter.

12.3 The Language Areas

Language areas are the regions of the brain, mostly in the cerebral cortex, that work together to understand and produce language, whether spoken, written, or signed. The first two were found in the 1860s and 1870s by doctors who studied patients after brain injuries.

Broca's area: building speech

In 1861, the French surgeon Paul Broca described patients who had lost the ability to speak after an injury to the lower back part of the left frontal lobe. His most famous patient, Louis Victor Leborgne, was nicknamed "Tan" because "tan" was the only syllable he could produce. Yet Leborgne seemed to understand what people said to him.

Broca's area is the region in the inferior (lower) frontal gyrus of the language-dominant hemisphere, usually the left, that helps plan and produce speech. It lies close to the motor areas that control the mouth and face, and it's usually described as two small regions called

Brodmann areas 44 and 45. In our restaurant, it's part of the kitchen line, assembling words and grammar into an ordered sequence the body can say out loud.

Wernicke's area: making sense of speech

In 1874, the German neurologist Carl Wernicke described a different kind of patient. These people spoke fluently but made little sense, and they had great trouble understanding others. Their damage was in the back part of the left temporal lobe, near the areas that process sound (you met the auditory cortex in Chapter 6).

Wernicke's area is the region in the posterior (back) part of the superior temporal gyrus of the language-dominant hemisphere, usually the left, that helps link the sounds of words to their meanings. It's the server in our restaurant. Even today, researchers don't fully agree on its exact borders. Some include nearby parts of the parietal lobe.

The bridge between them

A bundle of axons called the **arcuate fasciculus** arches from the back of the temporal lobe toward the frontal lobe. For more than a century it was taught as the "pass-through window" between Wernicke's and Broca's areas, and damage to it was blamed for trouble repeating words. Modern research has made this picture more complicated.

This table summarizes the three classic parts.

Structure	Where it is	Classic job	Restaurant role
Broca's area	Left inferior frontal gyrus (frontal lobe)	Planning and producing speech and grammar	Kitchen line
Wernicke's area	Left posterior superior temporal gyrus (temporal lobe)	Linking word sounds to meanings	Server
Arcuate fasciculus	White-matter bundle arching between them	Connecting sound to speech output	Pass-through window

Both areas get their blood from branches of the **middle cerebral artery**. A clot in one branch can damage Broca's area, while a clot in another can damage Wernicke's area. That's why strokes can take away language in such different ways.

The modern view: language is a network

The Broca-and-Wernicke story is a great starting map, but three findings changed how scientists think about language.

First, in 2007, a team led by Nina Dronkers used high-resolution MRI to re-examine the preserved brains of Broca's two original patients. Their damage reached much deeper than the surface area Broca described, so today's "Broca's area" doesn't perfectly match the damage in Broca's own patients (Dronkers et al., 2007).

Second, in 2007, researchers Gregory Hickok and David Poeppel proposed a **dual-stream model** of speech. In this model, a *ventral* (lower) stream running through the temporal lobe handles understanding what speech means. A *dorsal* (upper) stream connects sounds to the frontal areas that control speaking. The ventral stream works in both hemispheres, while the dorsal stream depends strongly on the left. A 2018 study of stroke patients found that problems with the motor side of producing speech mostly followed dorsal-stream damage, while problems understanding speech were more linked to the ventral stream. Tasks like naming objects or repeating sentences needed both. The same study found that patients with damage in different places could show similar problems, because each task relies on a wide network (Fridriksson et al., 2018).

Third, language isn't only about sound. In a 1996 study of 23 deaf sign-language users with damage to one side of the brain, left-hemisphere damage disrupted signing much more than right-hemisphere damage, the same pattern seen in speakers (Hickok, Bellugi, and Klima, 1996). The left-hemisphere network seems to handle language itself, not just hearing and moving the mouth.

Areas are hubs, not boxes



I like to think of Broca's and Wernicke's areas as busy hub stations in a subway map, not as sealed boxes. Damage to a hub disrupts a lot of traffic, but the trains also depend on the tracks (white matter) and on stations that never made it into the old textbooks.

12.4 Aphasia: When Language Breaks

Aphasia is a language disorder caused by damage to the parts of the brain that handle language. It can affect speaking, understanding, reading, and writing, and in deaf signers it can affect sign language too. It's not a hearing problem, a muscle problem, or a loss of intelligence. People with aphasia usually know what they want to say and still think clearly. Their access to language is what's damaged.

Aphasia is common. The National Institute on Deafness and Other Communication Disorders (NIDCD) reported in 2025 that about 2 million people in the United States live with aphasia, citing the National Aphasia Association. Stroke is the leading cause, and about one in three stroke survivors has aphasia. Head injuries, brain tumors, brain surgery, and brain infections can also cause it.

The vocabulary of a language exam

Before comparing the types of aphasia, you need five terms that doctors and speech-language pathologists use when they listen to a patient.

- **Fluency:** whether speech flows in normal-length phrases with normal rhythm. *Nonfluent* speech is slow, effortful, and broken into short pieces.
- **Telegraphic speech:** speech that leaves out small grammar words like "the," "is," and "of," like an old-fashioned telegram ("Walk dog. Park. Rain.").
- **Paraphasia:** a word error. A *phonemic* paraphasia swaps sounds ("wishdasher" for "dishwasher"). A *semantic* paraphasia swaps in a related word ("table" for "chair").
- **Neologism:** a made-up word that the listener can't recognize ("the tarvels came by").
- **Comprehension and repetition:** how well the person understands what others say, and how well they can repeat a sentence back word for word.

Comparing the major types

Now we can sort the major types of aphasia using three simple questions: Is speech fluent? Is comprehension good? Can the person repeat?

Type	Fluent?	Comprehension	Repetition	Typical speech	Classic damage site
Broca's (nonfluent)	No	Relatively good	Poor	Short, effortful, telegraphic; person is aware and often frustrated	Left frontal lobe, around Broca's area
Wernicke's (fluent)	Yes	Poor	Poor	Long, smooth sentences with paraphasias and neologisms; person often unaware of errors	Left posterior temporal lobe, around Wernicke's area
Conduction	Yes	Relatively good	Very poor	Fluent with sound errors; person notices and tries again and again to fix them	Classically the arcuate fasciculus region (now debated)
Global	No	Poor	Poor	Very little speech at all	Large areas of the left language network
Anomic	Yes	Good	Good	Normal sentences,	Can follow damage in

Type	Fluent?	Comprehension	Repetition	Typical speech	Classic damage site
				but frequent trouble finding the right word	many parts of the network

A few details help these types make sense:

- **Broca's aphasia** often comes with weakness on the *right* side of the body. The left frontal lobe also contains motor areas, and each hemisphere controls the opposite side of the body (Chapter 4).
- In **Wernicke's aphasia**, the person can't understand language well, including their own speech, so they often don't realize their sentences make no sense.
- **Conduction aphasia** was once explained simply as a broken pass-through window. Newer studies suggest damage to nearby cortex may matter as much as the fiber bundle itself.
- The table is a simplified map, not a complete list. It leaves out rarer types, such as the **transcortical** aphasias, in which repetition is surprisingly spared, and NIDCD also lists mixed and unspecified forms. Many real patients don't fit neatly into one box.
- **Primary progressive aphasia** isn't caused by a sudden injury. It's an early sign of a slowly worsening brain disease, such as a form of dementia, so the language problems grow over time. (Chapter 13 covers dementia and other neurodegenerative diseases.)

Three questions sort most aphasias



When you meet an aphasia case in the Brain Bee, ask the same three questions every time: Is the speech fluent? Does the person understand? Can they repeat? Those three answers narrow the list fast, and they usually point toward the front or back of the language network. Real patients can be messier than the textbook types.

Try it: sort the speech samples

Now you be the clinician. The MicroSim below shows ten short speech samples written for this book, each with a one-line clue about comprehension or repetition. Decide which category each fits.

Diagram: Aphasia Sorter



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch12-aphasia-sorter/

Open the Aphasia Sorter fullscreen

MicroSim specification: Aphasia Sorter

Type: microsim **sim-id:** ch12-aphasia-sorter
Library: p5.js
Status: implemented
Bloom Level: Analyze
Bloom Verb: classify
Learning Objective: The learner will classify short speech samples as Broca's aphasia, Wernicke's aphasia, conduction aphasia, or normal speech, using fluency, comprehension, and repetition, scoring at least 8 of 10.

Canvas: width-responsive; 560 px drawing area plus 85 px control area (iframe 647 px).

Controls: four category buttons (Broca's, Wernicke's, Conduction, Normal), Next, and Restart.

Behavior: 10 original items (3 Broca's, 3 Wernicke's, 2 conduction, 2 normal), shuffled at start and on Restart. One answer per item; feedback says "Correct" or "Not quite," names the right category, and explains the clue. A running score is shown, and a summary after item 10 reports whether the learner reached 8 of 10.

As you play, notice *which clue* settles each item. Fluent but meaningless speech with poor comprehension points to Wernicke's aphasia. Slow, telegraphic speech with good comprehension points to Broca's. Fluent speech with good comprehension, but repetition that falls apart, points to conduction aphasia.

Watch out for the "normal" samples. Healthy people say "um" and pause all the time. What matters is the overall pattern of fluency, meaning, comprehension, and repetition.

12.5 Hemispheric Lateralization: Why Language Leans Left

Your two cerebral hemispheres look almost like mirror images, but they don't do exactly the same jobs. **Hemispheric lateralization** is the tendency for some brain functions to depend more on one hemisphere than the other. Language is the classic example.

Think of handwriting: most people could write with either hand, but one hand is much better at it. Similarly, both hemispheres contribute to language, but in most people the left does the heavy lifting for producing words and grammar.

How often is the left hemisphere dominant? In a 2000 study, German researchers tested 326 healthy people with functional transcranial Doppler ultrasound, which tracks blood flow

to each side of the brain while a person silently thinks of words (Knecht et al., 2000). The results depended on handedness:

Group	Share with *right*-hemisphere language dominance
Strong right-handers	4%
Ambidextrous people	15%
Strong left-handers	27%

So left-hemisphere language is the rule for most people, but not everyone. Most left-handers are still left-dominant for language, yet a sizable minority are not. That's why a doctor can't assume which side handles language just by looking at which hand a person writes with.

Lateralization is also a matter of degree. Remember the dual-stream model: the ventral stream for understanding speech works in both hemispheres, while the dorsal stream for producing speech leans strongly left. The right hemisphere still contributes to understanding. It just isn't usually the main driver of speech output.

There are no left-brained people



Lateralization is about which hemisphere leads on a specific task, not about personality. Calling someone "left-brained" (logical) or "right-brained" (creative) is a pop-psychology myth, because almost every real task, including math and art, uses networks in both hemispheres.

12.6 Split-Brain Studies: Two Hemispheres, One Person

The two hemispheres normally share information constantly through the **corpus callosum**, the thick band of axons you met in Chapter 4. It's the main highway between the hemispheres. What happens if that highway is cut?

For a small number of people with severe epilepsy that medicines can't control, surgeons perform a **corpus callosotomy** as a last resort, cutting the corpus callosum so seizures spread less easily between hemispheres.

Split-brain studies are experiments on people whose corpus callosum has been cut, designed to test what each hemisphere can do on its own. Beginning in the early 1960s, Roger Sperry, Joseph Bogen, and Michael Gazzaniga developed clever ways to send information to just one hemisphere.

The trick uses the visual pathway from Chapter 5. If a person stares at a central dot, a picture flashed briefly to the *left* of the dot reaches only the *right* hemisphere, and one flashed to the *right* reaches only the *left* hemisphere. Here's what split-brain patients did.

What the patient experienced	Which hemisphere got the information	Could they say what it was?	Could they show what it was?
Picture flashed in the right visual field	Left	Yes, they named it	Yes
Picture flashed in the left visual field	Right	No, they often said they saw nothing	Yes, the left hand could pick out the matching object
Object felt with the left hand, out of sight	Right	No	Yes, by choosing it again by touch

In these patients, the left hemisphere controlled speech. The right hemisphere clearly *knew* what it had seen, because it guided the left hand to the right object. It just couldn't put the answer into words, and with the corpus callosum cut, it couldn't pass the answer to the left hemisphere.

Roger Sperry received half of the 1981 Nobel Prize in Physiology or Medicine "for his discoveries concerning the functional specialization of the cerebral hemispheres." David Hubel and Torsten Wiesel shared the other half for their work on the visual system, which you read about in Chapter 5.

Later studies found that some information can still pass between the hemispheres by other routes, so the "two separate minds" picture is more complicated than early textbooks suggested. Split-brain patients are also a small, special group whose brains had lived with severe epilepsy before surgery.

12.7 Attention: The Brain's Spotlight

Back at the hospital, Maya notices something about herself. When she's focused on what a patient is saying, she completely tunes out the beeping monitors and the TV in the hallway. But when someone across the room says her name, she hears it instantly.

Attention is the brain's ability to select some information for deeper processing while ignoring the rest. A useful analogy is a spotlight on a dark stage. Whatever falls inside the beam gets processed in detail. Things outside it are processed much less, or not at all.

The brain needs a spotlight because your senses send far more information than you could ever think about at once. Attention is how the brain chooses.

The spotlight's limits can be startling. In a 1999 experiment by Daniel Simons and Christopher Chabris, people counted basketball passes in a video while a person in a gorilla suit walked through the scene. About half of all the viewers never noticed the gorilla. This is called **inattentional blindness**: failing to see something in plain view because attention is busy elsewhere.

Where attention lives

Attention isn't in one spot. Brain-imaging and stroke studies point to networks that link the frontal and parietal lobes:

- A **dorsal (upper) attention network** lets you aim your spotlight on purpose, like when you look for a friend in a crowd.
- A **ventral (lower) attention network**, which leans toward the right hemisphere, grabs your spotlight when something unexpected and important happens, like hearing your name.

The myth of multitasking

When people switch back and forth between tasks, researchers measure a **switch cost**: right after a switch, people respond more slowly and usually make more errors. Preparing ahead shrinks the cost but doesn't erase it. For demanding tasks, "multitasking" is really rapid switching. When Maya texts while studying for the Brain Bee, she pays that price over and over.

12.8 Neglect Syndrome: Losing Half of the World

Neglect syndrome (also called hemispatial neglect) is a condition, usually after a stroke, in which a person fails to notice or respond to things on one side of space, even though their eyes and the visual pathway still work. It's most common and most severe after damage to the *right* hemisphere, especially the lower part of the parietal lobe, and it affects the *left* side of space.

A person with left neglect might:

- eat only the food on the right half of the plate, then say they're still hungry
- shave or put makeup on only the right side of the face
- bump into door frames on the left
- ignore someone standing on their left and talking to them
- insist nothing is wrong, because they're unaware of the problem (a symptom called **anosognosia**)

Neglect is not blindness. In **hemianopia**, damage to the visual pathway cuts off vision on one side (Chapter 5). In neglect, visual information reaches the brain normally, but the attention system doesn't "light it up." A person with hemianopia usually knows they can't see one side; a person with neglect often doesn't realize half the world is missing.

Why the right hemisphere? One explanation is that the right hemisphere attends to both sides of space, while the left mostly handles the right side. Damage on the left leaves the right to cover both sides, but damage on the right leaves nothing fully covering the left. The right-leaning ventral attention network also plays a role.

Doctors check for neglect with simple pencil-and-paper tests:

Test	What the patient does	What neglect looks like
Line bisection	Marks the middle of a horizontal line	Mark lands well to the right of center
Cancellation	Crosses out every small line or letter on a page	Targets on the left side are missed
Clock drawing	Draws a clock face with all the numbers	Numbers crowded onto the right half

Therapies such as prism adaptation (wearing prism glasses that shift the visual world during practice tasks) have been studied, and some patients improve. Researchers still consider the evidence limited, and many people recover some attention to the neglected side naturally in the weeks and months after a stroke.

12.9 Executive Function: The Brain's Manager

Remember the restaurant manager from Section 12.2? The manager doesn't cook or take orders, but sets goals, decides what matters most, stops unwise moves, and changes the plan when things go wrong.

Executive function is the set of mental skills that let you control your own thinking and behavior to reach a goal. Psychologist Adele Diamond describes three core executive functions:

1. **Inhibition**: stopping an automatic or tempting response (not blurting out an answer, or not checking your phone during practice), and filtering out distractions.
2. **Working memory**: holding information in mind and working with it, like keeping a phone number in your head while you dial (see Chapter 9).
3. **Cognitive flexibility**: switching between rules or points of view, like changing your soccer strategy when the other team changes theirs.

These core skills combine into planning, problem-solving, and reasoning. They depend heavily on the **prefrontal cortex** at the front of the frontal lobe, working with the anterior cingulate cortex, which helps detect errors, and with deeper structures.

Psychologists measure executive function with tasks like these:

- **Stroop task:** name the ink color of the word "RED" printed in blue ink, which requires inhibiting the urge to read the word.
- **Wisconsin Card Sorting Test:** sort cards by a hidden rule that secretly changes. People with frontal-lobe damage often keep using the old rule, a problem called **perseveration**.
- **Tower of London:** move colored balls into a goal pattern in as few moves as possible, which requires planning.

You met Phineas Gage in Chapter 4. After an iron rod shot through his skull in 1848, damaging mainly his left frontal lobe, people who knew him reported big changes in his self-control and planning. His case was an early hint that the frontal lobes support executive function.

According to the National Institute of Mental Health, the brain finishes maturing in the mid-to-late 20s, and the prefrontal cortex is one of the last areas to mature (Chapter 8). Executive function suffers from stress, lack of sleep, loneliness, and lack of exercise, and it can improve with practice.

12.10 Decision-Making and Reward Prediction Error

Some decisions are small, like which snack to grab. Some are big, like whether to go to a party the night before a test. **Decision-making** is the process of choosing between options by weighing their expected costs and benefits. It draws on everything in this chapter so far: attention picks which options you notice, executive function holds them in mind and keeps impulses in check, and value signals in the brain help you compare them.

The ventromedial prefrontal cortex: feeling the future

The **ventromedial prefrontal cortex** (the lower, middle part of the prefrontal cortex, just above the eyes) seems especially important for decisions about reward and risk. University of Iowa researchers tested people with damage here using a card game. Some decks paid big rewards right away but led to bigger losses over time; others paid less but came out ahead.

Healthy volunteers tended to shift away from the "big win, bigger loss" decks. People with ventromedial prefrontal damage kept choosing them, even as their losses grew. The

researchers described it as a kind of "myopia for the future": these patients were guided mainly by what happened right now, not by what would happen later.

Reward prediction error: learning from surprise

How does the brain learn which choices pay off? A big part of the answer is a signal carried by dopamine neurons in the midbrain (you met dopamine in Chapter 3).

Intuition first. Maya's coach usually brings oranges to practice. One day the coach brings pizza instead, and Maya is delighted. The next week, pizza again: she's happy, but less surprised. By the fifth week, pizza is just what happens at practice. Then one week the coach brings nothing, and she's disappointed, even though she's no worse off than a month ago.

What drives her feelings isn't the reward itself. It's the gap between what she expected and what she got. Neuroscientists call that gap a **reward prediction error**: the difference between the reward you actually receive and the reward you predicted.

$$\text{reward prediction error} = \text{reward received} - \text{reward predicted}$$

Wolfram Schultz recorded dopamine neurons in monkeys and found that they fire in a pattern matching this equation. A 1997 paper by Schultz, Peter Dayan, and Read Montague linked these recordings to mathematical theories of learning.

Situation	Prediction error	What dopamine neurons do	What the brain learns
Better than expected (surprise pizza)	Positive	Fire a burst above their normal rate	"Do that again"; raise the prediction
Exactly as expected (pizza for the fifth week)	Zero	Stay at their normal baseline rate	Nothing new to learn
Worse than expected (no snack at all)	Negative	Dip below their normal rate	"That didn't pay off"; lower the prediction

The equation is simpler than it looks



If equations make you nervous, just remember "surprise = got minus expected." Positive surprise, dopamine bursts; no surprise, nothing changes; negative surprise, dopamine dips. That's the whole idea.

Something else changes with learning. Once a cue reliably predicts the reward (say, seeing the coach's car pull up with pizza boxes), the dopamine burst moves from the reward itself to the earliest cue that predicts it. The reward has become expected, but the cue is now the surprise. This pattern was first recorded in monkeys and has since been found in rodents and humans (Schultz, 2016).

This signal works like a teacher. After each prediction error, the brain updates its expectations a little, so future predictions improve. Reward prediction errors help explain why a reward stops feeling exciting once it's routine, and why drugs of addiction are so powerful: they hijack and amplify the dopamine signal (Chapter 15).

At the Bedside: Two Strokes, Two Kinds of Silence

Meet the patients

Patient 1: Mr. Alvarez, 66, a retired bus driver, suddenly couldn't speak more than a word or two at a time during breakfast. His wife noticed his right hand was clumsy and the right side of his face drooped. She called 911 right away. In the emergency department he nods correctly to yes-or-no questions and follows commands like "close your eyes," but when he tries to answer questions he says things like "Wife... car... hospital," and he looks frustrated.

Patient 2: Mrs. Chen, 71, a retired librarian, was brought in by her son after she started "talking nonsense" during a phone call. She speaks quickly and confidently, with normal rhythm, but uses odd and made-up words. She has no weakness. When the doctor asks her to point to the window, she smiles and touches her watch. She doesn't seem worried at all.

What the doctor checks: A stroke team works fast, because the sooner blood flow returns, the more brain tissue can be saved. The neurologist checks strength, face, vision, and sensation, then does a quick bedside language exam built on the three questions from Section 12.4: listening to spontaneous speech (fluency), giving spoken commands

(comprehension), and asking the patient to repeat a sentence (repetition). An emergency CT or MRI scan shows whether a blocked artery or bleeding caused the stroke, and where. A speech-language pathologist later does a detailed evaluation.

Where is the problem? (localization): Mr. Alvarez has nonfluent, telegraphic speech, relatively good comprehension, poor repetition, awareness of his errors, and *right*-sided face and arm weakness. Nonfluent speech plus right-sided weakness points to the *left frontal lobe*, around Broca's area and the nearby motor cortex. That area is supplied by the upper branch of the left middle cerebral artery. Mrs. Chen has fluent speech full of paraphasias and neologisms, poor comprehension, poor repetition, no weakness, and little awareness of the problem. That pattern points to the *left posterior temporal lobe*, around Wernicke's area, supplied by the lower branch of the left middle cerebral artery. It's far from the motor cortex, which explains why she isn't weak.

Diagnosis: Mr. Alvarez: ischemic stroke in the left frontal lobe causing Broca's (nonfluent) aphasia with right-sided weakness. Mrs. Chen: ischemic stroke in the left posterior temporal lobe causing Wernicke's (fluent) aphasia.

Why it happens: Language depends on a left-leaning network. The frontal part, including Broca's area and the dorsal stream, turns plans into ordered speech. Damage there leaves understanding mostly intact but makes speaking slow and broken. The temporal part, including Wernicke's area and the ventral stream, links sounds to meanings. Damage there lets speech keep flowing but strips away meaning, both in what the person hears and in what they say, so they often don't notice their own errors.

Treatment today: For an ischemic stroke, emergency care aims to restore blood flow as fast as possible. For eligible patients, that can mean a clot-dissolving medicine given within a few hours of symptom onset, or a procedure called thrombectomy, in which a doctor threads a thin tube through an artery to pull out a clot in a large brain vessel. Doctors also work to prevent another stroke. For the aphasia itself, the main treatment is **speech-language therapy**. A 2016 Cochrane review of 57 randomized trials found that, in the trials comparing therapy with no therapy, therapy improved everyday communication. Many people improve a lot in the first few months, and gains can continue for years. Families learn to help by using short sentences, giving the person time to talk, and welcoming gestures, drawing, and pointing.

What's new in research: A 2017 randomized trial in *The Lancet* (FCET2EC) tested intensive therapy long after a stroke. It enrolled 158 people aged 70 or younger who had had aphasia

for at least six months, at 19 centers in Germany. Those who received at least three weeks of intensive speech-language therapy, at least 10 hours per week, improved their everyday verbal communication, while those whose therapy was delayed did not. The results suggest that language can still improve with enough practice long after the first months of recovery (Breitenstein et al., 2017).

Your turn: diagnose a variation

Mr. Okafor, 70, had a stroke yesterday. He speaks fluently, understands questions, and repeats sentences perfectly. But at lunch he eats only the food on the right side of his tray. When the nurse stands on his left and says hello, he doesn't turn. When asked to draw a clock, he crowds all twelve numbers into the right half. His left arm is weak, but he insists he's "fine" and doesn't need help. Where is the stroke, and what is this syndrome?

Answer: This is **neglect syndrome** (left hemispatial neglect), most likely from a stroke in the *right* hemisphere, especially the right parietal lobe. His language is normal because the left-hemisphere language network is undamaged. The left arm weakness also fits right-hemisphere damage, since each hemisphere controls the opposite side of the body. His belief that he's fine is anosognosia, which is common in neglect. It's not blindness: the visual information reaches his brain, but his attention system doesn't light up the left side of space.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Multitasking makes you more productive.
Reality: For demanding tasks, the brain mostly switches rapidly between them. Each switch costs time and accuracy, so finishing one task before starting another is often faster and more accurate.

Myth: Language lives only in the left hemisphere, for everyone.
Reality: Most people are left-dominant for language, but in one study about 4% of strong right-handers and 27% of strong left-handers were right-dominant. The right hemisphere also helps with understanding speech.

Myth: Some people are "left-brained" (logical) and others are "right-brained" (creative).
Reality: Lateralization describes which hemisphere leads on particular tasks, not

personality types. Real thinking, whether math, music, or art, draws on networks in both hemispheres.

Myth: People with aphasia have lost their intelligence.
Reality: Aphasia damages access to language, not intelligence. Many people with aphasia know exactly what they want to say. Treating them as less intelligent is both wrong and hurtful.

Myth: A person with neglect is just blind on one side.
Reality: In neglect, visual information still reaches the brain; the problem is attention. That's why a person with neglect often doesn't realize anything is missing.

Brain Bee Practice

1. A patient speaks in short, effortful phrases like 'Walk... dog... park,' understands simple questions, and has a weak right arm. What type of aphasia is this, and which lobe is most likely damaged?

This is Broca's (nonfluent) aphasia, most likely from damage to the left frontal lobe around Broca's area. The right arm weakness fits, because the left frontal lobe also contains motor areas that control the right side of the body.

2. What is the key difference between Wernicke's aphasia and conduction aphasia?

Both are fluent, but comprehension is poor in Wernicke's aphasia and relatively good in conduction aphasia. Conduction aphasia stands out for very poor repetition, with sound errors the person tries to correct.

3. In a split-brain patient, a picture of a key is flashed to the left visual field. What can the patient do, and why?

The patient usually can't name the key, but the left hand can pick it out from a group of objects. Only the right hemisphere saw it; it can guide the left hand but can't speak, and the cut corpus callosum keeps it from telling the left hemisphere.

4. Damage to which hemisphere most often causes neglect syndrome, and which side of space is ignored?

Damage to the right hemisphere, especially the parietal lobe, most often causes neglect. The person ignores the left side of space.

5. Define reward prediction error and describe what dopamine neurons do when a reward is better than expected.

A reward prediction error is the difference between the reward received and the reward predicted. When a reward is better than expected (a positive prediction error), midbrain dopamine neurons fire a burst above their baseline rate.

Exercises

Remember

1. Name the two classic language areas, the lobe each is in, and the scientist each is named after.
2. List the three core executive functions described by Adele Diamond.

Answer

1. Broca's area is in the frontal lobe (inferior frontal gyrus), named after Paul Broca. Wernicke's area is in the temporal lobe (posterior superior temporal gyrus), named after Carl Wernicke.
2. Inhibition (including self-control and filtering distractions), working memory, and cognitive flexibility.

Understand

1. Explain why a person with Wernicke's aphasia is often unaware that their speech makes no sense.
2. Explain why neglect syndrome is not the same thing as being blind on one side.

Answer

1. Wernicke's area helps link word sounds to meanings, so damage there impairs understanding of all language, including the person's own speech. They can't monitor their words, so they don't notice the errors.
2. In neglect, visual information still reaches the brain; the problem is that the attention system doesn't process the left side of space. In hemianopia, the visual pathway itself is damaged, so the information never arrives.

Apply

1. A patient speaks fluently and understands conversation well, but when asked to repeat "The red car is in the garage," says "The rel... the red car is in the... the gararge." Which type of aphasia fits best? Explain using the three questions from Section 12.4.
2. Maya expects a 90 on her Brain Bee practice test and gets a 98. The next week she expects a 98 and gets a 98. Describe the reward prediction error and the expected dopamine response for each week.

Analyze

1. Compare Mr. Alvarez's and Mrs. Chen's strokes in the Bedside case. Explain how the location of each stroke accounts for both the type of aphasia and the presence or absence of weakness.
2. The Knecht study found right-hemisphere language dominance in 4% of strong right-handers and 27% of strong left-handers. What can, and can't, you conclude from these numbers about a single left-handed patient about to have brain surgery?

Evaluate

1. An app claims it can "train your right brain to unlock creativity." Evaluate this claim using what you learned about lateralization.
2. A school allows phones on desks during study hall "because students can multitask." Judge this policy using evidence about switch costs, and suggest a better rule.

Create

1. Write three original speech samples (Broca's, Wernicke's, and normal) about the same topic, each with a one-line clue, that a classmate could sort correctly.
2. Design an experiment testing whether students make more homework errors when switching between homework and texting than when finishing the homework first. Name your groups, your measurements, and how you'll keep the comparison fair.

Key Takeaways

- Language depends on a mostly left-hemisphere **network**. Broca's area (left frontal lobe) helps produce speech, Wernicke's area (left temporal lobe) helps link sounds to meanings, and white-matter pathways connect them.
- **Aphasia** is a language disorder, most often from stroke, affecting about one in three stroke survivors, without removing intelligence. Fluency, comprehension, and repetition separate the main types.
- **Hemispheric lateralization** means some functions lean on one hemisphere. Most people are left-dominant for language, but a minority, more often left-handers, are right-dominant.
- **Split-brain studies** by Sperry, Bogen, and Gazzaniga showed that each hemisphere has special abilities. Sperry shared the 1981 Nobel Prize for this work.
- **Attention** is a limited spotlight run by frontal-parietal networks; multitasking really means costly switching. Damage to right-hemisphere attention networks causes **neglect syndrome**, in which the left side of space is ignored.
- **Executive function** (inhibition, working memory, cognitive flexibility) depends on the prefrontal cortex, which keeps maturing into the mid-to-late 20s.
- **Decision-making** uses value signals in the prefrontal cortex, and learning from outcomes depends on the dopamine **reward prediction error**: reward received minus reward predicted.

You can read a stroke from a sentence!



You can now listen to a patient's speech and point to where the damage is, which is real neurologist thinking. Next, in Chapter 13, we'll follow what happens to the brain as it ages, and why some people's neurons begin to fail in diseases like Alzheimer's and ALS.

Chapter 13: The Aging Brain and Neurodegeneration

Summary

Every brain changes with age, but dementia is not a normal part of aging. This chapter separates normal brain aging from **neurodegeneration**, the slow death of neurons that causes Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease. You will see how misfolded proteins clump into plaques and tangles, how biomarkers reveal disease years before symptoms, and what new medicines (anti-amyloid antibodies, antisense drugs, and gene therapy) can and cannot do.

Concepts Covered

1. Normal Brain Aging
2. Neurodegeneration
3. Protein Misfolding
4. Dementia
5. Alzheimer's Disease
6. Amyloid Plaque
7. Tau Tangle
8. Anti-Amyloid Antibody
9. Amyotrophic Lateral Sclerosis
10. Huntington's Disease
11. Antisense Oligonucleotide
12. Gene Therapy
13. Biomarker
14. Cognitive Reserve

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters
- Chapter 4: A Tour of the Brain
- Chapter 7: Movement
- Chapter 9: Learning, Memory, and Neuroplasticity

Brains that last a lifetime



I'm a sea slug, so I don't live long enough to worry about getting old. You will, and so will everyone you love. This chapter is about telling ordinary forgetfulness apart from disease, and about some of the newest medicines in neurology. By the end, you'll be able to read a headline about an "Alzheimer's breakthrough" and judge what it really means.

13.1 Is Forgetting My Name Normal?

Maya is home from soccer practice, studying Brain Bee flashcards at the kitchen table, when her grandfather comes to visit. He hugs her and says, "Good to see you, Priya." Priya is Maya's mom. He laughs it off. But later he asks Maya the same question about her team three times in one hour, and her mom mentions that he recently got lost driving to a grocery store he has used for twenty years.

Is this just what happens when people get old, or is something wrong with his brain? Families ask doctors this every day, and the answer can change a person's care and safety. To answer it, start with what a *healthy* aging brain looks like.

13.2 Normal Brain Aging

Think of your brain as a library that has been open for 80 years. The books are still there, but the librarians walk slower and finding a book takes longer. Almost everything still works. It

just takes more time.

That's **normal brain aging**: the gradual, expected changes in brain structure and thinking that happen as healthy people grow older, without disease. According to the National Institute on Aging (NIA), as people age:

- certain brain regions shrink, including some that are important for learning and complex thinking
- communication between neurons in some regions becomes less efficient
- blood flow in the brain may decrease
- inflammation may increase

These changes show up as slower thinking. An older adult may take longer to find a word or recall a name, find multitasking harder, or have small drops in attention. The good news is that older adults often have *larger* vocabularies than younger adults, and given enough time, they usually learn new tasks just as well.

The healthy aging brain shrinks somewhat, but it does not lose neurons in large numbers. That makes it very different from the diseases in the rest of this chapter.

Normal forgetting versus dementia

To tell normal aging from disease, doctors ask whether the memory or thinking problem **interferes with everyday life**. Forgetting a word now and then is normal. Getting lost on a familiar route, as Maya's grandfather did, is a warning sign. The table below sums up comparisons the NIA uses with families.

Normal aging	Possible sign of dementia
Making a bad decision once in a while	Making poor judgments much of the time
Missing one monthly payment	Having trouble managing bills at all
Forgetting which day it is, then remembering later	Losing track of the date or the season
Sometimes forgetting which word to use	Trouble following or having a conversation

Normal aging	Possible sign of dementia
Losing things from time to time	Misplacing things often and being unable to find them

Memory problems can also come from treatable causes, such as depression, thyroid problems, low vitamin B12, medication side effects, or poor sleep. That's one reason to see a doctor instead of assuming it's "just age."

13.3 When Neurons Die: Neurodegeneration and Protein Misfolding

Neurodegeneration is the progressive loss of the structure and function of neurons, ending in neuron death. "Progressive" means it keeps getting worse over time. Most neurons are never replaced. A dead skin cell is swapped for a new one, but a neuron that dies in your hippocampus or spinal cord is usually gone for good.

An origami problem

A protein is like a strip of paper folded into an exact origami shape. The shape is everything: a crane can "fly," but a crumpled ball of the same paper can't do anything. Cells fold every protein carefully into its working shape.

Protein misfolding is when a protein folds into the wrong shape. Misfolded proteins tend to be "sticky." They cling to each other and form clumps that cells struggle to clear, and over time the clumps damage the cell. Many very different brain diseases share this problem, as the table below shows. Each one has its own protein, its own target neurons, and its own symptoms.

Disease	Misfolded or toxic protein	Main neurons or region hit	First big symptoms
Alzheimer's disease	Beta-amyloid (outside cells) and tau (inside cells)	Hippocampus and entorhinal cortex first, then cortex	Memory loss

Disease	Misfolded or toxic protein	Main neurons or region hit	First big symptoms
Parkinson's disease (Chapter 7)	Alpha-synuclein (Lewy bodies)	Dopamine neurons of the substantia nigra	Slow movement, tremor
ALS (SOD1 type)	Misfolded SOD1	Motor neurons	Weakness, twitching
Huntington's disease	Abnormally long huntingtin protein, cut into toxic fragments	Striatum (part of the basal ganglia)	Uncontrolled movements, mood changes

Same mistake, different neighborhoods



The big idea of this chapter: many neurodegenerative diseases are "the wrong protein, piling up in the wrong place." Where the pile builds up decides whether a person first loses memory, movement, or muscle strength.

13.4 Dementia and Alzheimer's Disease

Dementia is not one disease. It is a general term for a loss of thinking, remembering, and reasoning severe enough to interfere with a person's daily life and activities (NIA). Some people with dementia also have trouble controlling emotions, or their personality changes. Dementia becomes more common with age: the NIA estimates that about one-third of people age 85 or older may have some form of it. But dementia is **not a normal part of aging**, and many people live into their 90s and beyond without any signs of it.

Dementia has many causes, including vascular dementia (from damaged blood vessels; see Chapter 14), Lewy body dementia, and frontotemporal dementia. The most common cause in older adults is **Alzheimer's disease**: a progressive brain disease that slowly destroys memory and thinking skills and, eventually, the ability to carry out simple tasks. According to the NIA fact sheet, estimates vary, but more than 6 million Americans, most of them 65

or older, may have Alzheimer's disease. The Alzheimer's Association's 2026 Facts and Figures report estimates that 7.4 million Americans age 65 and older are living with Alzheimer's in 2026, about 1 in 9 people in that age group.

A doctor, a microscope, and 1906

The disease is named after Dr. Alois Alzheimer. In 1906, he studied the brain of a woman who had died of an unusual mental illness that included memory loss, language problems, and unpredictable behavior. Under his microscope he saw abnormal clumps between cells and tangled bundles of fibers inside cells. Today we call them **amyloid plaques** and **tau tangles**, and more than a century later they are still the defining features of the disease.

Where Alzheimer's starts

Alzheimer's disease usually damages the **entorhinal cortex** and **hippocampus** first (NIA). You met the hippocampus in Chapter 9 as the structure that turns new experiences into lasting memories. That explains the classic first symptom: trouble forming *new* memories. A person may recall their wedding day but not that they already asked you a question. Later, the damage spreads to areas of the cortex used for language, reasoning, and social behavior. In the final stage, the brain has shrunk a great deal and the person depends on others for all care.

Many people pass through an in-between stage first. In **mild cognitive impairment (MCI)**, a person has more memory or thinking problems than is normal for their age but can still manage daily life. People with MCI have a higher risk of developing Alzheimer's disease, but not all of them do, and some even return to normal thinking.

13.5 Plaques and Tangles: Inside the Alzheimer's Brain

Amyloid plaques: trash piling up outside the cell

Brain cells make a larger protein called amyloid precursor protein. When it is cut up, one of the small pieces is **beta-amyloid**. One form, beta-amyloid 42, is thought to be especially toxic (NIA). In Alzheimer's disease, too much beta-amyloid clumps together *between* neurons. An **amyloid plaque** is one of these dense clumps of misfolded beta-amyloid outside cells. Plaques sit among synapses and disrupt how neurons function.

Tau tangles: a collapsed railroad inside the cell

Every neuron has a transport system. Long tubes called **microtubules** work like railroad tracks, carrying nutrients and other cargo from the cell body down the axon (the long fiber you met in Chapter 1). A protein called **tau** acts like the railroad ties that hold the tracks steady.

In Alzheimer's disease, chemical changes make tau let go of the microtubules. The loose tau sticks to other tau, forming threads that join into **neurofibrillary tangles**. A **tau tangle** is one of these twisted clumps of abnormal tau *inside* a neuron. With the tracks falling apart, cargo can't reach the synapses, and communication between neurons breaks down. Research summarized by the NIA suggests that when beta-amyloid builds up to a kind of tipping point, abnormal tau spreads rapidly through the brain.

The rest of the damage

The NIA describes other processes that add to the damage:

- **Synapse loss.** Losing synapses (Chapter 3) is one of the earliest signs linked to cognitive decline.
- **Glia that stop helping.** Microglia normally clear waste, including beta-amyloid. In Alzheimer's disease they may fail at this and instead release chemicals that cause long-lasting inflammation.
- **Blood vessel problems.** High blood pressure, diabetes, and small strokes can reduce blood flow and add to the damage.
- **Brain shrinkage.** As neurons die, regions shrink, a process called brain atrophy.

Genes and Alzheimer's disease

Most Alzheimer's disease appears after age 65 and doesn't follow a simple inheritance pattern. A small number of cases begin much earlier, between a person's 30s and mid-60s. According to MedlinePlus Genetics, some early-onset cases are caused by variants in the *APP*, *PSEN1*, or *PSEN2* genes. These variants lead to extra beta-amyloid, and they are passed down in an **autosomal dominant** pattern, meaning one altered copy of the gene is enough to cause the disease.

For the common late-onset form, the best-studied gene is *APOE*. A version called **APOE e4** raises a person's risk, and two copies raise it more. But APOE e4 is a risk factor, not a sentence. Some people with Alzheimer's disease don't carry it, and many carriers never develop the disease.

13.6 Biomarkers: Seeing Disease Before Symptoms

A **biomarker** is something measured in the body that signals a normal process, a disease process, or the body's response to a treatment. Blood sugar, for example, is a biomarker for diabetes. Brain biomarkers let doctors "see" inside the brain without opening the skull.

For a long time, the only sure way to diagnose Alzheimer's disease was to look at brain tissue after death. Now doctors can detect its biomarkers in living people:

- **Amyloid PET scan.** A small amount of a radioactive tracer that sticks to amyloid is injected into a vein. A PET scanner then shows where amyloid has built up.
- **Cerebrospinal fluid (CSF) tests.** A sample of the fluid around the brain and spinal cord, taken with a needle in the lower back (a lumbar puncture), can show amyloid and tau levels.
- **Blood tests.** On May 16, 2025, the FDA cleared the first blood test used to help diagnose Alzheimer's disease. It measures the ratio of two proteins in blood (a form of tau called pTau217, and beta-amyloid 42) to help detect amyloid plaques. It is cleared for adults 55 and older who already have symptoms, and results must be read along with other clinical information. More blood tests have been cleared since then, including Roche's Elecsys pTau181 in October 2025 (NeurologyLive), and Roche's Elecsys pTau217 and C2N's PrecivityAD2 in August 2026 (Psychiatric News). As of 2026, all of them are cleared to help evaluate people who already have memory or thinking symptoms, not to screen healthy people.

Why timing is everything

Biomarker research showed that **the brain changes start long before the symptoms**. The NIA says changes may begin a decade or more before symptoms appear.

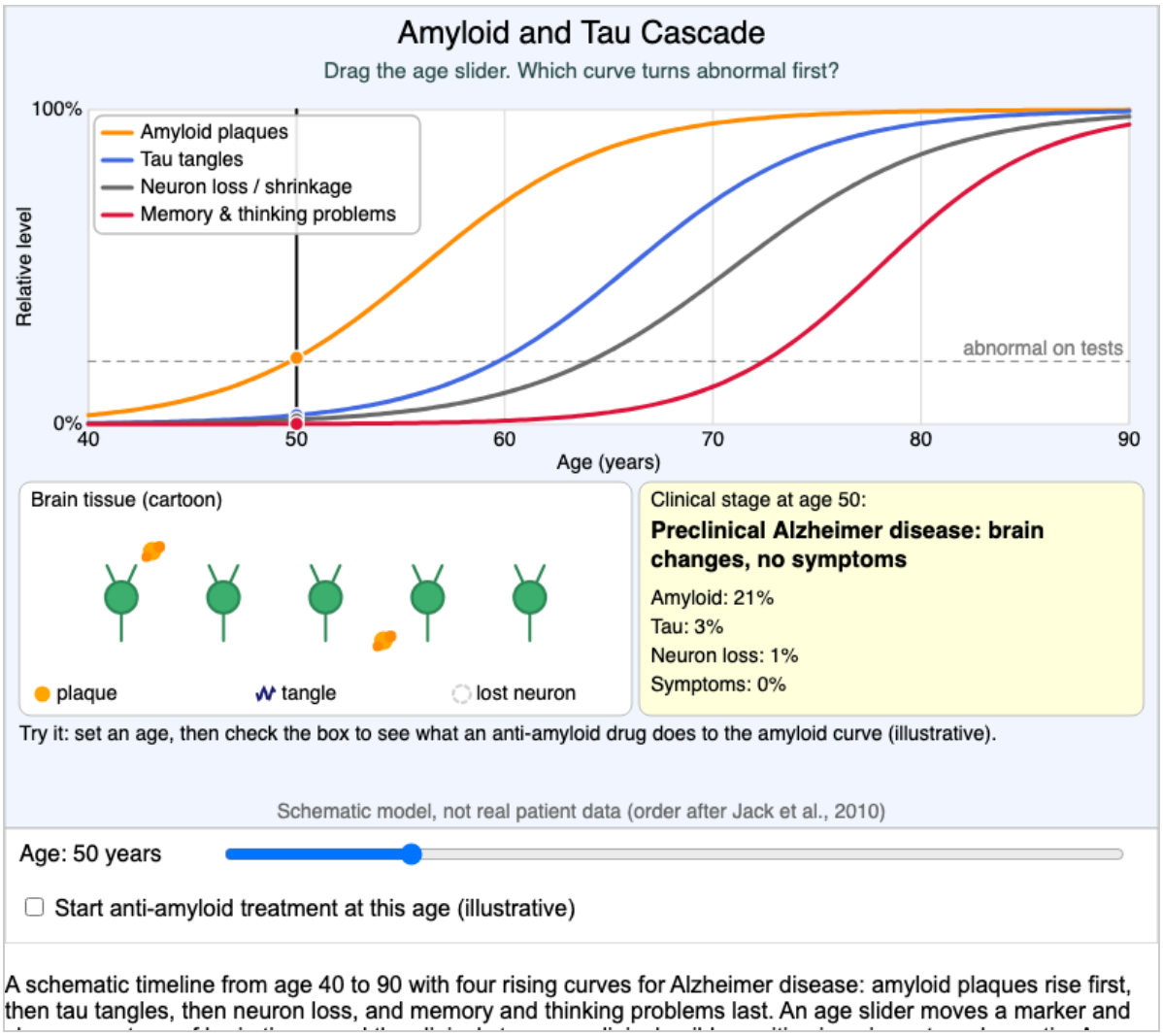
In 2010, Clifford Jack and colleagues proposed a widely cited hypothetical model of Alzheimer's biomarkers. In their model, amyloid biomarkers turn abnormal first, while the

person still thinks normally. After a delay that differs from person to person, markers of neuron injury (such as tau and brain shrinkage on MRI) turn abnormal. Symptoms come last. The authors estimated that in people who later develop dementia, amyloid buildup might begin as much as two decades before symptoms. They also noted that roughly 20 to 40 percent of older adults with normal thinking already have significant amyloid in their brains.

This adds a new stage of disease. **Preclinical Alzheimer's disease** is the stage when biomarkers show Alzheimer's brain changes but the person has no symptoms yet. The stages with symptoms are mild cognitive impairment and dementia.

Experts still disagree about what to call this stage. In June 2024, an Alzheimer's Association workgroup published revised criteria that define Alzheimer's disease *biologically*: it begins when Alzheimer's brain changes appear, even before symptoms. The same workgroup said biomarker testing in the clinic is meant for people who have symptoms, not for healthy people. Later in 2024, the International Working Group, another expert panel, disagreed. It proposed calling most people with abnormal amyloid but normal thinking "asymptomatic at risk of Alzheimer's disease," because many of them never develop symptoms. The MicroSim below lets you watch these stages unfold.

Diagram: Amyloid and Tau Cascade



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch13-amyloid-tau-cascade/

Open the Amyloid and Tau Cascade fullscreen

MicroSim specification: Amyloid and Tau Cascade

Type: microsim **sim-id:** ch13-amyloid-tau-cascade
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: explain
Learning Objective: The learner will explain why Alzheimer's brain changes are best detected and treated early, using the order in which amyloid, tau, neuron loss, and symptoms rise.

Canvas: width-responsive; drawing area 570 px plus control area 80 px (iframe 652 px).

Content: Four schematic curves in relative units (0 to 100% of each curve's maximum) from age 40 to 90: amyloid plaques, tau tangles, neuron loss/shrinkage, and memory and thinking problems. A dashed line marks "abnormal on tests" at 20%. A tissue cartoon shows plaques between five neurons, tangles inside them, and faded lost neurons. A stage box shows the clinical stage and the four levels.

Controls: Age slider (min 40, max 90, step 1, default 50 years). Checkbox "Start anti-amyloid treatment at this age (illustrative)."

Rules: Curves are logistic with midpoints 56 (amyloid), 66 (tau), 71 (neuron loss), 78 (symptoms). Stage: symptoms < 15% and amyloid < 20% = no measurable changes; symptoms < 15% and amyloid >= 20% = preclinical; 15% <= symptoms < 50% = mild cognitive impairment; 50% <= symptoms < 75% = dementia (mild stage); symptoms >= 75% = dementia (moderate to severe). When treatment is on, amyloid after the start age decays with a 1.5-year time constant; other curves do not change. A message explains the evidence for treatment at the starting stage.

Provenance: Curve order from Jack et al. (2010); curve shapes and ages are illustrative. The sim is labeled "Schematic model, not real patient data."

Chapter Anchors: In the model, amyloid crosses the abnormal line at about age 50, tau at about 60, neuron loss at about 65, and symptoms at about 73. Mild cognitive impairment begins at about age 72 and dementia at about age 78.

What to try. Start at age 50. Amyloid is already crossing the "abnormal on tests" line, yet there are no symptoms. Drag the slider slowly right and watch the order: amyloid crosses the line at about age 50, tau at about 60, neuron loss at about 65, and symptoms at about 73. In this schematic model, mild cognitive impairment begins around age 72 and dementia around age 78. That's roughly 20 years of silent disease.

Next, set the age to 74 and check the treatment box. Amyloid drops, but tau has already spread and many neurons are gone, and removing amyloid doesn't bring them back. Then uncheck the box, move to age 86, start treatment again, and read the message. The ages are illustrative, and real people vary a lot. The lesson is the order of events, and why doctors want to find Alzheimer's disease early.

13.7 Anti-Amyloid Antibodies: Treatments That Target the Disease

For decades, Alzheimer's medicines could only treat symptoms. Cholinesterase inhibitors (such as donepezil) slow the breakdown of acetylcholine, a neurotransmitter important for memory, and memantine acts on glutamate signaling (NIA). They can help for a while but don't change what's happening to the neurons.

How an antibody can clean up plaques

Your immune system makes **antibodies**, Y-shaped proteins that latch onto a specific target and mark it for removal. An **anti-amyloid antibody** is a lab-made antibody, given by infusion into a vein (and for lecanemab, now also by injection under the skin), that binds to beta-amyloid and helps the brain's immune cells clear plaques away. It's like putting bright "pick me up" tags on trash so the cleanup crew (the microglia) finds it.

Two anti-amyloid antibodies are FDA-approved and available as of October 2026. (An earlier one, aducanumab, received accelerated approval in 2021, but its maker discontinued it in 2024.)

Drug	FDA status	Key trial	Who it's approved for
Lecanemab (Leqembi)	Accelerated approval January 6, 2023; converted to traditional (full) approval July 6, 2023. An under-the-skin autoinjector (Leqembi Iqlik) was approved for maintenance doses in August 2025 and for starting treatment in July 2026	Clarity AD, 1,795 participants, 18 months	Mild cognitive impairment or mild dementia due to Alzheimer's, with confirmed amyloid
Donanemab (Kisunla)	FDA approval July 2, 2024	TRAILBLAZER-ALZ 2, 1,736 participants, 76 weeks	Mild cognitive impairment or mild dementia due to Alzheimer's, with confirmed amyloid

Sources: FDA announcements for lecanemab (with the current Leqembi prescribing information for the under-the-skin form) and donanemab; the NIA describes both as fully approved.

What the trials showed: real, but modest

Both drugs removed a lot of amyloid and slowed decline on memory and daily-living rating scales compared with placebo. But "slowed" is the key word.

In the lecanemab trial, people's scores on an 18-point dementia rating scale (where higher means more impaired) got worse by 1.21 points over 18 months on the drug and 1.66 points on placebo. That's a difference of 0.45 points, or about 27 percent less worsening than on placebo. The researchers called it "moderately less decline." The donanemab trial showed a slowing of similar size. People on these drugs still got worse, just more slowly. Neither drug stops the disease, reverses it, or brings back lost memories.

That fits the MicroSim. By the time symptoms appear, tau has spread and many neurons have died. Removing amyloid at that point is like clearing debris after a fire: it may slow further damage, but it doesn't rebuild the rooms.

The main risk: ARIA

The most important side effect has a long name: **amyloid-related imaging abnormalities (ARIA)**. ARIA shows up on MRI scans as temporary swelling in the brain, sometimes with small spots of bleeding. Usually it causes no symptoms. When it does, they can include headache, confusion, dizziness, vision changes, or nausea. Rarely, it is serious or life-threatening (FDA). Both drugs carry a **boxed warning**, the FDA's strongest label warning, about ARIA.

In the trials, ARIA with swelling showed up on scans in 12.6 percent of people taking lecanemab and 24.0 percent of people taking donanemab. (The two trials enrolled somewhat different groups, so these numbers are not a head-to-head comparison.) People with two copies of APOE e4 have a higher risk of ARIA, so the FDA labels say to test for APOE e4 before starting treatment. Patients get regular MRI scans to watch for ARIA. In July 2025, the FDA approved a more gradual starting schedule for donanemab after a trial called TRAILBLAZER-ALZ 6 found that it lowered ARIA with swelling at 52 weeks from 24.2 percent to 15.6 percent (NeurologyLive). The boxed warning remains.

Approved does not mean cure



Watch out for two opposite mistakes. "There's nothing doctors can do for Alzheimer's" is wrong, but so is "the new drugs cure it." The honest version: anti-amyloid antibodies modestly slow decline in early-stage disease, they carry real risks, and they aren't for everyone.

Can treatment start even earlier?

If amyloid builds up for years before symptoms, would treatment in the preclinical stage work better? Large clinical trials are testing this in people who have amyloid but no symptoms, such as the AHEAD 3-45 study of lecanemab and the TRAILBLAZER-ALZ 3 study of donanemab. As of October 2026, neither has reported its main results. Until those results are in, treating people without symptoms remains experimental.

13.8 Cognitive Reserve: Why Some Brains Hold Up Better

Two people can have similar plaques and tangles, yet one has dementia and the other thinks clearly. How?

Picture two cities hit by the same storm, which knocks out some roads. A city with one road to the hospital is in trouble. A city with many side streets reroutes traffic, and most people never notice. **Cognitive reserve** is the brain's ability to cope with damage by using its networks more efficiently or by switching to backup routes, so that thinking stays normal longer.

Neuropsychologist Yaakov Stern separates two related kinds of reserve in his 2012 review:

- **Brain reserve:** differences in the brain's physical structure, such as size or number of neurons and synapses, that let it tolerate more damage.
- **Cognitive reserve:** differences in *how* the brain uses its networks, built up through life experiences such as education, challenging work, and mentally stimulating activities.

Reserve doesn't stop plaques from forming. It changes how much damage the brain can absorb before symptoms show. Jack and colleagues suggested this may help explain why the delay between amyloid and symptoms varies so much.

Can you build reserve? In one NIA-funded study of almost 3,000 older adults, people who practiced four or five healthy behaviors (physical activity, not smoking, not drinking heavily, a Mediterranean-style diet, and mentally stimulating activities) had a 60 percent lower risk of Alzheimer's disease than people who practiced one or none (NIA). This was an observational study, so it can't prove the habits *caused* the lower risk. The NIA also notes that high blood pressure in middle age is linked to higher dementia risk, so protecting your heart may help protect your brain.

Reserve starts now



Cognitive reserve is built over a whole lifetime, and school counts. Learning hard things, staying active, sleeping well (Chapter 10), and keeping up friendships are investments your 80-year-old self will thank you for.

13.9 Amyotrophic Lateral Sclerosis (ALS)

Now we move from memory to movement. In Chapter 7, you learned that movement commands pass through two kinds of motor neurons. **Upper motor neurons** in the motor cortex send signals down to **lower motor neurons** in the brainstem and spinal cord, which connect to muscles.

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that kills motor neurons, the nerve cells that control voluntary movement and breathing. In the classic form, both upper and lower motor neurons die. ALS is also called Lou Gehrig's disease, after a famous baseball player who had it.

What ALS looks like

According to the NINDS, early symptoms include muscle twitches, cramps, stiffness, weakness in an arm, leg, or the neck, and slurred speech or trouble chewing and swallowing. Symptoms most often begin between ages 55 and 75. Over time, people lose the ability to walk, use their hands, speak, swallow, and breathe without help. Most people with ALS die of respiratory failure, usually within three to five years after symptoms begin, although about 1 in 10 people live 10 years or more.

Most people with ALS can still reason and remember, so they are aware of what's happening. About 20 percent, however, also develop frontotemporal dementia, which affects personality, behavior, and language (MedlinePlus Genetics).

The two kinds of motor neuron loss produce different signs, just as in Chapter 7 (NINDS):

Damaged neurons	Signs a doctor finds
Lower motor neurons	Weakness, muscle wasting (atrophy), twitches (fasciculations)
Upper motor neurons	Stiffness (spasticity), overactive reflexes

Finding *both* sets of signs in the same patient is a big clue pointing toward ALS.

Genes and ALS

NINDS reports that nearly all ALS is **sporadic**, meaning it appears without a clear family history. About 10 percent of cases are **familial**, running in families. Mutations in a gene

called *C9orf72* cause about 25 to 40 percent of familial cases, and mutations in the *SOD1* gene cause another 12 to 20 percent. The SOD1 gene normally makes an enzyme called superoxide dismutase, which breaks down harmful, charged oxygen molecules that cells make as by-products (MedlinePlus Genetics). Mutant SOD1 protein can misfold and clump inside motor neurons, and lowering it became one of the first goals of a genetic medicine for ALS.

Treatment

There is no cure. NINDS lists **riluzole**, which may reduce glutamate-related damage and extended survival by a few months in trials, and **edaravone**, which slowed functional decline in some people. Care teams also help with breathing, nutrition, speech devices, and mobility. For people with SOD1 mutations, a drug now targets the cause of their disease (Section 13.11).

13.10 Huntington's Disease

Huntington's disease is an inherited neurodegenerative disease that causes uncontrolled movements, emotional and psychiatric problems, and a decline in thinking ability. The adult form usually begins in a person's 30s or 40s (MedlinePlus Genetics).

A genetic stutter

Huntington's disease is caused by a change in the *HTT* gene, which makes a protein called **huntingtin**. Inside the gene is a short DNA "word" of three letters, **C-A-G**, repeated many times in a row like a stutter: CAG CAG CAG CAG...

The number of repeats is what matters. MedlinePlus Genetics gives these ranges.

Number of CAG repeats	What it means
10 to 35	Does not cause Huntington's disease (but 27 to 35 repeats can lengthen into the disease range when passed to a child)
36 to 39	May or may not develop Huntington's disease

Number of CAG repeats	What it means
40 or more	Almost always develop Huntington's disease

Too many repeats produce an abnormally long huntingtin protein. It is cut into toxic fragments that clump inside neurons, another example of protein misfolding. The neurons hit hardest are in the **striatum**, part of the basal ganglia (Chapter 7), which act like a brake on unwanted movements. When striatum neurons die, the brake fails, and the person develops **chorea**: jerky, dance-like movements they can't control. Depression, irritability, and trouble with planning and judgment are also common and can be among the earliest signs.

Inheritance: a coin flip

Huntington's disease is **autosomal dominant**: one altered copy of the gene is enough to cause it. So each child of a parent with Huntington's disease has a 50 percent chance of inheriting the gene variant (NINDS). The repeat can also grow longer as it passes from one generation to the next. Longer repeats tend to cause earlier symptoms, a pattern called **anticipation**.

A hard question, worth thinking about



This part is heavy. A simple blood test can show whether a healthy 20-year-old carries the Huntington's gene, yet no treatment can stop the disease. Whether to take that test is a very personal choice, which is why genetic counselors help families decide.

Treatment

NINDS states that no treatment can stop or reverse Huntington's disease. Medicines such as tetrabenazine, deutetrabenazine, and valbenazine can reduce chorea, and other medicines help with depression and other psychiatric symptoms. Researchers are testing genetic approaches to lower the harmful huntingtin protein, including experimental gene therapies. In September 2026, the company developing one of them (AMT-130) asked the

FDA to review it for accelerated approval, but as of October 2026 no gene therapy for Huntington's disease is FDA-approved.

13.11 Fixing the Message: Antisense Drugs and Gene Therapy

Alzheimer's antibodies attack a protein *after* it is made. Some newer medicines act earlier, on the gene's message. Recall the central idea from biology class.

DNA (gene) → mRNA (a working copy of the instructions) → protein

Think of DNA as a cookbook locked in the library (the nucleus). To cook, the cell photocopies one recipe (the mRNA) and carries it to the kitchen (the ribosomes), where the protein is made.

Antisense oligonucleotides: a sticky note on the recipe

An **antisense oligonucleotide (ASO)** is a short, lab-made strand of genetic letters designed to stick to one specific mRNA, the way one half of a zipper fits only its partner. Depending on its design, an ASO can tell the cell to destroy that mRNA, so less of a harmful protein is made. Or it can change how the mRNA is spliced (cut and joined), so more of a useful protein is made. It's like a sticky note on one recipe saying either "don't make this" or "make the full version."

Two ASOs are landmarks in neurology. Both are injected into the fluid around the spinal cord by lumbar puncture (an **intrathecal** injection), so the drug reaches the brain and spinal cord directly.

- **Nusinersen (Spinraza)** treats spinal muscular atrophy (SMA), an inherited disease in which children lose lower motor neurons because they lack enough of a protein called SMN. Nusinersen changes how the mRNA from a backup gene, *SMN2*, is spliced, so the cell makes more full-length SMN protein (Finkel et al., 2017). In December 2016, it became the first FDA-approved drug for SMA, showing that an ASO could change the course of a motor neuron disease.
- **Tofersen (Qalsody)** treats ALS caused by SOD1 mutations. It sticks to SOD1 mRNA and lowers the production of SOD1 protein, including the toxic mutant form (FDA). It was

the first approved treatment aimed at a genetic cause of ALS. Its story, told in the Bedside case below, shows how biomarkers now shape drug approval.

Gene therapy: delivering a new recipe

Gene therapy treats disease by modifying a person's genes. According to the FDA, it can work by replacing a disease-causing gene with a healthy copy, inactivating a gene that is not working properly, or introducing a new or modified gene. One common approach uses a harmless, emptied-out virus as a delivery truck that carries a working copy of a gene into cells.

The first gene therapy for SMA, **onasemnogene abeparvovec (Zolgensma)**, was approved by the FDA on May 24, 2019 for children under 2 years old. A single infusion into a vein delivers a working copy of the human *SMN* gene to motor neurons.

Approach	What it targets	Example	How it's given
Anti-amyloid antibody	A misfolded protein already made	Lecanemab, donanemab (Alzheimer's)	Into a vein (lecanemab also under the skin)
Antisense oligonucleotide	The mRNA message	Nusinersen (SMA), tofersen (SOD1-ALS)	Into spinal fluid, repeated doses
Gene therapy	The gene itself	Onasemnogene abeparvovec (SMA)	One-time infusion into a vein

At the Bedside: Two Patients, Two Misfolded Proteins

Meet the patient

Mr. Okafor is a 74-year-old retired accountant. Over two years, his wife has noticed that he repeats stories, misses appointments, and recently paid the same bill twice. He still drives, dresses himself, and plays chess with his grandson. He says, "My memory isn't what it was, but I'm fine." His wife is worried.

What the doctor checks: The neurologist takes a history from both Mr. Okafor and his wife, because people with memory loss often underestimate it. Blood tests rule out low vitamin B12 and thyroid problems. On a memory test he can't recall a word list after a few minutes, even with hints, but attention and language are mostly normal. An MRI shows mild shrinkage of the hippocampus on both sides and no stroke or tumor. An amyloid PET scan is positive, showing amyloid plaques across the cortex.

Where is the problem? (localization): Trouble *storing* new memories, with older memories and language still working, points to the hippocampus and entorhinal cortex in the medial temporal lobes. The shrinkage on MRI matches. Because he still manages most daily activities, his symptoms fit mild cognitive impairment or the edge of mild dementia, not normal aging.

Diagnosis: Early Alzheimer's disease (mild cognitive impairment due to Alzheimer's disease).

Why it happens: As the biomarker model predicts, beta-amyloid has probably built up for many years. Tau tangles have spread into his memory circuits, synapses have been lost, and hippocampal neurons have died.

Treatment today: His doctor discusses an anti-amyloid antibody, since he is in the early stage these drugs are approved for and his amyloid is confirmed. Before starting, he would have APOE e4 genetic testing and a baseline MRI, then regular MRIs to watch for ARIA. The doctor is honest about the trade-off. In trials, these drugs modestly slowed decline (they did not stop or reverse it), they require regular infusions or injections, and ARIA can rarely be serious. A cholinesterase inhibitor may also help symptoms. Just as important are safety planning (including driving), blood pressure control, exercise, social activity, and caregiver support.

What's new in research: On May 16, 2025, the FDA cleared the first blood test to help diagnose Alzheimer's disease, for adults 55 and older with symptoms. The FDA said this less invasive option could reduce reliance on PET scans and make diagnosis more accessible.

Your turn: diagnose a variation

A 47-year-old woman has had weakness in her right hand for six months. She now drops her keys and trips on her right foot. Her memory is fine. On exam, the muscles in her hand are thin and twitch under the skin, yet her reflexes are unusually brisk. Her father and an aunt both died of a "muscle disease" in their 50s. What do you suspect, and what new treatment might her doctors discuss?

Answer: Weakness, muscle wasting, and twitching (lower motor neuron signs) together with brisk reflexes (upper motor neuron signs), plus a family history, suggest **familial ALS**. Genetic testing could look for a *SOD1* mutation. If one is found, doctors may discuss **tofersen (Qalsody)**. It received **FDA accelerated approval on April 25, 2023**, based on its ability to lower **neurofilament light** in blood. Neurofilament light is a blood biomarker of axon injury and neurodegeneration. Accelerated approval is an FDA pathway for serious diseases when a drug improves a biomarker "reasonably likely" to predict real benefit. Continued approval may depend on trials confirming that benefit.

Be honest about the evidence: in the phase 3 VALOR trial, tofersen lowered SOD1 and neurofilament light, but it **did not meet its primary clinical endpoint**, the change in a function rating scale at 28 weeks (Miller et al., 2022). A 52-week follow-up hinted that starting earlier was better, but that was not the trial's main test. A confirmatory trial (ATLAS) is testing whether tofersen delays symptoms in SOD1 carriers who are still healthy. As of October 2026, it is still under way and has not reported results. Tofersen is given by lumbar puncture, and procedure-related side effects are common.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Dementia is a normal part of getting old.
Reality: Some slowing of memory and thinking is normal with age, but dementia is not. Dementia is caused by diseases that damage the brain, and many people live into their 90s and beyond without it.

Myth: There are no treatments at all for Alzheimer's disease.
Reality: Several medicines help with symptoms, and two anti-amyloid antibodies (lecanemab and donanemab) are FDA-approved for early-stage disease. They modestly slow decline but do not cure the disease.

Myth: Removing amyloid plaques will bring back lost memories.
Reality: By the time symptoms appear, tau has spread and many neurons have died.

Neurons that have died are not replaced, so clearing amyloid can slow decline but cannot restore what was lost.

Myth: If you carry the APOE e4 gene, you will definitely get Alzheimer's disease.
Reality: APOE e4 raises risk but doesn't decide anyone's fate. Many carriers never develop the disease, and many people with Alzheimer's disease don't carry it. Huntington's disease is different: with 40 or more CAG repeats, a person almost always develops it.

Brain Bee Practice

1. Name the two abnormal protein deposits that define Alzheimer's disease, and say where each is found.

Amyloid plaques, made of beta-amyloid, are found outside neurons. Neurofibrillary (tau) tangles, made of abnormal tau, are found inside neurons.

2. Which two brain structures does Alzheimer's disease usually damage first, and what symptom does that explain?

The entorhinal cortex and the hippocampus. Damage there explains early trouble forming new memories.

3. What type of neurons die in ALS, and what are two signs of damage to each type?

Motor neurons. Lower motor neuron damage causes weakness, muscle wasting, and twitching (fasciculations). Upper motor neuron damage causes stiffness (spasticity) and brisk reflexes.

4. What genetic change causes Huntington's disease, and what are the chances that a child of an affected parent inherits it?

An expanded CAG repeat in the *HTT* (huntingtin) gene. It is autosomal dominant, so each child has a 50 percent chance of inheriting it.

5. What is an antisense oligonucleotide? Name one approved for a neurological disease.

A short, synthetic strand of genetic material that binds a specific mRNA to reduce or change production of a protein. Examples: nusinersen for spinal muscular atrophy, or tofersen for SOD1-ALS.

Exercises

Remember

1. Define *neurodegeneration* in your own words.

Answer

Neurodegeneration is the progressive loss of the structure and function of neurons, ending in their death.

2. What is ARIA, and how do doctors check for it?

Answer

ARIA (amyloid-related imaging abnormalities) is temporary brain swelling, sometimes with small spots of bleeding, that can happen with anti-amyloid antibodies. Doctors check for it with regular MRI scans.

Understand

1. Explain why trouble forming new memories is often the first sign of Alzheimer's disease.

Answer

Alzheimer's damage usually begins in the entorhinal cortex and hippocampus, the structures that turn new experiences into lasting memories. Older memories stored elsewhere in the cortex are affected later.

2. Explain the difference between a *biomarker* and a *symptom*, using Alzheimer's disease as an example.

> **Answer**
>
> A symptom is something the person or family notices, such as forgetting appointments. A biomarker is something measured in the body, such as amyloid on a PET scan or in blood. Biomarkers can become abnormal years before symptoms appear.

Apply

1. A 30-year-old's mother has Huntington's disease. His genetic test shows 42 CAG repeats in one copy of *HTT*. Using the table in Section 13.10, what does this result mean for him, and what is the chance that each of his future children inherits the expanded gene?
2. Use the Amyloid and Tau Cascade MicroSim. Find the age at which each curve first crosses the "abnormal on tests" line, and calculate how many years pass between amyloid becoming abnormal and symptoms becoming abnormal in this schematic model.

Analyze

1. Compare an anti-amyloid antibody, an antisense oligonucleotide, and gene therapy. For each, identify the step in the DNA → mRNA → protein pathway it acts on and why that step fits the disease it treats.
2. Two 80-year-olds have similar amyloid on PET scans. One has dementia; the other manages her own money and plays bridge. Use cognitive reserve and the biomarker model to analyze possible reasons.

Evaluate

1. Tofersen received accelerated approval because it lowered neurofilament light, although its phase 3 trial missed its primary clinical endpoint. Is approving drugs based

on biomarkers a good idea for rare, fatal diseases? Defend your answer, weighing patients' urgent need against the risk of approving a drug that doesn't help.

2. A news headline says: "New Alzheimer's drug stops memory loss." Using what you know about the lecanemab and donanemab trials, judge how accurate this headline is and rewrite it to be accurate.

Create

1. Design a one-page family handout that separates normal forgetfulness from warning signs of dementia. Include four comparisons and one reason to see a doctor even if it seems like "just age."
2. Design a trial testing whether an anti-amyloid antibody delays symptoms when started in the preclinical stage. Say who you would enroll, which biomarker you'd use to choose them, your main outcome, and how you'd watch for ARIA.

Key Takeaways

- Normal aging brings slower thinking and some shrinkage, but not large-scale neuron loss. **Dementia is not a normal part of aging.**
- Many neurodegenerative diseases share one theme: a **misfolded protein** builds up in specific neurons, and the location decides the symptoms.
- **Alzheimer's disease**, the most common cause of dementia, is defined by **amyloid plaques** outside neurons and **tau tangles** inside them. It usually starts in the hippocampus and entorhinal cortex.
- **Biomarkers** (PET scans, spinal fluid, and now FDA-cleared blood tests) show that Alzheimer's brain changes begin a decade or more before symptoms.
- **Anti-amyloid antibodies** (lecanemab and donanemab) are FDA-approved for early Alzheimer's disease. They modestly slow decline, are not cures, and carry a risk of **ARIA**.
- **ALS** kills upper and lower motor neurons. **Huntington's disease** comes from an expanded CAG repeat in *HTT*, is autosomal dominant, and damages the striatum.

- **Antisense oligonucleotides** (nusinersen, tofersen) and **gene therapy** target genes and their messages. Tofersen's accelerated approval rested on a biomarker; its phase 3 trial missed its main clinical goal.

You made it through a tough chapter!



You can now explain plaques, tangles, CAG repeats, and antisense drugs, the vocabulary behind some of the newest work in medicine. Next, in Chapter 14, we look at damage that happens in seconds instead of decades: concussion, stroke, and seizures.

Chapter 14: Brain Injury, Stroke, and Epilepsy

Summary

The brain can be hurt in three very different ways: by a physical hit (traumatic brain injury and concussion), by losing its blood supply or bleeding (stroke), or by a burst of runaway electrical activity (a seizure). This chapter explains what goes wrong in neurons, blood vessels, and circuits in each case, and teaches what to do in the first minutes: remove an injured athlete from play, recognize stroke with BE-FAST and call 911, and give seizure first aid. It ends with spinal cord injury and a stroke map you can use to predict symptoms from a blocked artery.

Concepts Covered

1. Traumatic Brain Injury
2. Concussion
3. Return-to-Learn and Play
4. Chronic Traumatic Enceph.
5. Stroke
6. Ischemic Stroke
7. Hemorrhagic Stroke
8. BE-FAST Warning Signs
9. Clot-Busting Treatment
10. Seizure
11. Epilepsy
12. Seizure First Aid
13. Spinal Cord Injury

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters
- Chapter 4: A Tour of the Brain
- Chapter 5: Vision
- Chapter 6: Hearing, Touch, Taste, Smell, and Pain
- Chapter 7: Movement
- Chapter 12: Language, Attention, and Decision-Making

When Seconds Matter



I'm Ply, and this might be the most useful chapter in the whole book. Everything you learned about neurons, synapses, and brain maps comes together here, in real emergencies. By the end, you'll know what to do if a teammate takes a hard hit, a grandparent's face suddenly droops, or a classmate has a seizure.

14.1 A Header, Then a Fog

It's the second half of a Saturday soccer game. Maya, 16, rises for a header just as a defender jumps for the same ball, and their heads knock together. Maya doesn't black out. She shakes it off and jogs back into position. But the field seems too bright, her head is pounding, and when her coach shouts a play she has run a hundred times, she can't remember where to go. She tells a teammate she feels "foggy."

Maya wants to keep playing. She never lost consciousness, so how bad could it be? This chapter answers that question, then visits two other sudden brain emergencies: a stroke and a seizure. In all three, what bystanders do in the first few minutes can change the outcome.

14.2 Intuition First: Three Ways a City Can Fail

Picture the brain as a busy city. Its buildings (neurons) sit inside a hard wall (the skull), cushioned by a moat of fluid (cerebrospinal fluid). Fuel trucks (blood vessels) deliver oxygen and sugar around the clock, because the city has almost no storage. And the whole city runs on an electrical grid (the action potentials and synapses of Chapter 2 and Chapter 3).

A city like that can fail in three main ways:

- **An earthquake** shakes everything, stretching and snapping power lines. This is a traumatic brain injury.
- **A blocked road or a burst pipe** cuts off one neighborhood, which shuts down within minutes. This is a stroke.
- **A power surge** makes huge numbers of buildings switch on and off together. This is a seizure.

These problems are common. A 2024 *Lancet Neurology* study from the Global Burden of Disease (GBD) project found that nervous system conditions affected about 3.4 billion people in 2021, 43% of the world's population. Together, they were the leading cause of ill health and disability worldwide (GBD 2021 Nervous System Disorders Collaborators, 2024). The study measured burden in **disability-adjusted life years (DALYs)**, the years of healthy life lost to illness, disability, or early death. Out of 37 nervous system conditions, stroke ranked first by this measure, and epilepsy ranked seventh.

14.3 Traumatic Brain Injury: When Force Meets the Brain

A **traumatic brain injury (TBI)** is a brain injury caused by an outside force: a blow, bump, or jolt to the head or body, or an object that enters the skull (NINDS). TBIs range from mild to severe. Falls, car crashes, sports, and violence are common causes, and NINDS notes that adults 65 and older have the highest risk of being hospitalized or dying from a TBI, mostly because of falls.

Why can a hit to the *body* hurt the brain? The soft brain floats in fluid inside the skull. When the head speeds up or stops suddenly, the brain keeps moving for a split second and strikes the skull. Twisting motions are especially harmful because they stretch the long, thin axons

that connect brain regions (Chapter 1). Widespread stretching damage to white matter is called **diffuse axonal injury**, which NINDS lists as one of the most common kinds of TBI.

Concussion: a mild TBI that still matters

A **concussion** is a type of mild TBI caused by a bump, blow, or jolt to the head, or by a hit to the body that makes the head and brain move rapidly back and forth (CDC HEADS UP). "Mild" means it is usually not life-threatening. It does not mean the effects are minor.

Inside the brain, a chain of events called the **neurometabolic cascade** unfolds (Giza and Hovda, 2014):

1. Stretched neuron membranes let ions rush across. Potassium floods out, and sodium and calcium flow in.
2. Many neurons fire at once and release the excitatory neurotransmitter glutamate.
3. Sodium-potassium pumps work overtime to restore the ion balance, burning huge amounts of energy.
4. Meanwhile, blood flow to the area can drop. The brain enters an "energy crisis": high demand, low supply.

This crisis helps explain the symptoms. It also explains why a second hit before recovery is dangerous: NINDS warns that a second concussion soon after the first can cause lasting damage and, in rare cases, death.

No Blackout Needed



Maya figured she was fine because she never blacked out. But a concussion is a change in how the brain *works*, not a matter of being knocked out. The CDC has stated that most concussions happen without any loss of consciousness.

That statement comes from CDC testimony to Congress (CDC, 2010), and today's HEADS UP pages treat passing out as just one possible sign. The table sorts the main signs CDC lists for children and teens (CDC HEADS UP).

What others may see	What the athlete may feel or say
Appears dazed or confused	Headache
Sudden trouble with memory or concentration	Dizziness or balance problems
Slower answers and reactions	Feeling "foggy" or slowed down
More clumsy than usual	Sensitivity to light or noise
Mood or behavior changes; vomiting soon after the hit	Nausea, vision problems, fatigue, sleep changes

Some signs suggest something worse than a concussion, such as bleeding that presses on the brain. CDC says to call 911 or go to the nearest emergency department right away for any of these **danger signs**:

- a headache that gets worse and does not go away
- repeated nausea or vomiting
- slurred speech, weakness, numbness, or decreased coordination
- convulsions or seizures
- loss of consciousness with increasing drowsiness, inability to wake up, or inability to stay awake
- one pupil larger than the other, or double vision
- not recognizing people or places
- unusual behavior, increased confusion, restlessness, or agitation

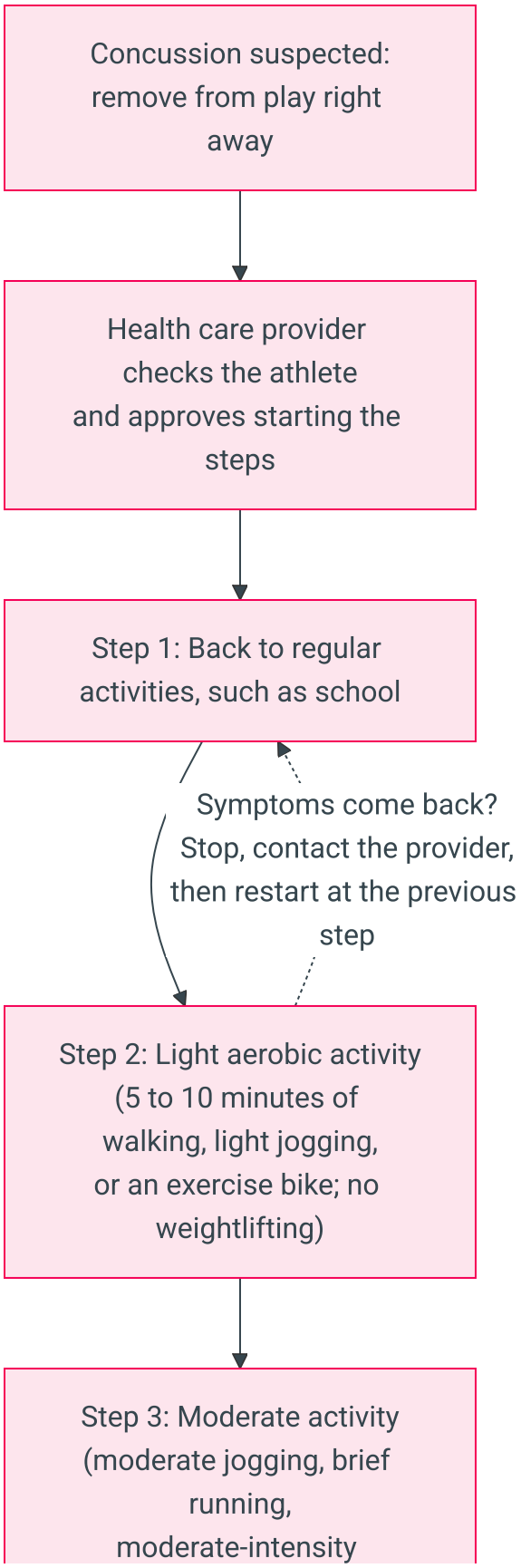
14.4 Healing After a Concussion: Return-to-Learn and Play

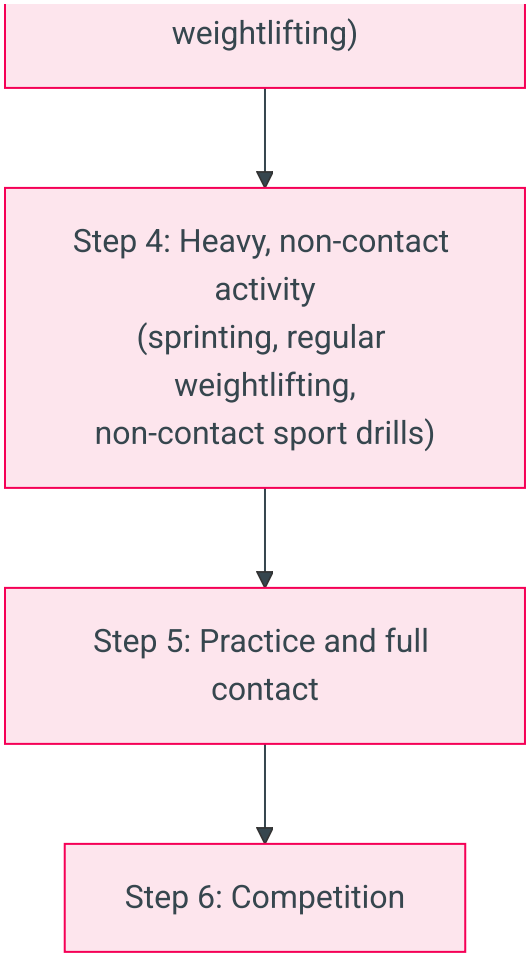
The first rule is simple. If a concussion is suspected, CDC says to **remove the athlete from play right away** and keep them out for the rest of that day and until a health care provider clears them (CDC HEADS UP: How to Respond). Coaches and parents shouldn't judge how bad the injury is. Deciding when to return is a medical decision.

Recovery then follows **return-to-learn and play**: a gradual, step-by-step return to school and daily life, then to sports, moving forward only if symptoms stay away. CDC's guidance says (CDC HEADS UP: What to Do After a Concussion):

- **First 1 to 2 days:** rest if needed, and limit screen time and physically or mentally demanding activities. But don't stay in a dark room all day. Light activity, such as short walks, is encouraged even with mild symptoms.
- **Back to school:** most children can return within 1 to 2 days, at first with supports such as rest breaks, homework help, and extra time on tests.
- **Most feel better within 2 to 4 weeks.** Some have symptoms for months and should keep working with a health care provider.

Returning to sports has its own ladder. CDC describes six steps, each usually lasting at least 24 hours, started only with a health care provider's approval (CDC HEADS UP: Returning to Sports). CDC also advises that a student be back to all regular non-sports activities, without extra supports, before fully returning to sports. The flowchart shows the steps and the rule for moving between them.


Concussion suspected: remove from play right away
Health care provider checks the athlete and approves starting the steps
Step 1: Back to regular activities, such as school
Symptoms come back? Stop, contact the provider, then restart at the previous step
Step 2: Light aerobic activity (5 to 10 minutes of walking, light jogging, or an exercise bike; no weightlifting)
Step 3: Moderate activity (moderate jogging, brief running, moderate-intensity



The dotted arrow shows the key rule: at any step, if symptoms return, the athlete stops, contacts their provider, and after more rest restarts at the previous step.

14.5 Many Hits Over Many Years: CTE

Most people recover fully from a single concussion. But some people exposed to many head impacts over years develop a progressive brain disease. **Chronic traumatic encephalopathy (CTE)** is a disorder in which the protein **tau** clumps inside neurons in a distinctive pattern, often around small blood vessels at the bottoms of the brain's folds (McKee et al., 2023). Tau also forms tangles in Alzheimer's disease, but its pattern in CTE is different.

Two facts about CTE are easy to get wrong:

- **It can currently be confirmed only after death,** by examining brain tissue. NINDS notes that researchers are working on tests to detect it in living people.

- **Living patients get a different label.** In 2021, a panel organized through NINDS published research criteria for **traumatic encephalopathy syndrome (TES)**: substantial exposure to repeated head impacts, problems with memory, thinking, or behavior control, a worsening course, and no better explanation (Katz et al., 2021).

14.6 Stroke: When the Brain Loses Its Blood Supply

A **stroke** happens when something blocks the blood supply to part of the brain, or when a blood vessel in the brain bursts, so that brain cells in that area are damaged or die (CDC). According to CDC's stroke facts page (last updated in 2024), more than 795,000 people in the U.S. have a stroke each year, about one every 40 seconds (CDC Stroke Facts).

Two kinds of stroke

An **ischemic stroke** happens when a blood clot or other particle blocks a vessel supplying the brain. ("Ischemia" means not enough blood flow.) The clot may form in a narrowed brain artery or travel up from elsewhere, often the heart. About 87% of strokes are ischemic, according to CDC.

A **hemorrhagic stroke** happens when a blood vessel in the brain leaks or bursts, and the leaked blood damages brain cells. Long-term high blood pressure can weaken small vessels until they rupture. A weak, ballooning spot in an artery, called an **aneurysm**, can also burst, often bleeding into the space around the brain (NINDS).

A **transient ischemic attack (TIA)**, or "mini-stroke," blocks blood flow only briefly, usually for less than 5 minutes. The symptoms go away, but CDC calls a TIA a medical emergency and a warning sign of a future stroke. Early symptoms can't tell a TIA from a major stroke, so both need a 911 call. The table summarizes the two main types.

Feature	Ischemic stroke	Hemorrhagic stroke
What goes wrong	A clot blocks an artery	A vessel leaks or bursts

Feature	Ischemic stroke	Hemorrhagic stroke
City analogy	A supply road is blocked	A water main bursts
Share of strokes (CDC)	About 87%	The rest
Clot-busting drugs?	Can help if given early	Never; they would worsen bleeding

"Time is brain"

Neurologist Jeffrey Saver estimated that in a typical large ischemic stroke, the brain loses about 1.9 million neurons for every minute blood flow is not restored (Saver, 2006). That's an estimate, not a rule for every patient, but it captures the slogan "time is brain." Around the dying core there is often a zone of stunned but still-living tissue that fast treatment can save.

The Stopwatch Starts at the First Symptom



I only have about 20,000 neurons, so losing millions a minute is hard for me to imagine! For a stroke, the most important number to remember is when the symptoms started. Doctors use it to decide which treatments are still possible.

14.7 BE-FAST: Spot a Stroke and Call 911

Stroke symptoms appear **suddenly**: numbness or weakness of the face, arm, or leg (especially on one side), confusion or trouble speaking or understanding, trouble seeing, trouble walking or loss of balance, or a severe headache with no known cause (CDC Stroke Signs). To make the quick check easy to remember, CDC uses the **BE-FAST warning signs**:

Letter	Check	What to look for
Balance	Is the person suddenly off-balance or dizzy?	Sudden trouble walking or standing

Letter	Check	What to look for
Eyes	Is there sudden trouble seeing?	Vision loss in one or both eyes
Face	Ask them to smile.	One side of the face droops
Arms	Ask them to raise both arms.	One arm drifts downward
Speech	Ask them to repeat a simple phrase.	Slurred or strange speech
Time	If you see any of these signs	Call 911 right away and note when symptoms started

CDC also advises calling 911 instead of driving to the hospital, because the ambulance crew can begin care on the way.

Treatment: reopen the road, or stop the flood

The two stroke types need opposite treatments, so one of the first things the hospital does is a brain scan, usually CT, to look for bleeding (NINDS).

For an ischemic stroke, the goal is to reopen the artery fast. **Clot-busting treatment** means giving a medicine through a vein that dissolves the clot and restores blood flow. The first of these drugs, tissue plasminogen activator (t-PA, or alteplase), came out of NINDS-funded research and became the first FDA-approved treatment for acute ischemic stroke. In that research, people treated within three hours of their first symptoms were 30% more likely to have little or no disability three months later. NINDS notes that most doctors now treat suitable patients within a 4.5-hour window.

In early 2025 (February 28), the FDA approved a second clot buster, tenecteplase (TNKase), for adults with acute ischemic stroke (FDA approval letter). The maker announced it on March 3 (Genentech, 2025). A January 2026 guideline from the American Heart Association and American Stroke Association lists alteplase and tenecteplase as options and says the drug should be started as quickly as possible within 4.5 hours of the first symptoms (Practical Neurology, 2026). These drugs work best when started early.

Clot busters don't work well on large arteries blocked by big clots. For those patients, doctors can perform a **thrombectomy**: a thin tube called a catheter is threaded from an artery in the leg into the brain, and a device grabs or suctions out the clot. Several large clinical studies have shown that this helps people with severe strokes from large clots (NINDS).

For a hemorrhagic stroke, clot busters would worsen the bleeding. Doctors instead control the bleeding source and pressure in the skull, and may seal an aneurysm with a surgical clip or tiny coils placed through a catheter.

Afterward, **rehabilitation** helps the brain adapt, and doctors work to prevent another stroke. CDC calls high blood pressure the leading cause of stroke. Smoking and diabetes also raise the risk.

14.8 Where Is the Stroke? Mapping Arteries to the Body

A stroke's symptoms depend on *which part* of the brain loses blood, so a careful exam can locate it. You need three ideas you already know. First, each side of the brain controls the **opposite** side of the body, because motor pathways cross the midline (Chapter 7). Second, the motor and touch strips are body maps, with the leg area near the top midline and the face and arm areas lower on the outer side (Chapter 6). Third, each occipital lobe handles vision for the opposite half of what you see (Chapter 5).

Three Arteries, One Big Idea



Artery names can feel like a pile of new vocabulary, but you only need three. Match each one to the part of the body map it feeds, and the symptoms almost predict themselves.

Each hemisphere gets blood from three main cerebral arteries:

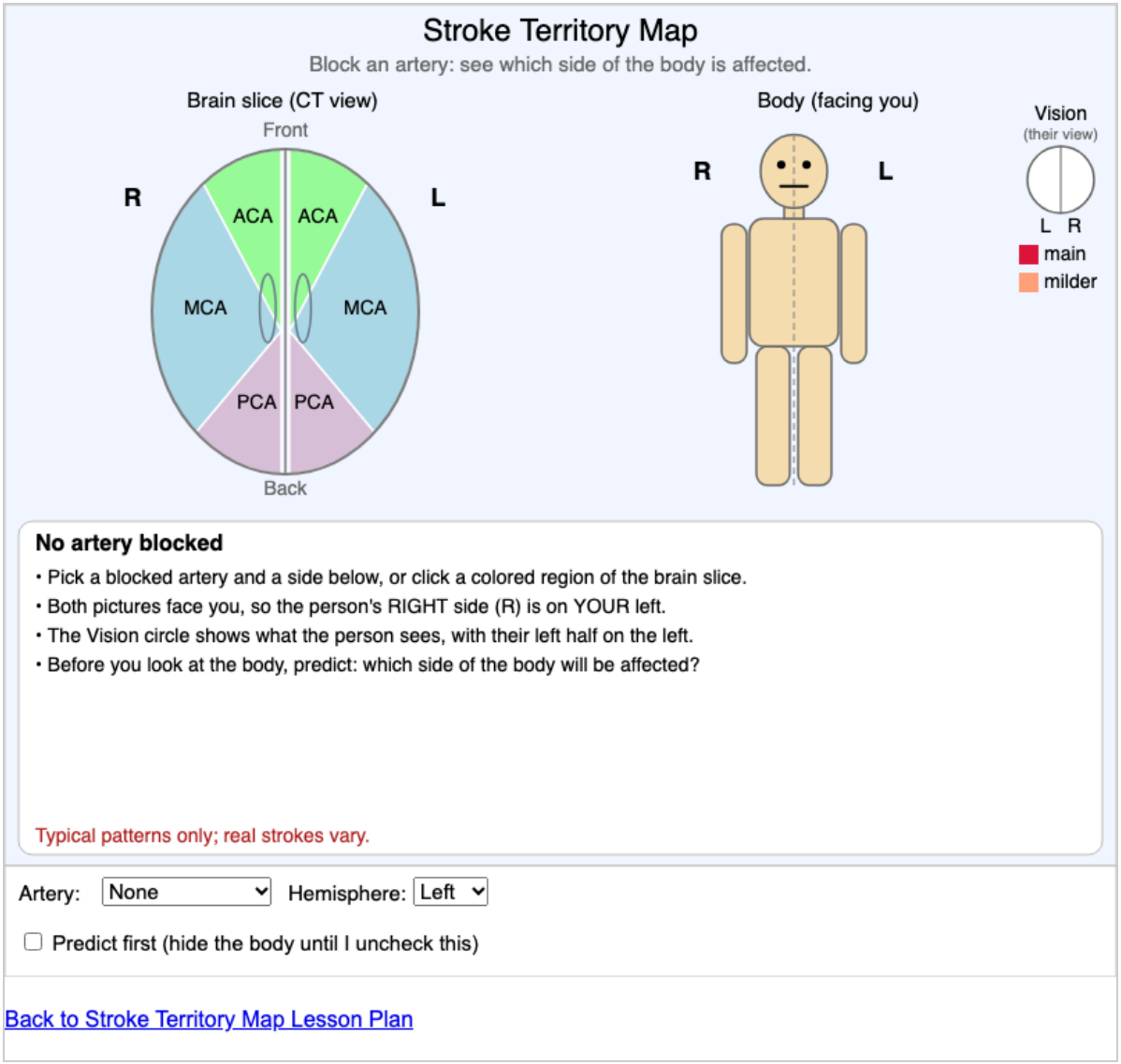
- The **anterior cerebral artery (ACA)** runs along the inner, midline surface of the frontal and parietal lobes, where the leg area of the motor and touch strips sits.
- The **middle cerebral artery (MCA)** fans out over the outer side of the hemisphere. It feeds the face and arm areas and, on the left side in most people, the language areas from Chapter 12.

- The **posterior cerebral artery (PCA)** supplies the back of the brain, including the occipital lobe (vision) and the inner temporal lobe.

The table below follows the stroke syndromes in the *Merck Manual* (Merck Manual Professional Version). These are typical patterns. Real strokes vary, and many involve only part of a territory.

Blocked artery	Typical problems (on the body side opposite the stroke)
ACA	Weakness and numbness worst in the leg; sometimes apathy, poor judgment, or bladder control problems
MCA, left hemisphere	Right face and arm weakness and numbness (worse than the leg); aphasia; possible loss of the right half of vision
MCA, right hemisphere	Left face and arm weakness and numbness (worse than the leg); neglect of the left side; possible loss of the left half of vision
PCA	Loss of the opposite half of vision in both eyes (homonymous hemianopia); sometimes memory problems; usually no limb weakness

Diagram: Stroke Territory Map



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch14-stroke-territories/

Open the Stroke Territory Map fullscreen

MicroSim specification: Stroke Territory Map

- **sim-id:** ch14-stroke-territories; **Library:** p5.js; **Bloom level:** Apply (predict)
- **Learning objective:** Given which cerebral artery (ACA, MCA, or PCA) is blocked and in which hemisphere, the learner will predict which side of the body and which functions are typically affected.
- **Canvas:** width-responsive; 620 px drawing area plus 80 px of controls (iframe 702 px).
- **Controls:** artery select (None, ACA, MCA, PCA); hemisphere select (Left, Right); a "Predict first" checkbox that hides the body until unchecked. Clicking a territory on the brain slice also selects it.
- **Behavior:** a CT-style brain slice (person's right on the viewer's left) shows three territories per hemisphere; the chosen one darkens. A body facing the viewer highlights the opposite face, arm, and leg, a vision circle shades the lost half-field, and an info panel lists typical deficits (*Merck Manual*) with the note "Typical patterns only; real strokes vary."

Try this: check **Predict first**, choose **MCA** and the **Left** hemisphere, and say which side of the body will be weak and whether speech will suffer. Then uncheck the box. Next, try the **ACA** and notice that the leg takes the main hit. Finally, pick the **PCA**: the limbs are spared, but half of the visual world disappears.

Notice that the highlights always land on the *opposite* side, and that the CT view puts the person's right on your left, the way doctors read real scans (you'll learn more about CT in Chapter 16).

14.9 Seizures: An Electrical Storm

In a healthy brain, excitation and inhibition stay balanced: glutamate synapses push neurons to fire, and GABA synapses hold them back (Chapter 3). Now imagine that balance tips. A group of neurons starts firing too much and in lockstep, spreading the extra activity to its neighbors.

A **seizure** is a sudden, temporary burst of abnormal, excessive, synchronized electrical activity in the brain that changes how a person moves, feels, behaves, or is aware. What it looks like depends on where it starts and how far it spreads. NINDS divides seizures into two broad groups (NINDS):

- **Focal seizures** start in one area. A seizure in the motor strip might make a hand jerk; one in the temporal lobe might bring a strange smell or a sense of déjà vu, or make the person stare without awareness. About 60% of people with epilepsy have focal seizures.
- **Generalized seizures** involve both sides of the brain from the start. In a **tonic-clonic seizure**, the person loses consciousness, the muscles stiffen (tonic phase), and the body jerks rhythmically (clonic phase). In an **absence seizure**, the person stares, unaware, for a few seconds.

Afterward, many people are confused or sleepy for a while. Some seizures are **provoked** by a clear, temporary cause, such as very low blood sugar, a high fever in a young child, or alcohol withdrawal. In people prone to seizures, triggers such as stress, missed meals, and lack of sleep can set one off. NINDS calls sleep deprivation a powerful trigger.

Epilepsy

Epilepsy is a brain disorder in which a person has a lasting tendency to have unprovoked seizures. It is usually diagnosed after two or more unprovoked seizures more than 24 hours apart. The International League Against Epilepsy also allows the diagnosis after one unprovoked seizure when the risk of more is high, or when the person has a recognized epilepsy syndrome (Fisher et al., 2014). Doctors use an EEG (a recording of the brain's electrical activity) and brain imaging to find the type and cause.

CDC estimates that during 2021 and 2022 about 2.9 million U.S. adults (about 1%) had active epilepsy, and that about 456,000 U.S. children (2022 data) have it (CDC). Causes include genes, brain injury, stroke, tumors, and infections, but NINDS notes that about half of people with epilepsy don't know the cause. Treatments include:

- **Medications:** more than 40 antiseizure medicines exist, and NINDS notes that most seizures can be controlled with one drug.
- **Surgery:** removing or disconnecting the small area where seizures start can greatly reduce or stop them for many people.
- **Devices:** vagus nerve, responsive, and deep brain stimulation deliver small electrical pulses.
- **Diet:** a supervised ketogenic diet helps some people, especially children with certain epilepsies.

Epilepsy is a medical condition, not a personal failing, and many people with epilepsy go to school, play sports, and work. Person-first language ("a person with epilepsy," not "an epileptic") keeps the focus on the person.

14.10 Seizure First Aid: Stay, Safe, Side

Most seizures end on their own within a few minutes. **Seizure first aid** is the set of simple steps any bystander can take to keep a person safe during and after a seizure and to know when to call for help. The Epilepsy Foundation teaches three words, **Stay, Safe, Side** (Epilepsy Foundation), and CDC's guidance matches (CDC):

1. **STAY** with the person and time the seizure. Stay calm and check for a medical ID.
2. **Keep them SAFE.** In CDC's words: ease them to the ground if they appear to be falling, clear the space around them to prevent injury, put something soft and flat under their head (like a jacket), take off their eyeglasses, and loosen anything around the neck that could block breathing.
3. **Turn them on their SIDE** if they are not awake and aware. CDC says to turn them gently onto one side with their mouth pointing to the ground, which keeps their airway clear.

What **not** to do matters just as much:

- **Do not put anything in their mouth.** Nobody can swallow their tongue during a seizure, and CDC warns that an object in the mouth can hurt their teeth or jaw.
- **Do not hold them down** or stop their movements. CDC warns this could injure you or them.
- **Do not give food, water, or pills** until they are fully alert. Stay until they are alert, then calmly tell them what happened.

Nothing in the Mouth!



Putting a spoon or wallet in someone's mouth during a seizure is an old idea that is wrong and dangerous. Protect the head, turn them on their side, and watch the clock instead.

Call 911 if, in CDC's words, the seizure lasts longer than 5 minutes; they have another seizure soon after the first one; they have trouble breathing or waking up after the seizure; they are injured during the seizure; or the seizure happens in water. CDC also says to call 911 if the person has never had a seizure before (a **first seizure**), has diabetes and loses consciousness, or is pregnant. The Epilepsy Foundation adds calling 911 if the person does not return to their usual state or is sick. A seizure that lasts too long, or seizures that keep coming without recovery, is an emergency called **status epilepticus**, and NINDS notes that five minutes is enough to begin damaging neurons.

Schools are paying attention, too. Minnesota Statutes section 121A.24, "Seizure Training and Action Plan," requires public and charter schools, starting in the 2022-2023 school year, to put seizure action plans in place and train staff for students whose families report a diagnosed seizure disorder with prescribed seizure medication (Minnesota Department of Health).

14.11 Spinal Cord Injury: Cutting the Cable

The spinal cord is the main cable between brain and body, carrying motor commands down and sensations up (Chapter 6, Chapter 7). A **spinal cord injury (SCI)** is damage to the cord, directly or through broken or displaced spinal bones, that disrupts signals between the brain and the body (NINDS). NINDS lists car crashes and serious falls as the most common U.S. causes, and people aged 16 to 30 are at higher risk.

Two features decide what an SCI does:

- **Level.** Everything below the injury can be affected. A high neck injury can affect all four limbs (**tetraplegia**, or quadriplegia). A lower injury usually affects the legs (**paraplegia**). Injuries at C1 to C4 can stop breathing, and about one-third of people with an SCI need temporary or permanent help breathing.
- **Complete or incomplete.** In an incomplete injury, some signals still get through. In a complete injury, none pass below that level.

Central nervous system axons regrow very poorly, so care focuses on stabilizing the spine, relieving pressure on the cord, and rehabilitation. NINDS-supported researchers are testing spinal cord stimulation and brain-computer interfaces.

At the Bedside: Three Emergencies, Three Brains

Case 1: Maya's Concussion

Meet the patient

Maya, 16, bumped heads with a defender during a soccer game. She didn't black out but felt "foggy," had a headache, was bothered by bright light, and forgot a familiar play. Her coach pulled her from the game, and her parents took her to her doctor the next morning.

What the doctor checks: how the injury happened and each symptom, plus memory, concentration, balance, eye movements, strength, and reflexes. Strength and reflexes are normal, and there are no danger signs.

Where is the problem? (localization): No single spot. Fogginess, slowed thinking, light sensitivity, and poor balance point to a temporary, brain-wide change in how neurons work, not a bleed in one area. With no danger signs, the doctor decides she doesn't need a CT scan.

Diagnosis: Concussion (a mild traumatic brain injury).

Why it happens: The collision moved Maya's brain rapidly inside her skull. Stretched neurons leaked ions, released a burst of glutamate, and entered an energy crisis.

Treatment today: No sports until cleared. A day or two of lighter activity and limited screens, then school with temporary supports. Once she's back to normal school without supports and her provider approves, she climbs CDC's six-step return-to-play ladder, moving up only if symptoms stay away.

What's new in research: In April 2024, the FDA cleared Abbott's i-STAT TBI cartridge for whole blood. It measures two proteins released by injured brain cells, GFAP and UCH-L1, in about 15 minutes to help doctors decide whether a CT scan is needed (U.S. Army, 2024). It is cleared for adults 18 and older (Practical Neurology, 2024), so it wouldn't be used for Maya, and it doesn't diagnose concussion by itself.

Your turn: diagnose a variation

Two hours later, Maya's headache is much worse, she has vomited three times, and one pupil is bigger than the other. What should her family do?

Answer: Call 911 or go to the emergency department now. These danger signs can mean bleeding inside the skull pressing on the brain, a more serious TBI than a concussion. Doctors would order an urgent CT scan.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Case 2: Grandpa's Sudden Face Droop

Meet the patient

Maya's grandfather, 72, has high blood pressure. At breakfast he suddenly can't get his words out, and coffee dribbles from the right side of his mouth. When Maya asks him to raise both arms, his right arm drifts down. She remembers BE-FAST, calls 911 at 8:10 a.m., and notes that he was fine at 8:00.

What the doctor checks: the time he was last known well, a stroke severity score (the NIH Stroke Scale), and an immediate CT scan, which shows no bleeding. A CT angiogram (a scan of the blood vessels) shows a clot in his left middle cerebral artery.

Where is the problem? (localization): Right face and arm weakness worse than the leg points to the face and arm areas of the left motor strip. Trouble producing words points to the left-hemisphere language areas. Both are fed by the left MCA.

Diagnosis: Acute ischemic stroke in the left MCA territory.

Why it happens: A clot, perhaps from an artery narrowed by years of high blood pressure or from the heart, cut off blood to the outer left hemisphere, and neurons began failing within minutes.

Treatment today: With no bleeding and a fast arrival, he receives a clot-busting medicine through a vein, plus a thrombectomy because a large artery is blocked. Then come rehabilitation and blood pressure control.

What's new in research: In early 2025 (February 28), the FDA approved tenecteplase (TNKase) for acute ischemic stroke in adults. Its maker announced the approval on March 3 and called it the first stroke medicine approved by the FDA in nearly 30 years. It is given as a single five-second injection into a vein, instead of alteplase's quick injection followed by a one-hour infusion (Genentech, 2025).

Your turn: diagnose a variation

A 58-year-old woman suddenly has the worst headache of her life and vomits. She has no weakness, and the CT shows blood around the brain. Should she get a clot buster?

Answer: No. This is a hemorrhagic stroke, likely from a burst aneurysm, and a clot buster would worsen the bleeding. Doctors would control the bleeding source (often by clipping or coiling the aneurysm) and manage pressure in the skull. This is why the scan comes first.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Case 3: A Teen's First Seizure

Meet the patient

Jordan, 15, stayed up almost all night before a school day. At lunch he suddenly cries out, falls, and his whole body stiffens and then jerks. A friend times it at about 90 seconds. Afterward Jordan is confused, very sleepy, and doesn't remember what happened. He has never had a seizure before.

What the doctor checks: Because it was a first seizure, his friends called 911. Doctors check his blood sugar and blood salts, ask about sleep, drugs, and illness, and find a normal neurological exam once he is fully awake. An EEG and an MRI are scheduled.

Where is the problem? (localization): Loss of consciousness with stiffening and jerking on both sides suggests a generalized tonic-clonic seizure involving networks on both sides of the brain (or a focal seizure that spread quickly). The EEG and MRI help find where it began.

Diagnosis: A first tonic-clonic seizure. One seizure is not epilepsy unless tests show a high risk of more or a specific epilepsy syndrome.

Why it happens: The balance between excitation and inhibition tipped, so large groups of neurons fired together. NINDS describes sleep deprivation as a powerful seizure trigger.

Treatment today: Seizure first aid, an emergency evaluation, and neurology follow-up, with advice to keep regular sleep. If more unprovoked seizures occur, epilepsy is diagnosed and usually treated first with one antiseizure medication.

What's new in research: NINDS-supported BRAIN Initiative projects aim to predict when seizures will start and deliver stimulation to stop them, and other teams use machine learning to locate where seizures begin (NINDS).

Your turn: diagnose a variation

A classmate with known epilepsy has a tonic-clonic seizure in the gym. You time it at 6 minutes, and it hasn't stopped. What do you do?

Answer: Call 911 now. A seizure lasting more than 5 minutes may be status epilepticus, which can damage neurons. Keep them safe and on their side, put nothing in their mouth, and alert the school nurse in case their seizure action plan includes a rescue medicine.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: You have to be knocked out to have a concussion.
Reality: A concussion is a change in how the brain works after a hit or jolt. CDC has stated that most concussions happen without loss of consciousness.

Myth: Put something in a person's mouth during a seizure so they don't swallow their tongue.
Reality: Nobody can swallow their tongue, and an object in the mouth can hurt their teeth or jaw. Keep the person safe, turn them on their side, and time the seizure.

Myth: After a concussion, stay in a dark room until every symptom is gone.
Reality: CDC advises limiting screens and hard activities for 1 to 2 days, but not isolating in a dark room. Light activity and a gradual return to school help recovery.

Myth: Strokes only happen to old people.
Reality: Risk rises with age, but strokes happen at any age. CDC reports that in 2014, 38% of people hospitalized for stroke were younger than 65 (CDC Stroke Facts).

Myth: If stroke symptoms go away in a few minutes, there's no need to call for help.
Reality: That may be a TIA, which CDC calls a medical emergency and a warning of a future stroke. Call 911 either way.

Brain Bee Practice

1. A patient has left leg weakness much worse than left arm weakness, with a normal face. Which artery is most likely blocked, and on which side?

The right anterior cerebral artery (ACA). It feeds the midline area where the leg part of the motor strip sits, and the right hemisphere controls the left side of the body.

2. What does BE-FAST stand for?

Balance, Eyes, Face, Arms, Speech, Time. "Time" reminds you to call 911 right away and note when symptoms started.

3. Why must doctors scan the brain before giving a clot-busting drug?

Clot busters help ischemic strokes but would worsen a hemorrhagic stroke. A CT scan shows whether there is bleeding.

4. Which protein builds up in CTE, and how is CTE definitively diagnosed today?

Tau, in a distinctive pattern around small blood vessels at the depths of the brain's folds. CTE can currently be confirmed only by examining brain tissue after death.

5. How is epilepsy usually defined?

Two or more unprovoked seizures more than 24 hours apart. It can also be diagnosed after one unprovoked seizure if the risk of more is high, or if the person has an epilepsy syndrome.

Exercises

Remember

1. List the six letters of BE-FAST and what each one checks.
2. Name the three steps of seizure first aid taught by the Epilepsy Foundation.

Answer

1. Balance (sudden loss of balance), Eyes (sudden vision trouble), Face (drooping), Arms (one drifts down), Speech (slurred or strange), Time (call 911 and note the time).
2. Stay with the person and time the seizure; keep them Safe; turn them on their Side.

Understand

1. Explain, using ions and energy, why a concussed brain is vulnerable to a second hit.
2. Explain why a stroke in the left hemisphere usually weakens the right side of the body.

Answer

1. Ions flood across stretched membranes and glutamate is released. Pumps burn large amounts of energy to restore balance while blood flow may drop. A second hit lands on neurons already in an energy crisis.
2. Motor pathways cross the midline, so each hemisphere controls the opposite side of the body.

Apply

1. A teammate falls, hits their head, and says they "feel fine" but is confused about the score. Using CDC guidance, describe what should happen today and over the next weeks.
2. Use the Stroke Territory Map to predict the main problems after a right MCA stroke. Then check your prediction in the sim and explain any differences.

Analyze

1. Two patients have right-sided weakness. Patient A's face and arm are weaker than her leg, and she struggles to find words. Patient B's leg is much weaker than his arm, and his speech is normal. Compare the likely blocked arteries and explain your reasoning.
2. One person has a seizure after a night without sleep and never has another. Another has three unprovoked seizures in a year. Which person meets the usual definition of epilepsy, and why?

Evaluate

1. A coach says a player who "just got their bell rung" and never blacked out can return to the championship game if they feel better after 15 minutes. Evaluate this argument using evidence from the chapter.
2. Judge this plan: "If Grandma's face droops, I'll drive her to the hospital myself because it's faster." What would you recommend instead, and why?

Create

1. Design a one-page seizure first aid poster for your school with the three key steps, two "don'ts," and when to call 911.
2. Write a 60-second public service announcement that teaches teens BE-FAST and explains "time is brain."

Key Takeaways

- A **concussion** is a mild **traumatic brain injury**; most happen without loss of consciousness.
- Remove anyone with a suspected concussion from play right away, then follow a gradual **return-to-learn and play** plan cleared by a health care provider.
- Repeated head impacts are linked to **CTE**, a tau disease that can currently be confirmed only after death.
- A **stroke** is either **ischemic** (a blocked artery, about 87% of strokes) or **hemorrhagic** (bleeding); a scan must tell them apart before **clot-busting treatment**.
- Use **BE-FAST** and call 911 immediately, because "time is brain."

- The blocked artery predicts the symptoms: ACA hits the opposite leg, MCA the opposite face and arm (plus language or attention), and PCA the opposite half of vision.
- A **seizure** is an electrical storm; **epilepsy** is a lasting tendency to have them. **Seizure first aid**: Stay, Safe, Side, nothing in the mouth, and 911 for a seizure over 5 minutes or a first seizure.

Ready for the First Five Minutes



You can now spot a concussion, a stroke, and a seizure, and you know what to do first. Next, in Chapter 15, we'll look at brain conditions you can't see on a scan: depression, anxiety, ADHD, and addiction.

Chapter 15: Psychiatric Disorders, Developmental Disorders, and Addiction

Summary

Mental illnesses are common, real, and treatable conditions that involve the brain, the body, and life experiences. This chapter surveys depression, anxiety disorders, schizophrenia, autism, and ADHD, and explains why "a chemical imbalance" is too simple a story for any of them. It then follows the brain's reward pathway to show how addictive drugs, including nicotine and opioids, change synapses through tolerance and withdrawal. The chapter ends at the bedside with an opioid overdose, the medicine that reverses it (naloxone), and the treatments and attitudes that help people recover.

Concepts Covered

1. Mental Illness
2. Depression
3. Anxiety Disorders
4. Schizophrenia
5. Autism Spectrum Disorder
6. ADHD
7. Psychiatric Medication
8. Reward Pathway
9. Addiction
10. Tolerance and Withdrawal
11. Nicotine and Vaping
12. Opioids
13. Naloxone

14. Stigma and Treatment Access

Prerequisites

- Chapter 1: Neurons, Glia, and the Nervous System
- Chapter 2: The Action Potential
- Chapter 3: Synapses and Neurotransmitters
- Chapter 4: A Tour of the Brain: Neuroanatomy
- Chapter 8: The Developing and Teenage Brain
- Chapter 9: Learning, Memory, and Neuroplasticity
- Chapter 11: Emotion, Stress, and the Body

Brains that struggle are still brains



Hi, I'm Ply, and this may be the most personal chapter in the book. Almost everyone knows someone with depression, anxiety, ADHD, autism, or a substance use problem. Here, everything you learned about synapses and learning explains these conditions with science instead of blame, and knowing how to spot an overdose could let you save a life.

15.1 Maya's Friend and the Vape

Maya is 16, plays soccer, and is studying for the Brain Bee. After practice, her friend Jordan pulls out a small, colorful vape. "It's not like smoking," Jordan says. "It just helps me relax before a test." Lately Jordan vapes before first period, between classes, and on the bus. On a weekend trip without the vape, Jordan was irritable, couldn't focus, and talked about little else.

Maya has a Brain Bee question of her own: what is nicotine doing to Jordan's brain? To answer it, we need to know how the brain decides what is worth repeating (the reward pathway), how synapses adjust to a drug that keeps flooding them (tolerance), and why stopping feels so bad (withdrawal). First, though, we'll survey the conditions psychiatrists treat, because many involve the same circuits.

If you need help now

If you or someone you know is struggling, call or text **988** (the Suicide & Crisis Lifeline in the U.S.). It is free, confidential, and available 24/7. You can also chat at 988lifeline.org.

For substance use or mental health treatment referrals, call **SAMHSA's National Helpline at 1-800-662-4357** (1-800-662-HELP). It is free, confidential, open 24/7, 365 days a year, and available in English and Spanish.

If someone may be overdosing, **call 911**.

15.2 What Is a Mental Illness?

Start with an everyday picture. Think of the brain as a sound mixing board with thousands of sliders: how alert you feel, how much you worry, how much you enjoy things. Everyone's board is set a little differently, and the settings shift with sleep, stress, and life events. Usually the board adjusts itself. Sometimes a group of sliders gets stuck far out of range for weeks or months, and studying, sleeping, or connecting with others suffers. That is closer to what a mental illness is. The picture has a limit, though: the real brain has no single slider for worry or joy. Each "setting" comes from many circuits, genes, and experiences working together.

A **mental illness** is a condition that affects a person's thinking, emotions, or behavior in a lasting way and causes real distress or makes daily life harder. The National Institute of Mental Health (NIMH) separates "any mental illness" (mild to severe) from "serious mental illness," which seriously limits major life activities. These conditions involve the brain, genes, the body, relationships, and environment. None are character flaws.

Mental illness is common. In 2025, an estimated **54.6 million U.S. adults, or 20.6%, had a mental illness** in the past year, according to the National Survey on Drug Use and Health (NSDUH). Teens are affected too. In the same survey, about **15.1% of U.S. adolescents aged 12 to 17** (3.7 million) had a major depressive episode in the past year, down from 20.8% in 2021 (SAMHSA, 2025 NSDUH). The survey changed how it estimates adult mental illness in 2025, so these adult numbers can't be compared directly with older published figures, such as the 23.1% for 2022 that NIMH still lists (NIMH).

How do doctors tell a disorder from a hard week? They look at:

- **How long** the symptoms last (for example, at least two weeks for depression)
- **How much** the symptoms disrupt school, work, relationships, or self-care
- **Whether something else** explains the symptoms better, such as a thyroid problem, a medication, or a drug

Clinicians use criteria from the *Diagnostic and Statistical Manual of Mental Disorders* to make these calls consistently. The current version is the DSM-5-TR, a text revision of the fifth edition released in 2022 (American Psychiatric Association). No single blood test or brain scan diagnoses these conditions today. Diagnosis comes from a careful interview and observation, plus tests to rule out other medical causes.

15.3 Depression and Anxiety Disorders

Depression

Everyone feels sad sometimes. **Depression** (also called major depressive disorder or clinical depression) is different. It is a mood disorder in which a person has a low or "empty" mood, or loses interest and pleasure in most activities, for **most of the day, nearly every day, for at least two weeks** (NIMH). Other common symptoms include:

- Hopelessness, guilt, or feeling worthless
- Fatigue, trouble concentrating, and changes in sleep and appetite
- Aches and pains without a clear physical cause
- Thoughts of death or suicide

Notice how many symptoms involve the body, not just mood. Sleep, appetite, and energy depend partly on the hypothalamus and the stress system from Chapter 11. NIMH describes the causes of depression as a mix of genetic, biological, environmental, and psychological factors.

Depression is treatable. Evidence-based talk therapies include **cognitive behavioral therapy (CBT)**, which helps people change unhelpful thoughts and behaviors. Antidepressant medicines usually take **about 4 to 8 weeks** to work. When other treatments haven't helped, doctors may use brain stimulation, such as electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) (NIMH).

Is depression a "chemical imbalance"?

You may have heard that depression is caused by "low serotonin." This idea, the **monoamine hypothesis**, guided drug development for decades because many antidepressants raise serotonin or norepinephrine at synapses. The full story is more complicated.

- If low serotonin were the whole cause, antidepressants should work within hours, because they raise serotonin at synapses quickly. Instead, they take weeks.
- Not everyone responds to medicines that target serotonin.
- A 2022 umbrella review in *Molecular Psychiatry* looked across many kinds of serotonin research and found **no consistent evidence that depression is caused by lowered serotonin** (Moncrieff et al., 2022). Other scientists debated some of its methods and conclusions. Most experts now describe depression as having many interacting causes rather than one missing chemical.

Still, "not caused by low serotonin" does **not** mean "antidepressants don't work" or "depression isn't real." Antidepressants help many people, possibly by changing how brain circuits adapt over weeks. One idea links long-term stress to lower levels of brain growth factors, and antidepressants to higher levels (OpenStax, 14.2). Current views treat depression as the result of many interacting biological, psychological, and social factors.

A traffic jam, not an empty tank



I like to picture depression less like a car with an empty gas tank and more like a city with a long-lasting traffic jam. Many roads, signals, and drivers are involved, so there is more than one way to help traffic flow again: medicine, therapy, sleep, exercise, and support can each open a different road.

Anxiety disorders

Anxiety is a normal alarm. Before Maya's Brain Bee competition, her heart races, a response driven by the amygdala and stress hormones from Chapter 11. **Anxiety disorders** are conditions in which fear or worry is too strong, lasts too long, shows up across many situations, and interferes with daily life. They are among the most common mental health conditions: based on large national surveys done in the early 2000s, NIMH reports that

about a third of U.S. adolescents and adults experience an anxiety disorder at some point (NIMH).

The table below compares the main types.

Anxiety disorder	Core experience	Example
Generalized anxiety disorder (GAD)	Hard-to-control worry on most days for at least 6 months, plus symptoms like restlessness, fatigue, muscle tension, or poor sleep	Constant worry about grades, family, and health, even when things are going fine
Panic disorder	Repeated, unexpected surges of intense fear with a pounding heart, shortness of breath, or dizziness	Sudden fear in class that feels like a heart attack
Social anxiety disorder	Intense fear of being judged or embarrassed in social situations	Avoiding raising a hand or eating in the cafeteria
Specific phobias	Strong fear of a specific object or situation	Fear of needles that makes a person skip doctor visits

For GAD, NIMH calls CBT the "gold standard" talk therapy. Medicines such as SSRIs and SNRIs (two antidepressant classes) can also help, though they take several weeks. Benzodiazepines act quickly, but people can develop tolerance and dependence, so doctors use them with caution and usually only briefly (NIMH).

15.4 Schizophrenia

Schizophrenia is a serious mental illness that affects how a person thinks, feels, and behaves. People are usually first diagnosed between **ages 16 and 30**, after a first episode of **psychosis**, a state in which a person loses some contact with reality (NIMH). Doctors group the symptoms into three families (NIMH):

- **Psychotic (positive) symptoms** are experiences added to normal life: **hallucinations** (hearing or seeing things others don't, often voices), **delusions** (firm beliefs that are not true, such as being watched), and disorganized thinking or speech.

- **Negative symptoms** are abilities that are reduced: less motivation, less emotional expression, less speech, and pulling away from friends. They are sometimes mistaken for depression.
- **Cognitive symptoms** are problems with attention, concentration, and memory that make school or work harder.

Schizophrenia runs in families, but no single gene causes it. Many genes each add a little risk, which may combine with life experiences such as stressful surroundings or exposures before birth. Imaging studies find subtle differences in the size of some brain areas and in their connections.

The best-known chemical clue involves **dopamine**. Most older antipsychotic medicines block dopamine D2 receptors, and they reduce hallucinations and delusions. This led to the "dopamine hypothesis": too much dopamine signaling in certain pathways may drive psychotic symptoms. Like the serotonin story for depression, this is only part of the picture. Antipsychotics help negative and cognitive symptoms much less, and newer medicines act on several receptor types (OpenStax, 14.2). In September 2024, the FDA approved xanomeline and trospium chloride (Cobenfy) for adults with schizophrenia. It is the first antipsychotic that targets acetylcholine (cholinergic) receptors instead of dopamine receptors, more evidence that dopamine is not the whole story (FDA).

Treatment works best as a team effort: antipsychotic medicine reduces psychotic symptoms, and psychosocial treatments help with daily skills, school, and work. For first-episode psychosis, **coordinated specialty care**, a team-based, recovery-focused approach that includes the person and their family, is more effective at reducing symptoms than typical care (NIMH).

Two facts fight stigma. Schizophrenia is **not** "split personality," which is a different condition (dissociative identity disorder). And most people with schizophrenia are not violent. In fact, they are more likely than people without the illness to be harmed by others (NIMH).

15.5 Developmental Differences: Autism and ADHD

Neurodevelopmental conditions begin in early brain development and shape how a person experiences the world from childhood on. The **neurodiversity** perspective points out that human brains naturally vary, and that some differences bring real strengths as well as real challenges. Supports should help people thrive, not force everyone into one mold.

A note on language: many autistic people prefer identity-first language ("autistic person"), while others prefer person-first language ("person with autism"). This chapter uses both. When you're unsure how someone describes themselves, ask, and use what they prefer.

Autism spectrum disorder

Autism spectrum disorder (ASD) is a neurological and developmental condition that affects how people communicate, interact with others, learn, and behave. It has two core features (NIMH):

1. Differences in **social communication and interaction**, such as reading facial expressions, taking turns in conversation, or understanding unwritten social rules.
2. **Restricted interests and repetitive behaviors**, such as deep focus on favorite topics, strong preference for routines, repeated movements, or being over- or under-sensitive to sounds, lights, or textures.

It is called a **spectrum** because autistic people have a wide range of characteristics, needs, strengths, and challenges. One person may speak little and need daily support; another may excel at programming but find crowded hallways exhausting. Signs usually appear in the first two years of life.

The CDC's monitoring network estimated that **about 1 in 31 (3.2%) 8-year-old children** had been identified with autism in 2022 (the latest estimate as of 2026, published in 2025), and boys were identified more than three times as often as girls (CDC).

The primary causes are not fully known. Genes play a large role, and risk factors include having an autistic sibling, older parents, certain genetic conditions, and very low birth weight. **Vaccines do not cause autism.** For example, a Danish study that followed **657,461 children** found that the measles, mumps, and rubella (MMR) vaccine did not increase autism risk, even in children with an autistic sibling (Hviid et al., 2019). The American Academy of Pediatrics says decades of large, high-quality studies have found the same thing (AAP, HealthyChildren.org).

There is no single best approach to support. Behavioral, speech-language, and occupational therapies, along with school services, work best when started early. Medicines are not used to change autism itself, but doctors sometimes prescribe them for specific problems that can come with it, such as anxiety, attention difficulties, or irritability.

ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition marked by a lasting pattern of **inattention** (trouble staying focused, organized, or on task), **hyperactivity** (restlessness, excessive movement or talking), and **impulsivity** (acting or interrupting without waiting). Some people have mostly inattentive symptoms, some mostly hyperactive-impulsive symptoms, and some have both. To count as ADHD, symptoms must begin in childhood, show up in more than one setting, and interfere with daily life (NIMH).

ADHD is real and common. An estimated **7 million U.S. children aged 3 to 17 (11.7%)** had a current ADHD diagnosis in 2024, according to a national survey of parents (CDC). Studies suggest that genes play a large role, and symptoms usually continue into the teen years and adulthood.

Recall from Chapter 8 that the **prefrontal cortex**, the brain's planning and self-control center, matures last, and attention and impulse control depend on it. Standard ADHD treatment includes behavioral strategies, parent training, school supports, CBT, and medicine. The most common medicines are **stimulants** such as methylphenidate and amphetamine. They increase dopamine and norepinephrine signaling, especially in the prefrontal cortex (OpenStax, 14.2). It may seem odd that a stimulant helps a hyperactive person, but boosting prefrontal control can make it easier to filter distractions and hold back impulses.

15.6 Psychiatric Medication: Acting at the Synapse

A **psychiatric medication** is a medicine used to treat a mental health condition by changing how brain cells signal. Most act at synapses, which you studied in Chapter 3. There are only a few basic moves a drug can make at a synapse:

- **Block reuptake**, so a neurotransmitter stays in the synapse longer (like plugging a drain)
- **Block a receptor** (an **antagonist**), so the neurotransmitter can't deliver its message
- **Activate a receptor** (an **agonist**), copying the neurotransmitter's message
- **Boost a receptor's response** to its natural messenger
- **Increase release** of a neurotransmitter

The table below matches each medication class from this chapter to its main move. These are general mechanisms only; this book never gives doses, and only a licensed clinician can decide whether a medicine is right for someone.

Medication class	Main action at the synapse	Used for (examples)
SSRIs (selective serotonin reuptake inhibitors)	Block serotonin reuptake	Depression, anxiety disorders
Benzodiazepines	Boost the response of GABA-A receptors to GABA, the brain's main "brake"	Short-term relief of severe anxiety
Antipsychotics	Block dopamine D2 receptors (newer ones also act on serotonin and other receptors)	Schizophrenia and other psychotic disorders
Stimulants (methylphenidate, amphetamine)	Increase dopamine and norepinephrine signaling	ADHD
Esketamine nasal spray	Acts on the glutamate system	Treatment-resistant depression in adults; FDA-approved in 2019 and given only in a certified clinic

Medicines are often **combined with therapy**, and for many conditions therapy alone works well. Medicines also have real side effects and warnings. For example, the FDA advises that children, teens, and young adults under 25 who start antidepressants be watched closely for new or worsening suicidal thoughts, especially early in treatment or after a dose change (NIMH). Never start, stop, or change a medicine without talking to a doctor.

15.7 The Reward Pathway

Back to Maya's question. First, an analogy. Imagine a teacher with a yellow highlighter. Every time something good or surprising happens (a goal in soccer, a tasty meal, a text

from a friend), the teacher highlights it and writes "do this again!" Later, when you see a soccer ball or smell that food, you feel a pull toward it. Your brain has its own highlighter.

That system is the **reward pathway**, a set of connected brain regions that signal when something is valuable and help you learn to seek it again. Its main messenger is **dopamine**. The main players are:

- The **ventral tegmental area (VTA)**, a small cluster of dopamine-making neurons in the midbrain
- The **nucleus accumbens (NAc)**, a region deep in the front of the brain that is central to motivation and "wanting"
- The **prefrontal cortex (PFC)**, the front of the brain, which plans, makes decisions, and can say "not now"

Dopamine neurons in the VTA send axons along two main routes. The **mesolimbic pathway** runs to the nucleus accumbens, and the **mesocortical pathway** runs to the prefrontal cortex (OpenStax, 14.3). The prefrontal cortex, in turn, sends signals to the nucleus accumbens that help control whether you act on an urge. Memory and emotion regions, such as the hippocampus and amygdala, also connect to this circuit, which is how a place or a song can become linked to a reward.

Scientists still debate exactly what dopamine "means," but it is probably not a simple "pleasure chemical." The leading ideas say dopamine signals **surprise and importance**: it rises when a reward is better than expected, and it makes reward-linked cues feel worth chasing. That is a form of learning, like the synaptic strengthening in Chapter 9.

Nearly all addictive drugs, though they act on different receptors, end up increasing dopamine signaling in the nucleus accumbens (OpenStax, 14.3). The difference from natural rewards is size and speed: drugs can produce much larger dopamine surges, which powerfully teach the brain to repeat drug use (NIDA).

15.8 Addiction, Tolerance, and Withdrawal

Addiction is a chronic, relapsing disorder in which a person compulsively seeks and uses a drug despite harmful consequences (NIDA). Doctors usually call it a **substance use disorder**. It involves lasting changes in brain circuits for reward, stress, and self-control. It is

not the same as physical dependence: a person taking a prescribed pain medicine can become dependent without being addicted.

Who develops addiction? Genes, including epigenetic effects, account for an estimated **40 to 60 percent** of a person's risk. The environment matters too: stress, trauma, family drug use, peers, and drug availability all play roles. Starting young raises risk, because the teenage brain is still building its prefrontal "brakes" (NIDA).

Tolerance: the brain turns down the volume

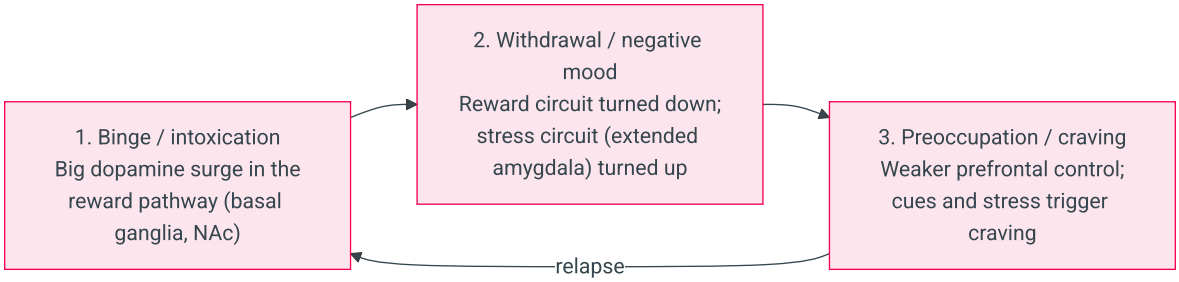
Picture living next to a train track. The first night, every train wakes you up. After a few weeks, you sleep right through it. **Tolerance** is the brain's version of this. When a drug floods synapses with dopamine again and again, neurons protect themselves by turning down the volume. They can **remove receptors** from their surface (called **downregulation**), release less dopamine, and change other signaling steps. The liver can also break the drug down faster (OpenStax, 14.4).

The result is that the same amount of drug gives a smaller effect, so the person needs more to feel the same high, or even just to feel normal. Because the reward circuit has become less responsive, everyday pleasures like food, friends, or music also feel less rewarding (NIDA).

Withdrawal: the volume is down and the music stops

Withdrawal is the set of unpleasant symptoms that appear when a person who has developed dependence stops or cuts back on the drug. The brain has adjusted to the drug's constant presence, so taking it away leaves the system below its normal set point. Stress systems, especially in a region called the **extended amygdala**, become overactive and produce anxiety, irritability, and unease (NIDA). Physical withdrawal often fades over about a week, but psychological symptoms such as low mood and anxiety, and cravings triggered by cues, can last much longer (OpenStax, 14.4).

Researchers describe addiction as a repeating three-stage cycle, each stage linked to different brain regions. The flowchart below summarizes it.



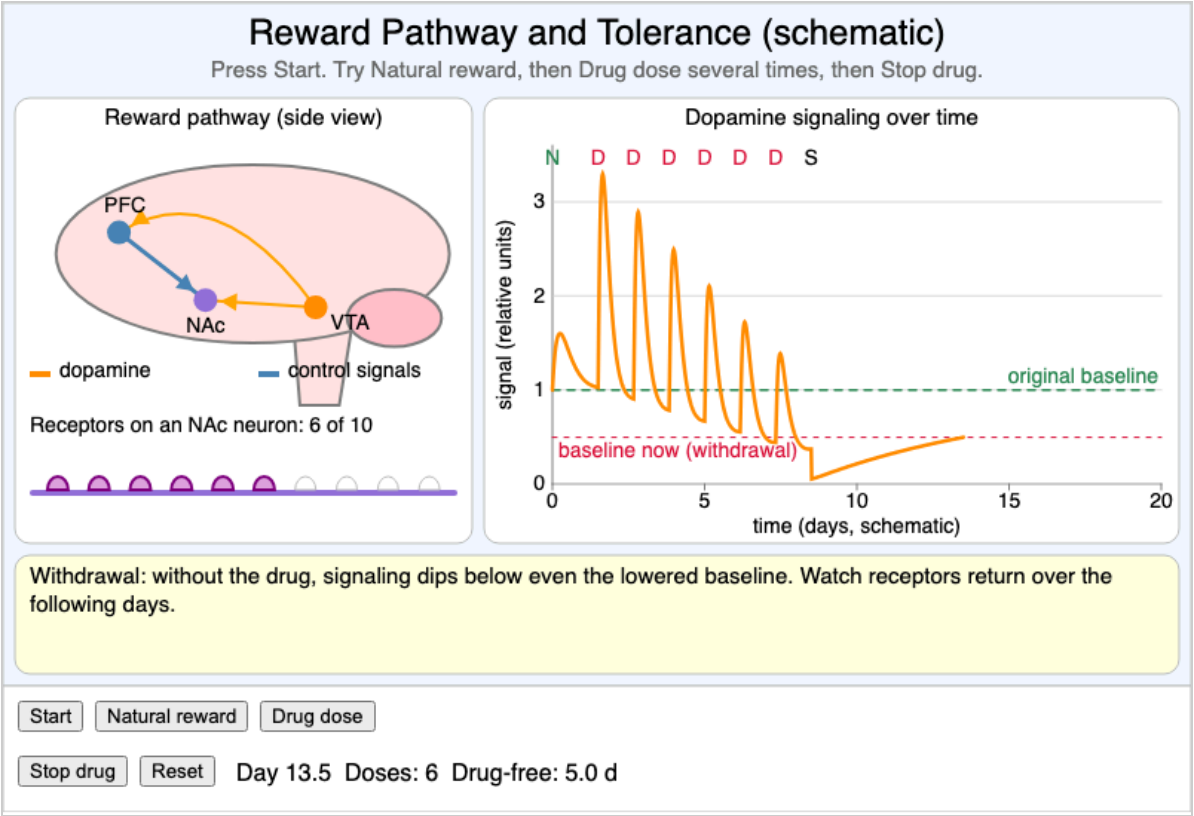
This cycle helps explain why "just stop" is hard advice to follow: each stage pushes toward the next. Each stage is also a treatment target. Medicines can blunt a drug's effect, ease withdrawal, or reduce craving, and therapy can strengthen self-control and weaken responses to cues.

Tolerance looks a bit like habituation



In Chapter 9, you saw my gill-withdrawal reflex shrink when I was touched over and over. Tolerance looks similar on the surface, because a repeated stimulus gives a smaller response, but it involves different molecules and much longer-lasting changes in the reward circuit.

Diagram: Reward Pathway and Tolerance



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch15-reward-tolerance/

Open the Reward Pathway and Tolerance fullscreen

MicroSim specification: Reward Pathway and Tolerance

Type: microsim **sim-id:** ch15-reward-tolerance
Library: p5.js
Status: Implemented
Bloom Level: Understand
Bloom Verb: explain
Learning Objective: The learner will explain how repeated drug doses produce tolerance (smaller dopamine responses and a lower baseline from receptor downregulation) and how stopping produces a below-baseline withdrawal dip that recovers over days.

Canvas: drawing area 460 px plus control area 85 px (iframe 547 px); width-responsive.

Controls: Start/Pause, Natural reward, Drug dose, Stop drug, Reset. Starts paused; pressing Natural reward, Drug dose, or Stop drug also starts the clock.

Behavior: Left panel: a side view of the brain with the VTA sending dopamine to the nucleus accumbens (NAc) and prefrontal cortex (PFC), the PFC sending control signals to the NAc, and a row of 10 receptor icons on an NAc neuron. Right panel: dopamine signaling (relative units, original baseline = 1) over a scrolling 20-day window. Natural reward adds a bump of 0.6 times receptor availability; Drug dose adds a faster spike of 2.4 times receptor availability and removes 0.12 of receptor availability (floor 0.35). Stop drug adds a withdrawal dip equal to 0.5 times the receptors lost; the dip fades and receptors recover toward normal over about 20 to 30 simulated days. A message box explains each stage. All values are schematic, not measurements of any real drug.

Try this in order. Press **Start**, then **Natural reward**, and watch the small bump. Press **Drug dose** once and compare the spike. Then give five or six more doses, a second or two apart. Watch three things change at once: each spike gets shorter, the trace between spikes settles below the green "original baseline," and receptor icons disappear. That is tolerance.

Now press **Natural reward** again. The bump is smaller than before, because fewer receptors receive the signal. Finally, press **Stop drug**. The signal drops below even the lowered baseline (withdrawal), then climbs back slowly over the following "days" as receptors return. Recovery is real but slow, which is one reason support during early recovery matters. The sim does not show learned, cue-driven craving, which can outlast these receptor changes.

15.9 Nicotine and Vaping in the Teenage Brain

Now we can answer Maya's question. **Nicotine** is the addictive chemical in tobacco, and most e-cigarettes ("vapes") contain it. Nicotine fits into a type of acetylcholine receptor that

is actually named after it, the **nicotinic acetylcholine receptor**. Activating these receptors leads to dopamine release in the reward pathway (Wikipedia: Nicotinic acetylcholine receptor). When nicotine is inhaled in cigarette smoke, levels peak within about **10 seconds** (NIDA), and fast arrival plus a dopamine boost is a strong recipe for learning to repeat a behavior.

Vaping has declined in recent years but is still common. In the **2025 National Youth Tobacco Survey**, about **1.44 million middle and high school students (5.2%)** reported currently using e-cigarettes, down from 5.9% in 2024. That included **7.1% of high school students**. Among students who vaped, **89.4%** used flavored products and **27.5%** vaped every day (FDA).

Why does it matter more for teens? According to the CDC, brain development continues until about **age 25**, and nicotine during adolescence can harm parts of the brain that control attention, learning, mood, and impulse control. Teens can show signs of nicotine addiction quickly, sometimes before they vape regularly, and adolescents who use nicotine may be at higher risk for addiction to other drugs later (CDC).

When a person dependent on nicotine stops, withdrawal can bring irritability, restlessness, anxiety, low mood, trouble sleeping or concentrating, hunger, and cravings. That matches what Maya saw in Jordan on the weekend trip. These symptoms are temporary and fade as the brain readjusts. Free help designed for teens is available at teen.smokefree.gov, a National Cancer Institute site with a text-message quit program, and the free quitline 1-800-QUIT-NOW offers coaching by phone.

15.10 Opioids and Naloxone

How opioids work

Opioids are drugs that act on the body's opioid receptors. Some are prescription pain medicines (such as morphine and oxycodone), some are illegal (heroin), and **fentanyl** is a synthetic opioid used in medicine but also made illegally. Your body makes its own opioid-like molecules, such as endorphins, that help control pain. Opioid drugs act on the same receptors, especially the **mu-opioid receptor**.

Opioid receptors sit in pain pathways, the reward pathway, and **brainstem regions that control breathing** (the medulla and pons). That last location is what makes opioids deadly: too much opioid slows breathing until the brain and heart are starved of oxygen. Fentanyl is

especially dangerous. The CDC describes it as up to **50 times stronger than heroin and 100 times stronger than morphine** (CDC). Some counterfeit pills made to look like prescription medicines contain fentanyl, and people taking them often don't know it (NIDA).

Overdose deaths have fallen but remain high. In 2024, there were **79,384 drug overdose deaths** in the United States, and **54,045** involved an opioid. The overdose death rate fell **26.2%** from 2023 to 2024 (CDC NCHS Data Brief 549). Early numbers for 2025 show a third straight year of decline: CDC estimated about **69,973 overdose deaths in 2025**, about 44,564 of them involving opioids. These 2025 figures are provisional, which means they may change as more death records come in (CDC NCHS, May 2026).

Recognizing an overdose

The CDC lists these signs of an opioid overdose (CDC):

- Unconsciousness, or the person can't be woken up
- Slow or shallow breathing, or choking, gurgling, or snoring sounds
- Discolored skin, especially the lips and nails
- Small, constricted **"pinpoint pupils"** that don't react to light

Doctors remember the classic combination of **decreased consciousness, pinpoint pupils, and slowed breathing**.

Naloxone: the antidote

Naloxone is a medicine that rapidly reverses an opioid overdose. It is an opioid **antagonist**: it attaches to opioid receptors, displaces the opioid, and blocks its effects. Breathing can recover within minutes. It comes as a nasal spray or an injection, and anyone can give it without medical training. In **March 2023**, the FDA approved **Narcan nasal spray for over-the-counter use**, making it the first naloxone product available without a prescription (FDA). The FDA has since approved other over-the-counter naloxone nasal sprays, most recently in June 2026 (FDA). A related antidote, nalmefene nasal spray, was approved by prescription later in 2023.

Every reader should know these facts (NIDA):

1. Naloxone has **no effect on a person with no opioids in their body**, so giving it when you aren't sure is generally safe.
2. It does **not** reverse overdoses from non-opioid drugs such as cocaine or methamphetamine.
3. It works for only about **30 to 90 minutes**, but many opioids last longer. The person can stop breathing again after naloxone wears off, so **emergency care is still needed**.
4. Strong opioids like fentanyl may need **more than one dose**.
5. A person who is dependent on opioids may go into **withdrawal** within minutes of naloxone. This is very unpleasant but usually not life-threatening.

Naloxone is not the end of the emergency



If you suspect an overdose, give naloxone if you have it **and call 911**. Stay with the person, try to keep them breathing, and lay them on their side, because naloxone can wear off before the opioid does.

Treating opioid use disorder

Naloxone saves a life in the moment but does not treat addiction. **Opioid use disorder** is a chronic, treatable condition with effective, FDA-approved medicines (NIDA):

- **Methadone** activates mu-opioid receptors slowly and lasts a long time, so it reduces cravings and withdrawal without an intense high. For opioid use disorder, it is given through approved opioid treatment programs.
- **Buprenorphine** partly activates mu-opioid receptors and also blocks other opioids from attaching. Since 2023, any clinician whose DEA registration allows prescribing this class of controlled medicine (Schedule III) can prescribe it for opioid use disorder, if state law allows (SAMHSA).
- **Naltrexone** only blocks opioid receptors, so opioids can no longer produce a high. It is usually started after a person has fully stopped opioids.

These medicines reduce the risk of overdose death, yet NIDA reports that **fewer than 1 in 5** people with opioid use disorder are treated with them. The 2025 national survey agrees: of about 4.0 million people aged 12 or older with opioid use disorder, only **15.7%** received one

of these medicines in the past year (SAMHSA, 2025 NSDUH). Taking a prescribed medicine for opioid use disorder is treatment, not "trading one addiction for another," much as taking a daily medicine for any other chronic illness is treatment.

15.11 Stigma and Treatment Access

Stigma means negative attitudes, stereotypes, and discrimination aimed at people because of a condition. **Treatment access** means whether people can actually get care, which depends on cost, insurance, location, wait times, and whether they feel safe asking. The two are linked. NIDA notes that feeling stigmatized can make people with substance use disorders less willing to seek treatment (NIDA). In mental health more broadly, only about **half (50.9%) of U.S. adults with a mental illness** received mental health treatment in the past year in 2025 (SAMHSA, 2025 NSDUH).

Words matter. Labeling a whole person by their illness can make them sound hopeless or blameworthy. The table below shows swaps recommended by NIDA, plus one for mental illness.

Instead of...	Say...	Why
"addict," "junkie," "abuser"	"person with a substance use disorder"	Puts the person first, not the condition
"clean" / "dirty" (drug test)	"tested negative" / "tested positive"	Medical terms, no moral judgment
"former addict"	"person in recovery"	Recognizes recovery as ongoing
"a habit"	"substance use disorder"	"Habit" implies a person can simply choose to stop
"replacement therapy"	"medication for opioid use disorder"	Treatment, not a substitute drug
"schizophrenic," "crazy," "psycho"	"person with schizophrenia" or "person with a mental illness"	Avoids slurs and stereotypes

Recovery is common, not a rare miracle. Relapse happens too, as it does in other chronic illnesses. NIDA estimates relapse rates of **40 to 60%** for substance use disorders, compared with **50 to 70%** for hypertension and asthma. Relapse means treatment may need to be restarted or adjusted, not that it failed (NIDA).

Asking for help is a brain skill



This chapter covers heavy topics, and it's okay if some of it hit close to home. Reaching out to a trusted adult, a doctor, or 988 uses your prefrontal cortex exactly the way it is meant to be used: planning a way forward.

At the Bedside: An Overdose at a Dorm Party

Meet the patient

Sam is a 19-year-old college student. At a party, Sam took a pill a friend said was a prescription pain reliever. Later, Sam's roommate found Sam slumped on a couch, unable to be woken, making slow, snoring breaths, with bluish lips. The roommate gave one spray of naloxone from the campus health center and called 911. Within minutes, Sam began breathing faster, woke up confused, and started sweating, shaking, and vomiting.

What the doctor checks: In the emergency department, the doctor checks Sam's airway, breathing rate, and blood oxygen level. The roommate reports that Sam's pupils were tiny before the naloxone. The team checks blood sugar and other causes of unresponsiveness, asks what Sam took, and watches for breathing to slow again as the naloxone wears off. A urine drug screen may be sent, but the standard opiate screen often misses fentanyl unless a fentanyl-specific test is ordered, so the doctor relies mainly on the clinical picture.

Where is the problem? (localization): Slow breathing localizes to the **brainstem breathing centers** in the medulla and pons, and decreased consciousness reflects depressed brain arousal. Together with pinpoint pupils, these form the classic opioid triad. The fast response to naloxone, an opioid receptor blocker, confirms that opioid receptors were involved.

Diagnosis: Opioid overdose, most likely from a counterfeit pill containing fentanyl.

Why it happens: Fentanyl strongly activates mu-opioid receptors. In the brainstem, this weakens the drive to breathe, so oxygen falls. Naloxone displaced fentanyl from the receptors, so breathing returned. Sam's sweating and vomiting suggest withdrawal, which hints that Sam's brain may already have adapted to regular opioid use (tolerance and dependence, Section 15.8).

Treatment today: Emergency teams support breathing, give more naloxone if needed, and keep watching the patient (NIDA advises monitoring for another 2 hours after the last naloxone dose), because naloxone can wear off before fentanyl does. If the patient has opioid use disorder, the team can start a medication such as buprenorphine and connect the person to ongoing treatment, and can encourage the patient and family to keep naloxone on hand.

What's new in research: Starting treatment in the emergency department works. In a randomized trial of 329 patients with opioid dependence, **78%** of those started on buprenorphine in the emergency department were engaged in addiction treatment 30 days later, compared with **37%** of those given a referral alone (D'Onofrio et al., *JAMA*, 2015). Access has also widened. In late 2022, Congress removed the special federal "X-waiver" that clinicians once needed to prescribe buprenorphine for opioid use disorder (SAMHSA), and naloxone nasal spray became available over the counter in 2023.

Your turn: diagnose a variation

Riley is 16. Riley started vaping a year ago "just at parties," but now vapes first thing every morning, can't get through first period without feeling irritable and restless, and has trouble sleeping and concentrating whenever the vape runs out. Riley has tried to stop twice and gave up after a day. Riley is fully awake, breathing normally, and has normal-sized pupils. What is going on, and what would help?

Answer: This is **nicotine dependence** from vaping, not an overdose. Riley shows tolerance (vaping more often), withdrawal (irritability, restlessness, poor sleep and focus), and failed quit attempts, all signs that the reward pathway has adapted to nicotine. Naloxone would do nothing, because nicotine does not act on opioid receptors. Helpful steps include talking with a doctor or school nurse, counseling, and teen quit programs such as the text program at teen.smokefree.gov. Withdrawal symptoms are temporary.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: Addiction is just a lack of willpower.
Reality: Addiction involves measurable changes in the brain's reward, stress, and self-control circuits, and genes account for an estimated 40 to 60% of the risk. Repeated drug use weakens the very prefrontal "brakes" a person needs to choose differently, which is why medicines and therapy help.

Myth: Mental illness is rare.
Reality: About 20.6% of U.S. adults (one in five) had a mental illness in 2025, and about a third of teens and adults experience an anxiety disorder at some point. You almost certainly know someone affected.

Myth: ADHD isn't real; it's just kids being lazy or hyper.
Reality: ADHD is a well-studied neurodevelopmental condition with a strong genetic component. It affects attention, activity, and impulse control in multiple settings and often continues into adulthood. Effective treatments exist.

Myth: Depression is simply a "chemical imbalance" of low serotonin.
Reality: Large reviews have not found consistent evidence that low serotonin causes depression. Depression arises from many interacting biological, psychological, and social factors. Antidepressants and therapy still help many people.

Myth: People with schizophrenia have a "split personality" and are dangerous.
Reality: Schizophrenia involves psychosis, not multiple personalities. Most people with schizophrenia are not violent, and they are more likely than people without the illness to be harmed by others.

Brain Bee Practice

1. Name the midbrain region where the dopamine neurons of the reward pathway begin, and one region they project to.

The ventral tegmental area (VTA). Its dopamine neurons project to the nucleus accumbens (mesolimbic pathway) and to the prefrontal cortex (mesocortical pathway).

2. A patient is unresponsive with pinpoint pupils and a breathing rate of 6 breaths per minute. What drug class is most likely involved, and what is the antidote?

Opioids. The antidote is naloxone, an opioid receptor antagonist that displaces opioids from their receptors and restores breathing.

3. What is the difference between tolerance and withdrawal?

Tolerance is a reduced response to the same amount of a drug after repeated use, for example from receptor downregulation. Withdrawal is the set of symptoms, often opposite to the drug's effects, that appears when a person who has adapted to the drug stops taking it.

4. Which receptor does nicotine activate, and how does that lead to reinforcement?

Nicotine activates nicotinic acetylcholine receptors. This leads to dopamine release in the reward pathway, which reinforces (teaches the brain to repeat) nicotine use.

5. Name the three symptom groups of schizophrenia and give one example of each.

Psychotic or positive symptoms (hallucinations, delusions), negative symptoms (reduced motivation or emotional expression), and cognitive symptoms (trouble with attention or memory).

Exercises

Remember

1. List the three FDA-approved medications for opioid use disorder discussed in this chapter.
2. State the two core features of autism spectrum disorder.

Answer

1. Methadone, buprenorphine, and naltrexone.
2. Differences in social communication and interaction, and restricted interests and repetitive behaviors.

Understand

1. Explain why naloxone is generally safe to give to an unresponsive person even when you aren't sure they took opioids.
2. Explain in your own words why antidepressants taking several weeks to work is evidence against a simple "low serotonin" theory of depression.

Answer

1. Naloxone only blocks opioid receptors. If no opioids are present, there is nothing for it to reverse, so it has no effect. If opioids are present, it may save the person's life.
2. Antidepressants raise serotonin at synapses within hours. If low serotonin were the whole cause, mood should improve just as fast. The delay suggests that slower changes in brain circuits, not the serotonin level itself, drive recovery.

Apply

1. In the Reward Pathway and Tolerance MicroSim, give six drug doses, then press Natural reward. Compare the bump with the one at the start, and use the receptor icons to explain the difference.
2. A classmate faints at a party but is breathing normally and has normal pupils. Someone wants to give naloxone. What should you do first, and is naloxone likely to help?

Analyze

1. Compare how nicotine and opioids each lead to dopamine release in the reward pathway, and explain why only opioids commonly cause deaths from stopped breathing.

2. Two students vaped for a year. One quit easily; the other could not. Analyze how genes, environment, and brain development could explain the difference.

Evaluate

1. A website claims, "Medications for opioid use disorder just replace one drug with another." Evaluate this claim using evidence from this chapter.
2. Should your school stock naloxone nasal spray and teach students to use it? Weigh benefits and risks, and recommend a decision.

Create

1. Design a 30-second teen public service announcement about vaping that is accurate, avoids scare tactics, and uses two facts from this chapter.
2. Write a short fictional case of a teen with depression, an anxiety disorder, ADHD, or autism. Include what the family notices, what a doctor would ask, and respectful language throughout.

Key Takeaways

- Mental illnesses are common, real, and treatable; they involve the brain, genes, the body, and life experiences, not personal weakness.
- Depression, anxiety disorders, and schizophrenia are each more complex than a single "chemical imbalance," and treatment often combines therapy, medicine, and support.
- Autism and ADHD are neurodevelopmental conditions that begin early in life; a neurodiversity view pairs real supports with respect for different kinds of minds.
- The reward pathway (VTA to nucleus accumbens and prefrontal cortex) uses dopamine to mark what is worth repeating, and addictive drugs hijack it with unusually large dopamine surges.
- Repeated drug use causes tolerance (fewer receptors, smaller responses, lower baseline), and stopping causes withdrawal; recovery of these changes takes time.
- Opioids can stop breathing by acting on the brainstem; naloxone reverses an overdose, but always call 911, and medications for opioid use disorder save lives.

- Stigma keeps people from care. Use person-first, non-judgmental language, and know the numbers: **988** for crisis support and **1-800-662-4357** for SAMHSA's National Helpline.

You made it through a big one!



You can now trace mood, attention, and addiction back to synapses and circuits, and you know how to help in an overdose. Next, in Chapter 16, we put on the white coat and learn how doctors examine the brain, from the neurological exam to MRI.

Chapter 16: How Doctors Examine the Brain

Summary

This capstone chapter puts you in the doctor's chair. You'll learn how a neurologist listens to a patient's story, runs the neurological exam from mental status to gait, and uses the findings to answer the most important question in neurology: *where is the problem?* Then you'll compare the tools that look inside the head (CT, MRI, fMRI, PET, and EEG), learn when a lumbar puncture helps, and see how doctors build a differential diagnosis. Finally, you'll follow one fictional patient from the ambulance to a diagnosis, using ideas from every earlier chapter.

Concepts Covered

1. Neurological Exam
2. Mental Status Exam
3. Cranial Nerve Exam
4. Reflex Testing
5. Lesion Localization
6. Computed Tomography (CT)
7. Magnetic Resonance Imaging
8. Functional MRI
9. PET Scan
10. Lumbar Puncture
11. Differential Diagnosis

Prerequisites

This chapter draws on the whole book. The most important earlier chapters are:

- Chapter 1: Neurons, Glia, and the Nervous System (myelin, motor neurons, multiple sclerosis)
- Chapter 4: A Tour of the Brain (lobes, brainstem, spinal cord, cranial nerves, meninges, cerebrospinal fluid)
- Chapter 6: Hearing, Touch, Taste, Smell, and Pain (dermatomes)
- Chapter 7: Movement (reflex arcs, the corticospinal tract, upper vs lower motor neurons, the cerebellum)
- Chapter 10: Sleep and Brain States (the EEG)
- Chapter 12: Language, Attention, and Decision-Making (aphasia and neglect)
- Chapter 14: Brain Injury, Stroke, and Epilepsy (stroke, BE-FAST, clot-busting treatment, seizures)

You're the doctor now



I'm Ply, and I've been with you since your first neuron. In this last chapter, everything you've learned turns into a skill: figuring out what's wrong with a real nervous system using your questions, your hands, and a few clever machines. This is how neurologists think, and it's exactly what the patient-diagnosis round of the Brain Bee tests.

16.1 You're the Doctor Now

Maya, 16, has made it to her regional Brain Bee after months of studying between soccer practices. The round she fears most is patient diagnosis. On the screen, a man walks with a stiff, swinging leg, and a short written history sits beside the video. In the International Brain Bee format, students watch patient videos, read a written history, and pick three diagnostic tests before naming a diagnosis (International Brain Bee; rules change, so check your own competition's).

Maya knows dozens of diseases. But the real question isn't "Which disease do I remember?" It's "Where in the nervous system is this coming from?" Now imagine you're a doctor in an emergency room. A patient arrives with weakness on one side of the body. What do you do first? Order a scan? Grab a reflex hammer? This chapter answers that question step by step.

16.2 Where Before What: The Detective's Rule

Before any vocabulary, picture an electrician called to an apartment building with a power problem.

- If **one lamp** in one room is dark, the problem is probably that lamp's bulb or cord.
- If **every outlet on the left side of the 5th floor** is dead, the problem is in that floor's left-side circuit panel.
- If **every floor below the 3rd floor** is dark, the problem is in the main cable that runs down through the building, at about the 3rd floor.

The electrician first asks **where** the fault must be to explain the *pattern* of what's broken. Only then does she ask **what** broke: a blown fuse, a chewed wire, water damage.

Neurologists work the same way. The nervous system is wired in a very orderly way (Chapter 4, Chapter 7), so the pattern of symptoms points to a location. This skill is called **lesion localization**: using symptoms and exam findings to figure out where in the nervous system the damage (the *lesion*) must be. A lesion is any area of damaged or abnormal tissue, from a stroke, tumor, infection, or injury. Once the "where" is clear, the doctor asks "what," building a list of possible causes called the differential diagnosis (Section 16.8).

Where, then what



Here's the big idea of this whole chapter: localize first, then name the disease. A blocked artery and a tumor can sit in the same spot and cause the same signs. The *pattern* tells you where; the *timing* and tests tell you what.

16.3 The History: Listening to the Patient's Story

The first tool a neurologist uses isn't a machine. It's a conversation. The **history** is the patient's story: what happened, when it started, how it changed, and what else is going on in their health. The exam begins during the history, because the doctor is already watching how the patient talks, moves, and walks (Merck Manual). A good history answers a few questions:

- **What exactly is the problem?** "Weak" might mean loss of strength, clumsiness, numbness, or tiredness.
- **When did it start, and how fast?** This is often the best clue to *what* the lesion is.
- **Is it getting better, worse, or staying the same?**
- **What else is going on?** Headache, fever, a recent seizure, past strokes, medicines, or family history.

Timing tells a story

How fast symptoms appear hints at their cause. The table below summarizes a common rule of thumb. It's a guide, not a law.

How symptoms began	Often suggests	Example from this book
Seconds to minutes	A blood vessel problem or a seizure	Stroke (Chapter 14)
Hours to days	Infection or inflammation	Meningitis; a multiple sclerosis flare (Chapter 1)
Weeks to months	Something growing or pressing	A tumor pressing on a nerve or the spinal cord
Months to years	Slow nerve-cell loss (neurodegeneration)	Alzheimer's or Parkinson's disease (Chapters 7 and 13)

For a suspected stroke, the key question is *when was the patient last known to be normal?* Clot-busting treatment only helps within a limited time window, so doctors ask right away (NINDS).

16.4 The Neurological Exam: A Head-to-Toe Tour

The **neurological exam** is a set of hands-on tests that checks each major part of the nervous system: thinking, cranial nerves, movement, reflexes, feeling, coordination, and

walking. Its purpose is to decide whether the nervous system works normally and, if not, to connect each abnormal finding to a structure (Merck Manual). The basics take only a few minutes. Here's a map of the tour; we'll visit each stop below.

Part of the exam	What it checks	Example test
Mental status	Alertness, orientation, attention, memory, language	"What's today's date? Where are we?"
Cranial nerves	The 12 nerves of the head and face	Follow my finger with your eyes
Motor	Muscle bulk, tone, strength	Push against my hand
Reflexes	Stretch reflexes and the plantar (sole) response	Tap the knee with a reflex hammer
Sensation	Touch, pain, temperature, vibration, position sense	Is this sharp or dull?
Coordination	Smooth, accurate movement (cerebellum and its connections)	Touch your nose, then my finger
Gait	Walking and balance	Walk heel-to-toe in a straight line

Mental status: is the "boss" online?

The **mental status exam** checks the brain's highest functions. The doctor first notes the level of consciousness (alert, drowsy, or hard to wake), then checks (Merck Manual):

- **Orientation:** Does the patient know who they are, where they are, and the date?
- **Attention:** Can they spell a word forward and backward?
- **Memory:** Can they remember three words after a few minutes? Do they recall recent events?

- **Language:** Can they speak fluently, understand commands, name objects, and repeat a sentence?
- **Other abilities:** calculation, judgment, mood, and copying a drawing.

These findings are powerful localizing clues. Trouble with language or calculation points to the dominant hemisphere, the left one in most people (recall the aphasias from Chapter 12). Ignoring one side of space (neglect) usually points to the right hemisphere. Screening tests such as the Mini-Mental State Examination and the Montreal Cognitive Assessment (MoCA) score these abilities, for example when checking for Alzheimer's disease.

The cranial nerve exam: twelve nerves, quick checks

You met the 12 **cranial nerves** in Chapter 4. They leave the brain and brainstem directly, not through the spinal cord. The **cranial nerve exam** tests each one with a quick task. Because most of them start in the brainstem, an abnormal finding hints that the problem is in the brainstem or in that nerve. The table summarizes the bedside tests (Merck Manual).

Nerve	Main job	Quick bedside test
I (olfactory)	Smell	Identify a familiar smell, one nostril at a time
II (optic)	Vision	Read an eye chart; check side vision; shine a light in the pupils
III, IV, VI (oculomotor, trochlear, abducens)	Eye movements, eyelid, pupil size	Follow a finger in all directions; look for a droopy lid
V (trigeminal)	Feeling in the face; chewing muscles	Light touch and pinprick on the face; clench the jaw
VII (facial)	Facial expression; taste on the front of the tongue	Raise eyebrows, close eyes tight, smile
VIII (vestibulocochlear)	Hearing and balance	Whisper a word; look for jerky eye movements (nystagmus)

Nerve	Main job	Quick bedside test
IX, X (glossopharyngeal, vagus)	Swallowing, voice, gag	Say "ah" and watch the palate rise
XI (accessory)	Neck and shoulder muscles	Shrug the shoulders and turn the head against resistance
XII (hypoglossal)	Tongue movement	Stick out the tongue; a weak side makes it point toward that side

One finding deserves a spotlight: the **forehead rule**. When a stroke in the cortex weakens the face, the lower face droops but the forehead still wrinkles. When the facial nerve itself (cranial nerve VII) is damaged, the *whole* half of the face is weak, forehead included (Merck Manual). Why? The nerve cells for the forehead get signals from *both* hemispheres, while those for the lower face get signals mainly from the *opposite* one (Wikipedia: Central facial palsy). If one hemisphere is damaged, the other still runs the forehead. If the nerve is cut off, nothing gets through.

Check the forehead



Whenever you see a droopy face, ask the patient to raise their eyebrows. A forehead that still wrinkles points to the brain (a central pattern). A forehead that stays flat points to the facial nerve (a peripheral pattern).

The motor exam: strength, bulk, and tone

The motor exam starts by looking. Are any muscles wasted (shrunken)? Are there **fasciculations**, tiny twitches under the skin? Then the doctor checks **tone**, the resistance a relaxed limb gives when moved, and tests **strength** muscle by muscle, comparing sides. Strength is graded 0 to 5 on the UK Medical Research Council scale (Merck Manual):

Grade	What the doctor sees
0	No muscle contraction at all
1	A flicker of contraction, but no real movement
2	Movement only when gravity is taken away (for example, sliding the arm across a bed)
3	Movement against gravity, but not against the examiner's push
4	Movement against some resistance
5	Full, normal strength

A sensitive test for mild arm weakness is **pronator drift**: with both arms held straight out, palms up, eyes closed, a weak arm slowly drifts down and turns inward.

Reflex testing: the knee-jerk and its cousins

In Chapter 7 you learned that tapping a tendon stretches the muscle, and a quick loop through the spinal cord makes it contract: the stretch reflex. **Reflex testing** means triggering these reflexes with a rubber hammer, grading the response, and checking the sole of the foot for an abnormal toe response. Reflexes are graded 0 to 4+ (Wikipedia: Stretch reflex):

Grade	Response	Meaning
0	No response	Always abnormal
1+	Slight but present	May or may not be normal
2+	Brisk, ordinary response	Normal
3+	Very brisk	May or may not be normal

Grade	Response	Meaning
4+	Clonus (repeated rhythmic beats)	Always abnormal

Each reflex tests particular spinal cord segments, so reflexes form a built-in map of the cord: biceps (C5 and C6), triceps (C7), knee jerk (mainly L3 and L4), and ankle jerk (S1) (Merck Manual; Wikipedia: Patellar reflex). C, L, and S mean cervical (neck), lumbar (lower back), and sacral (base of the spine).

The most famous reflex test isn't a tendon tap. When the doctor strokes the outer sole, a healthy adult's big toe curls *down*. If it goes *up* and the other toes fan out, that's the **Babinski sign**, described by the French neurologist Joseph Babinski in 1896 (Wikipedia: Babinski sign). In adults, it means damage along the corticospinal tract, the main motor pathway from cortex to spinal cord. In babies, an upgoing toe is normal; it usually switches to downgoing by about 12 months.

Why would damage *above* the spinal cord make reflexes *stronger*? The brain normally sends calming signals down to the reflex loops. Cut that brake, and the reflexes run hot. So brisk reflexes, sustained clonus, and a Babinski sign all signal upper motor neuron damage (Merck Manual).

The sensory exam: mapping what the patient feels

The sensory exam checks light touch, pinprick (sharp versus dull), temperature, vibration (with a tuning fork), and **position sense**, the ability to tell which way a toe is being moved with eyes closed. These feelings travel up the cord in different pathways, so the pattern of loss is another clue.

The doctor also maps the edge of any numb area. Recall **dermatomes** from Chapter 6: each spinal nerve supplies a band of skin. Two landmarks: the nipple line is about T4, and the belly button is about T10 (Wikipedia: Dermatome). Numbness below a horizontal line on *both* sides is called a **sensory level**, a classic sign of spinal cord damage at or above that level.

In the **Romberg test**, the patient stands with feet together, eyes open, then closed. Falling once the eyes close is a positive test: the patient was using vision to make up for lost

position sense, often from damage to the spinal cord's dorsal columns or the sensory nerves. It is not a test of the cerebellum (Wikipedia: Romberg's test).

Coordination and gait: the cerebellum's report card

In **finger-to-nose**, the patient touches their nose, then the doctor's finger, back and forth. In **heel-to-shin**, they slide one heel down the other shin. A side-to-side wobble as the hand moves (an intention tremor) suggests a problem in the cerebellum, which you met in Chapter 7. But weakness can also spoil these tests, so they're read alongside strength (Merck Manual).

Walking tests almost everything at once. A wide, unsteady gait suggests cerebellar trouble. A stiff gait with scraping toes suggests upper motor neuron damage to the legs. Small, shuffling steps suggest Parkinson's disease (NINDS).

So many tests!



That's a lot of hammers and tuning forks, I know. For now, just remember the seven stops from the top down: mental status, cranial nerves, motor, reflexes, sensation, coordination, gait.

16.5 Lesion Localization: Putting the Clues Together

Now comes the detective work. Neurologists localize by asking three questions in order:

1. **Is it the central or the peripheral nervous system?** (Upper or lower motor neuron?)
2. **Which side?**
3. **What level?** (Cortex, brainstem, spinal cord, nerve, or muscle?)

Question 1: Upper or lower motor neuron?

Recall from Chapter 7 that movement uses a two-neuron chain. An **upper motor neuron** runs from the motor cortex down the corticospinal tract. A **lower motor neuron** runs from the brainstem or spinal cord out through a nerve to the muscle. Damage to each causes

weakness with a different signature (Wikipedia: UMN lesion; Wikipedia: LMN lesion; Merck Manual). The table compares the signs you just learned to test.

Finding	Upper motor neuron lesion (brain or spinal cord)	Lower motor neuron lesion (nerve root or nerve)
Tone	Increased (spastic)	Decreased (floppy, or flaccid)
Reflexes	Brisk (hyperreflexia), sometimes clonus	Reduced or absent
Babinski sign	Present (big toe goes up)	Absent
Muscle wasting	Little, at least early on	Often marked over time
Fasciculations	Absent	Often present
Facial weakness	Lower face only (forehead spared)	Whole half of the face

Real patients don't always match the table. ALS (Chapter 13) damages both kinds of motor neuron and mixes the two sets of signs. So doctors use the whole pattern, never one sign alone.

Question 2: Which side?

About 90% of the fibers in the corticospinal tract cross to the other side at the bottom of the medulla, in a spot called the pyramidal decussation (Wikipedia: Pyramidal decussation). This crossing creates the most useful rule in localization:

- A lesion **above** the crossing (cortex, deep white matter, most of the brainstem) causes weakness on the **opposite** side of the body.
- A lesion **below** the crossing (spinal cord) causes weakness on the **same** side, below the level of the lesion.

So right-sided weakness plus language trouble shouts "left hemisphere." Most cranial nerves, though, don't cross before reaching their muscles. That creates a famous brainstem

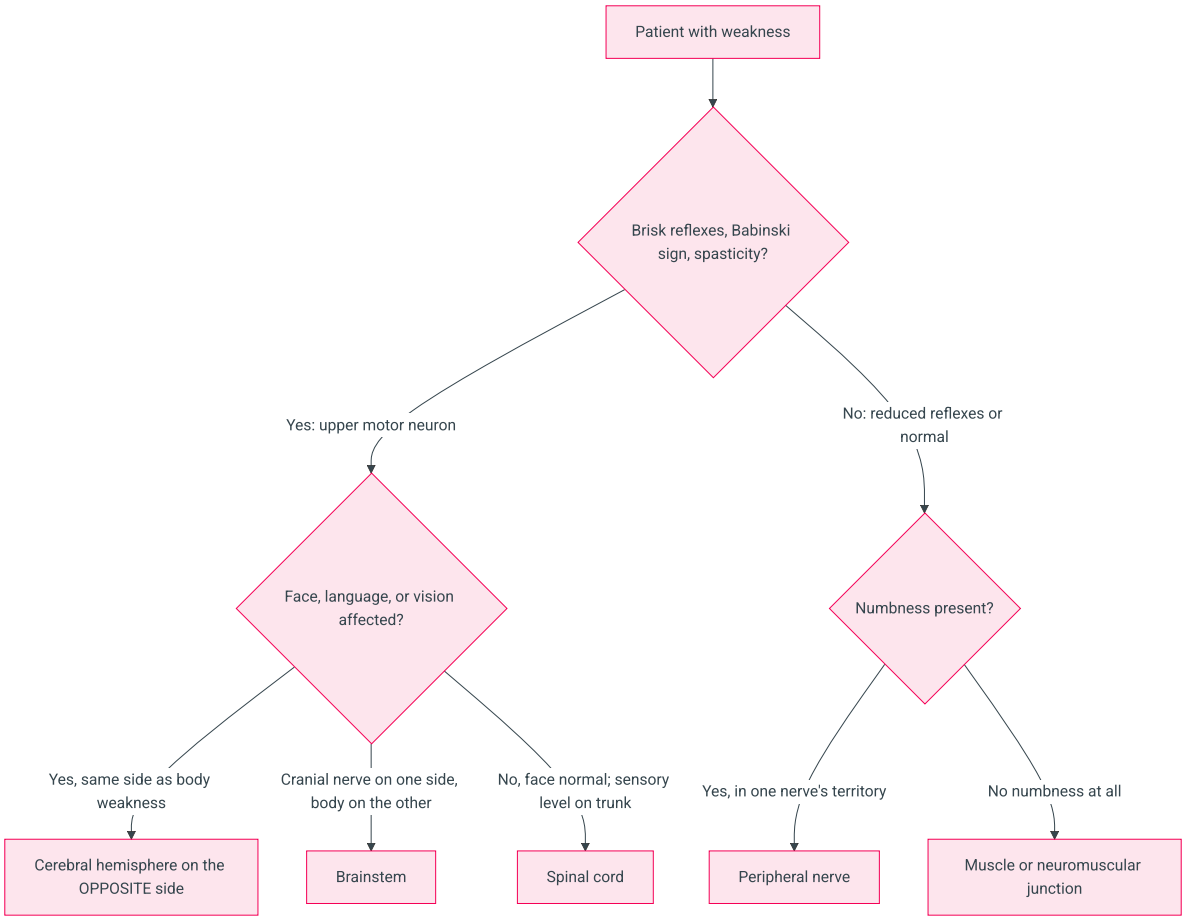
clue, **crossed signs**: one brainstem lesion damages a cranial nerve on one side *and* the not-yet-crossed corticospinal tract, causing a cranial nerve problem on one side and arm and leg weakness on the other (Wikipedia: Alternating hemiplegia).

Question 3: What level?

Each level of the nervous system leaves its own fingerprint:

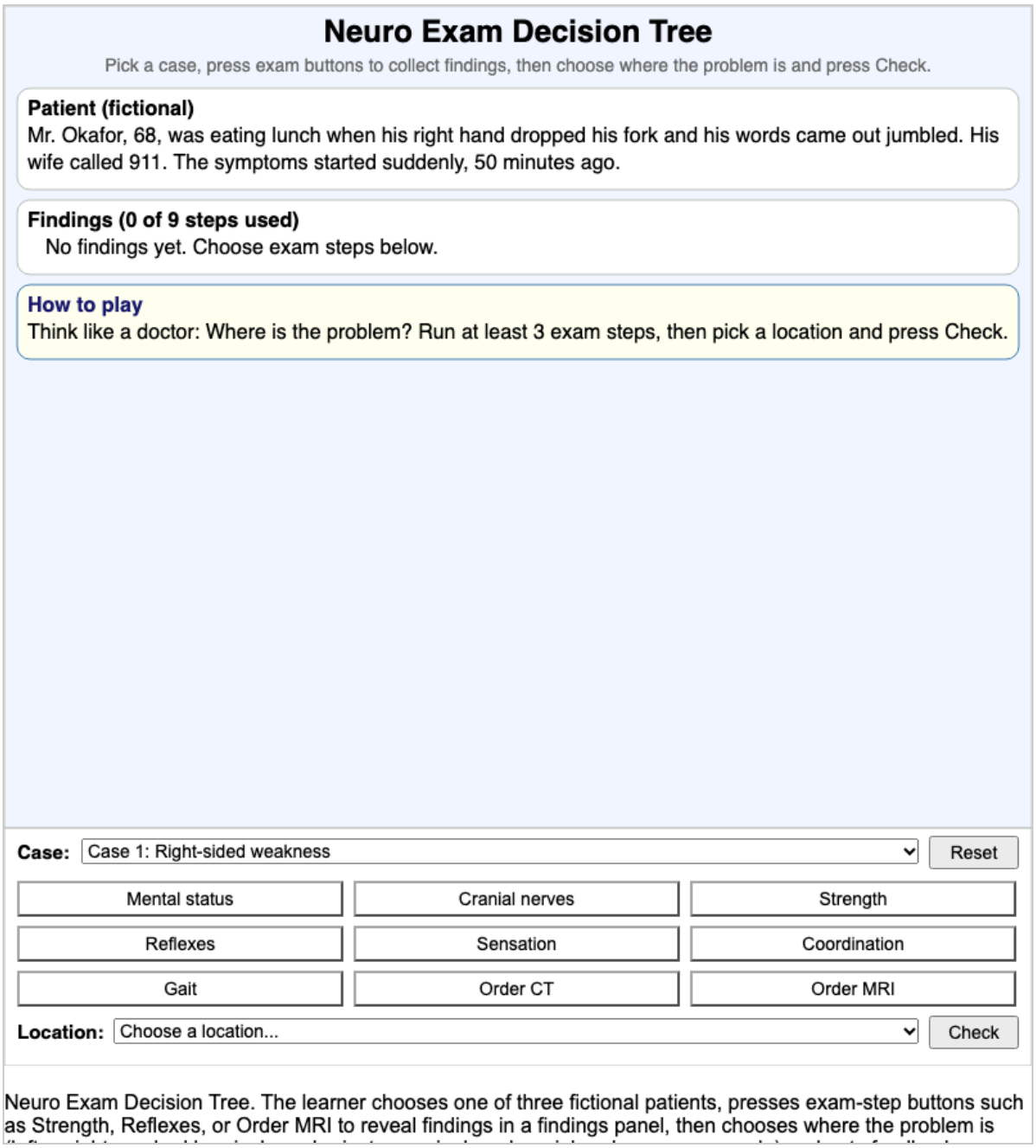
- **Cerebral hemisphere:** weakness and numbness on the opposite side, plus "cortical" signs such as aphasia, neglect, or loss of half the visual field, which can only come from the brain.
- **Brainstem:** crossed signs, double vision, trouble swallowing, slurred speech, or dizziness.
- **Spinal cord:** normal face, normal thinking, a sensory level across the trunk, upper motor neuron signs below the lesion, and often bladder problems.
- **Peripheral nerve:** weakness and numbness in the territory of a nerve, with reduced reflexes.
- **Muscle:** weakness without any numbness, often on both sides and often in the larger muscles close to the trunk, such as those of the hips and shoulders.

The flowchart below turns the three questions into a simplified decision path, the same logic you'll use in the MicroSim.



Notice the last box includes the **neuromuscular junction**, the synapse between nerve and muscle. Myasthenia gravis from Chapter 3 lives there, which is why it causes weakness without numbness.

Diagram: Neuro Exam Decision Tree



Screenshot of the interactive simulation. Try it online: https://aaryavvatts-lab.github.io/neuroscience-textbook/sims/ch16-neuro-exam/

Open the Neuro Exam Decision Tree fullscreen

MicroSim specification: Neuro Exam Decision Tree

Type: microsim **sim-id:** ch16-neuro-exam
Library: p5.js
Status: Implemented
Bloom Level: Analyze
Bloom Verb: differentiate
Learning Objective: The learner will differentiate lesion locations (left or right cerebral hemisphere, brainstem, spinal cord, peripheral nerve, muscle) by analyzing a pattern of exam findings in three fictional cases.

Canvas: width-responsive; fixed height 825 px (640 drawing area + 185 control area).

Controls: case menu (3 cases) and Reset; nine exam-step buttons (Mental status, Cranial nerves, Strength, Reflexes, Sensation, Coordination, Gait, Order CT, Order MRI); location menu (6 choices) and Check.

Cases (fictional composites): (1) sudden right-sided weakness with aphasia and forehead-sparing facial droop; answer: left cerebral hemisphere. (2) whole right half-face weakness including the forehead, everything else normal; answer: peripheral nerve (facial nerve, CN VII). (3) three weeks of stiff, weak legs, brisk leg reflexes with Babinski signs, a sensory level near the belly button (T10), and bladder urgency; answer: spinal cord.

Behavior: each exam step adds a short finding to a findings list and shows a longer explanation. Checking requires at least 3 steps. Correct and incorrect answers get case-specific feedback naming the reasoning (or the misconception behind a wrong choice). After two wrong attempts the correct location is revealed. Feedback boxes use both color and a text label.

Try Case 1 first. Before pressing any button, predict which hemisphere is damaged from the summary alone, then watch whether each finding supports your guess. Next, compare Case 1 with Case 2: both patients have a droopy face, but the forehead behaves differently, and that one difference moves the lesion from the brain to a nerve. In Case 3, notice what a head CT *can't* tell you.

Then try the challenge: can you localize each case with only 3 exam steps? That's the kind of choice the Brain Bee patient-diagnosis round asks you to make.

16.6 Looking Inside: Brain Imaging and Recording

Once the exam points to a location, doctors often want to see it. Think of the tools as different cameras: an X-ray camera, a magnetic camera, a "blood flow" camera, a "fuel use" camera, and a microphone for electricity.

Computed tomography (CT)

Computed tomography (CT) uses X-rays. An X-ray source spins around the head, detectors measure how much passes through, and a computer builds thin cross-sectional "slices" (NIBIB). Dense bone looks white, and fresh blood shows up bright too, so CT is very good at spotting bleeding in the brain. CT is fast and widely available. Its downsides: it uses ionizing radiation (the cancer risk from one scan is generally small, but exposure adds up over a lifetime), and it shows soft brain tissue in less detail than MRI. Godfrey Hounsfield and Allan Cormack shared the 1979 Nobel Prize in Physiology or Medicine for developing it (NobelPrize.org).

Why CT often comes first in a suspected stroke. A stroke is either a blocked artery (ischemic) or a burst one (hemorrhagic), and most are ischemic (Chapter 14; CDC). Clot-busting medicine can save brain tissue in an ischemic stroke but would make a bleed worse, so bleeding must be ruled out first. A plain head CT is the most widely used test for that job, and with an injected dye, CT can also show a blocked artery (CT angiography) (NINDS). Speed matters: one widely cited estimate found that a typical large-vessel ischemic stroke destroys about 1.9 million neurons each minute it goes untreated (Saver, 2006). Doctors sum this up as "time is brain."

A normal CT isn't the all-clear



In the first hours of an ischemic stroke, the CT often looks completely normal. The CT's job in that moment is to look for blood, not to prove there's no stroke. The exam and the history still drive the decision.

Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) uses a powerful magnet and radio waves instead of X-rays. The magnet lines up protons in the body's water; radio pulses knock them out of line, and the scanner detects the energy they release as they realign. Different tissues do this at different speeds, so MRI can tell them apart (NIBIB).

MRI shows the brain and spinal cord in finer detail than CT, clearly separates gray from white matter, and uses no ionizing radiation. A method called diffusion-weighted imaging can show an ischemic stroke earlier than plain CT, especially a small one (NINDS). MRI also reveals the plaques of multiple sclerosis (Chapter 1; NINDS). But it costs more, takes longer, is loud, and means lying still in a narrow tube. Because the magnet pulls on iron-containing metal, some implants, such as certain pacemakers and cochlear implants, can make it unsafe. Paul Lauterbur and Peter Mansfield shared the 2003 Nobel Prize in Physiology or Medicine for discoveries about MRI (NobelPrize.org).

Functional MRI (fMRI)

Regular MRI shows structure. **Functional MRI (fMRI)** shows which areas become more active during a task, but it doesn't record neurons firing. When an area works harder, extra oxygen-rich blood rushes in, more than the area uses. Oxygen-rich and oxygen-poor blood behave differently in a magnetic field, and fMRI detects the change: the **BOLD signal** (blood-oxygen-level dependent), discovered by Seiji Ogawa and colleagues in 1990 (Wikipedia: fMRI). Blood flow is slow, so the BOLD response peaks about 4 to 6 seconds after the activity. fMRI shows *where* (to within millimeters) far better than *when*, and it is used mostly in research.

PET scans

A **PET scan** (positron emission tomography) tracks chemistry. The patient receives a small amount of a radioactive tracer, which gives off particles that produce pairs of gamma rays; detectors map where the tracer collects (NIBIB). The common tracer FDG is a slightly modified glucose molecule, so FDG-PET shows which areas are burning fuel and which have gone quiet. Other tracers bind specific targets: florbetapir, approved in the United States in 2012, binds the beta-amyloid plaques of Alzheimer's disease (Chapter 13; Wikipedia: Florbetapir). PET involves a small radiation dose, and its pictures are less detailed than MRI.

EEG: listening to the brain's electricity

You met the **EEG** (electroencephalogram) in Chapter 10: scalp electrodes record the summed electrical activity of many cortical neurons. Hans Berger recorded the first human EEG in 1924 and published in 1929 (Wikipedia: Hans Berger). EEG follows changes

millisecond by millisecond but is poor at pinpointing where a signal comes from. Its main clinical job is diagnosing epilepsy (Wikipedia: EEG).

Choosing the right tool

The table below compares all five side by side.

Tool	What it measures	Biggest strength	Main limits	Typical use
CT	X-ray density (structure)	Fast, widely available, great for blood and bone	Radiation; less soft-tissue detail	Suspected stroke or head injury in the emergency room
MRI	Behavior of water protons in a magnet (structure)	Fine detail of brain and spinal cord; no radiation	Slow, loud, costly; some metal implants unsafe	Small strokes, MS, tumors, spinal cord problems
fMRI	Blood oxygen changes (BOLD) linked to activity	Shows where activity happens, to millimeters	Indirect; lags by a few seconds	Mostly research on brain function
PET	Where a radioactive tracer collects (chemistry)	Shows fuel use or specific molecules like amyloid	Radiation; less detailed images	Dementia workups, such as amyloid PET
EEG	Electrical activity at the scalp	Millisecond timing; cheap; portable	Poor at locating deep sources	Seizures and sleep

16.7 Lumbar Puncture: Sampling the Brain's Fluid

Sometimes the answer is floating in the fluid around the brain. Recall from Chapter 4 that cerebrospinal fluid (CSF) bathes the brain and spinal cord inside the meninges. A **lumbar puncture** (spinal tap) is a procedure in which a doctor inserts a thin needle between two vertebrae in the lower back, usually at the L3-L4 or L4-L5 space, to collect a small sample of CSF (Merck Manual).

A needle near the spine sounds scary, but there's a clever reason this spot is used. In adults, the spinal cord usually ends around the first lumbar vertebra (L1). Below that, the sac holds only loose nerve roots floating in fluid, which tend to slide out of the needle's way (Wikipedia: Lumbar puncture). Heinrich Quincke introduced the needle technique in 1891.

The lab checks the fluid's pressure, cells, protein, and glucose, and looks for germs. This helps diagnose:

- **Meningitis**, an infection of the meninges: the fluid may contain white blood cells and bacteria.
- **Bleeding around the brain** (subarachnoid hemorrhage): the fluid may be bloody.
- **Multiple sclerosis**: special proteins called oligoclonal bands can support the diagnosis.

About 1 in 10 patients gets a headache afterward. More seriously, if a mass in the brain is raising the pressure inside the skull, removing fluid from below could make brain tissue shift dangerously. So when there are warning signs, such as swelling of the optic nerve or new focal deficits, doctors get a CT or MRI first (Merck Manual).

16.8 Differential Diagnosis: Ranking the Suspects

Now you build the **differential diagnosis**: a ranked list of the conditions that could explain the patient's findings, from most to least likely, keeping dangerous ones in mind even when they're unlikely. Then tests cross suspects off the list. For sudden one-sided weakness, stroke is the top suspect, but several **stroke mimics** can look like one:

- **Low blood sugar (hypoglycemia)** can cause stroke-like symptoms (Wikipedia: Stroke). A finger-stick test takes seconds, so it's checked early.
- **A seizure** can leave temporary weakness, called Todd's paresis, that usually fades within 48 hours (Wikipedia: Todd's paresis). Witnesses can say whether the patient shook or stared first.

- **Migraine with aura** can cause temporary changes in vision, pins-and-needles feelings, or trouble speaking (NINDS: Migraine).
- **A brain tumor** can cause similar signs, but they usually build up over weeks, not seconds.

The *pattern* narrows the location, and the *timing* ranks the causes. A sudden left-hemisphere deficit is most likely vascular; the same deficit creeping in over two months points toward something growing. Here's a differential for a 68-year-old with sudden right arm weakness and aphasia that began 50 minutes ago:

Possibility	For it	Against it	Test that decides
Ischemic stroke (left hemisphere)	Sudden onset; pattern fits one artery	None so far	CT (no blood), then CT angiography or MRI
Hemorrhagic stroke	Sudden onset	Can't tell without a scan	CT shows bright blood
Hypoglycemia	Can mimic anything	Patient isn't diabetic	Finger-stick blood sugar
Todd's paresis after a seizure	Causes one-sided weakness	No shaking or staring seen	History from witnesses; EEG if unclear
Brain tumor	Can cause the same signs	Onset was sudden, not gradual	MRI

That one table uses the crossing motor pathway (Chapter 7), aphasia (Chapter 12), and seizures and stroke (Chapter 14). A differential diagnosis is where everything you've learned works together.

At the Bedside: Sudden Weakness on One Side

Meet the patient

Mr. Harold Jensen, 71, was watching TV when his wife saw his left arm slide off the armrest. His speech was slurred, and he didn't seem to notice anything was wrong. She called 911. He was last seen normal 35 minutes earlier. He has high blood pressure and an irregular heartbeat. (Mr. Jensen is a fictional composite.)

What the doctor checks: His finger-stick blood sugar is normal. A focused neurological exam, scored with the NIH Stroke Scale (NINDS), finds:

- *Mental status:* awake, but he ignores people on his left and insists his arm is fine (left-sided neglect). Speech is slurred, but language is normal: he names objects and follows commands.
- *Cranial nerves:* eyes prefer to look right; left lower face droops, but the forehead wrinkles evenly; he misses fingers held up on his left.
- *Motor:* left arm 1/5, left leg 3/5; right side 5/5.
- *Reflexes:* 2+ on both sides at first, with a Babinski sign on the left.
- *Sensation:* he barely notices touch on his left arm.
- *Coordination and gait:* right side normal; he can't stand safely.

A non-contrast head CT shows **no bleeding**. CT angiography shows a **blocked right middle cerebral artery**.

Where is the problem? (localization): (1) A Babinski sign and forehead-sparing facial weakness are upper motor neuron signs: central nervous system. (2) The weakness is on the *left*, and the motor pathway crosses: *right* hemisphere. (3) Neglect, eyes deviating toward the lesion side, and loss of the left half of vision are cortical signs, and neglect points to the non-dominant (usually right) hemisphere (Wikipedia: Middle cerebral artery). Face and arm weaker than leg fits the middle cerebral artery territory (RCEMLearning). Normal language fits, since language usually lives on the left.

Diagnosis: Acute ischemic stroke caused by a blockage of the right middle cerebral artery.

Why it happens: His irregular heartbeat (atrial fibrillation) raises stroke risk, because blood clots can form in the heart and travel to the brain (Wikipedia: Atrial fibrillation). When a clot lodges in an artery, the neurons it feeds lose oxygen and glucose. Without fuel, their ion

pumps fail (recall the sodium-potassium pump from Chapter 2), and the cells begin to die, including the upper motor neurons and cortical areas for the left side of the body.

Treatment today: With no bleeding and an early arrival, he is a candidate for clot-dissolving medicine (thrombolysis). NINDS notes that t-PA can be effective within three hours of symptom onset and that most clinicians now treat within a four-and-a-half-hour window. Because a large artery is blocked, doctors also consider thrombectomy: a catheter threaded from an artery in the leg up into the brain pulls the clot out. Perfusion imaging can identify some patients who still benefit from clot removal up to 24 hours after symptoms start (NINDS). Afterward, care turns to preventing another stroke and to rehabilitation.

What's new in research: Alteplase, the standard clot-busting drug, is given as an injection followed by an hour-long drip. A large Canadian trial called AcT found that tenecteplase, given as a single quick injection, worked about as well as alteplase for acute ischemic stroke (Menon et al., 2022, *The Lancet*). Based on that trial, the FDA approved tenecteplase (TNKase) for acute ischemic stroke in adults in early 2025; the drug's maker announced the approval on March 3, 2025 (NeurologyLive). In January 2026, the American Heart Association and American Stroke Association stroke guideline recommended either tenecteplase or alteplase for eligible adults treated within 4.5 hours of symptom onset (Prabhakaran et al., 2026, *Stroke*). A single injection can save minutes when every minute counts.

Your turn: diagnose a variation

Same patient, same exam, same timing. But this time the non-contrast head CT shows a bright white area deep in the right hemisphere. What changed, and should he get clot-busting medicine?

Answer: The bright area is fresh blood: a **hemorrhagic stroke** in the right hemisphere. The localization is the same, but the cause is different. Clot-busting medicine must **not** be given, because it could make the bleeding worse. Care instead focuses on finding and controlling the cause of the bleeding (NINDS). This is exactly why the CT comes first.

This is a fictional teaching case. It is not medical advice. If you or someone you know has symptoms like these, talk to a doctor.

Common Misconceptions

Myth: A brain scan can read your thoughts.
Reality: Scans measure physical things: X-ray density (CT), water protons (MRI), blood oxygen (fMRI), tracer chemistry (PET), or scalp electricity (EEG). An fMRI can show that a language area got busier, not the sentence you were thinking. Doctors use scans to find damage, not to read minds.

Myth: fMRI shows neurons firing directly.
Reality: fMRI detects blood-oxygen changes that *follow* neural activity by a few seconds, an indirect, delayed signal. EEG records electrical activity far more directly and quickly, but it's poor at locating sources.

Myth: If the CT scan is normal, it can't be a stroke.
Reality: In the first hours of an ischemic stroke, the CT is often normal. In an emergency, the CT's main job is to rule out bleeding. MRI with diffusion imaging can show a fresh ischemic stroke earlier.

Myth: Damage to the left side of the brain weakens the left side of the body.
Reality: Most motor fibers cross at the bottom of the medulla, so a lesion in the left hemisphere weakens the *right* side. Only below the crossing, in the spinal cord, does weakness appear on the same side as the lesion.

Myth: Any drooping face means a stroke.
Reality: A stroke usually spares the forehead, but facial nerve damage, as in Bell's palsy, weakens the whole half of the face (NINDS: Bell's Palsy). Any sudden face droop still needs an urgent medical check, because only a doctor can safely tell the difference.

Brain Bee Practice

1. What is the Babinski sign, and what does it mean in an adult?

When the outer sole of the foot is stroked, the big toe goes up and the other toes fan out. In an adult, it indicates damage to the corticospinal tract (an upper motor neuron lesion). It's normal in infants up to about 12 months.

2. A patient's left lower face droops, but she can wrinkle her forehead normally. Is the lesion more likely in the brain or in the facial nerve?

In the brain (a central lesion), most likely in the right hemisphere. The forehead gets signals from both hemispheres, so it is spared when only one hemisphere is damaged. Facial nerve damage would weaken the whole half of the face, forehead included.

3. Why is a non-contrast CT usually done first when a stroke is suspected?

It's fast and widely available, and it's very good at showing fresh blood. Doctors must rule out bleeding before giving clot-busting medicine, which would make a hemorrhage worse.

4. What does fMRI actually measure?

The BOLD (blood-oxygen-level dependent) signal: changes in blood oxygen that follow increases in neural activity. It measures activity indirectly and with a delay of a few seconds.

5. Why is a lumbar puncture done below the second lumbar vertebra?

In adults, the spinal cord usually ends around L1. Below that, only loose nerve roots float in the fluid, so the needle can collect CSF without hitting the cord.

Exercises

Remember

1. List the seven main parts of the neurological exam in the order used in this chapter.
2. Name the imaging tool that uses X-rays and the one that uses a strong magnet and radio waves.

Answer

1. Mental status, cranial nerves, motor (strength), reflexes, sensation, coordination, gait.
2. CT uses X-rays; MRI uses a magnet and radio waves.

Understand

1. Explain why damage to upper motor neurons makes reflexes brisker instead of weaker.
2. Explain why a lesion in the spinal cord causes weakness on the same side, while a lesion in the cortex causes weakness on the opposite side.

Answer

1. The brain normally sends signals that calm the reflex loops in the spinal cord. Upper motor neuron damage removes that brake, so the reflexes become exaggerated.
2. Most corticospinal fibers cross at the bottom of the medulla. A cortical lesion is above the crossing, so it affects the opposite side. A spinal cord lesion is below it, so the fibers there already serve the same side.

Apply

1. A 30-year-old has weakness and numbness in both legs, brisk knee and ankle reflexes, upgoing toes, normal arms, and numbness from the nipple line down. Where is the lesion, and about what level? Which imaging test would you order?
2. A patient arrives 40 minutes after sudden right arm weakness and trouble finding words. Put these steps in a sensible order and explain why: MRI of the brain, finger-stick blood sugar, non-contrast head CT, history from the family.

Analyze

1. Compare a patient with an upper motor neuron lesion to one with a lower motor neuron lesion in the same leg. Make a table of at least four exam findings that would differ.
2. A patient has a weak, droopy left eyelid and an eye that can't move inward on the left, plus weakness of the right arm and leg. Using the idea of crossed signs, localize the lesion as precisely as you can.

Evaluate

1. A hospital can buy either a second CT scanner or a second MRI scanner for its emergency department. Using the strengths and limits of each tool, argue which would

help stroke patients more, and why.

2. A website claims that a company can use fMRI to tell whether someone is lying. Using what you know about how fMRI works, evaluate this claim.

Create

1. Write your own fictional patient case for a classmate to localize. Include a short history, findings from at least five parts of the neurological exam, and an imaging result. Make sure every finding fits one lesion location, and write an answer key.
2. Design a one-page "pocket card" for a Brain Bee competitor that summarizes how to tell cortex, brainstem, spinal cord, nerve, and muscle lesions apart.

Key Takeaways

- Neurologists localize first ("where?") and name the disease second ("what?"). The timing of symptoms is one of the best clues to the cause.
- The **neurological exam** checks mental status, cranial nerves, strength, reflexes, sensation, coordination, and gait, and connects each abnormal finding to a part of the nervous system.
- Upper motor neuron lesions cause spasticity, brisk reflexes, and a Babinski sign. Lower motor neuron lesions cause floppy weakness, reduced reflexes, wasting, and fasciculations.
- Because most motor fibers cross at the bottom of the medulla, brain lesions weaken the opposite side, while spinal cord lesions weaken the same side. A forehead-sparing face droop points to the brain; whole-face weakness points to the facial nerve.
- CT is fast and good at finding blood, so it usually comes first in a suspected stroke. MRI shows more detail without radiation. fMRI tracks blood oxygen, PET tracks chemistry, and EEG tracks electricity in real time.
- A **lumbar puncture** samples cerebrospinal fluid below the end of the spinal cord to help diagnose infections, bleeding, and multiple sclerosis.
- A **differential diagnosis** ranks every condition that could explain the findings, including stroke mimics such as low blood sugar and seizures, and uses tests to narrow the list.

From neuron to bedside!



You did it: you started with a single neuron and finished at the bedside, reasoning like a neurologist. Every big idea really does start at a single synapse! Next, the appendices will help you plan for the Brain Bee and explore careers in neuroscience and medicine.

Appendix A: Brain Bee Strategy and Mock Exam

Please read first: this book is independent

From Neuron to Bedside is an independent, free textbook. It is **not affiliated with, sponsored by, or endorsed by** the International Brain Bee (IBB), the Society for Neuroscience (SfN), or any local or national Brain Bee. The mock exam below is original and is **not** made from real Brain Bee questions.

Rules, formats, age limits, eligibility, and official study materials **vary by chapter, by country, and by year**. Always check two places before you plan your studying: your **local or national Brain Bee chapter** and the **official IBB website**, thebrainbee.org. If anything in this appendix disagrees with them, they are right and we are wrong.

Welcome, competitor!



I'm a sea slug with about 20,000 neurons, and even I can learn with practice. You have tens of billions of neurons, so you're starting with a big advantage! This appendix turns everything in the book into a plan you can follow, then lets you test yourself with a full mock exam.

A.1 What Is the Brain Bee?

The **Brain Bee** is a neuroscience competition for high school students. The idea is a little like a spelling bee, except the questions are about the brain: how neurons signal, where structures sit, how we sense and move, and what goes wrong in brain disorders. Its stated goals are to get students excited about the brain and to inspire them toward careers in neuroscience or medicine (IBB FAQ).

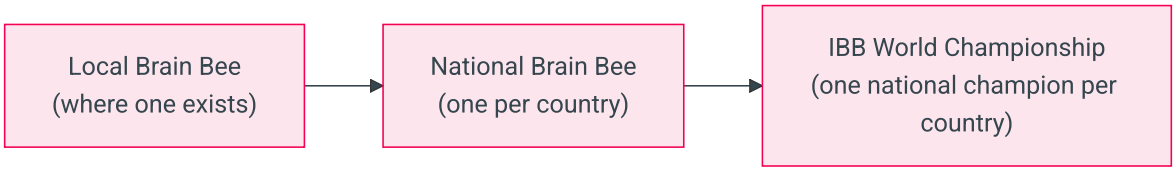
A short history

The Brain Bee was founded by **Dr. Norbert Myslinski**, a neuroscientist at the University of Maryland. The IBB's own history page dates the founding to **1998** (IBB: About), and the

Society for Neuroscience reports that the first Brain Bee was held at the University of Maryland that same year (SfN, 2014). You may see a different year (such as 1999) in other places, but this book follows the IBB's own history and the SfN report, which both give 1998.

Three levels

The competition is organized as a ladder (IBB home page):



1. **Local (or regional) Brain Bee.** Many students start here, often at a nearby university.
2. **National Brain Bee.** Local winners advance to their country's national competition.
3. **IBB World Championship.** Each national champion can represent their country at the world level.

If your country has no national Brain Bee, the IBB says students can enter the **IYNA Virtual Brain Bee**, whose winner qualifies for the World Championship (IBB FAQ).

Who can compete?

According to the IBB, Brain Bees are **typically open to students aged 13 to 19**, and national champions **may not be older than 19** to compete at the World Championship. Some competitions also require you to be enrolled in high school. The IBB also says students may enter only one local and one national Brain Bee per year (IBB FAQ). Your chapter may have its own rules on top of these, so check them.

What the rounds look like

There is no single Brain Bee format. Here is what official sources describe, as examples only.

At a local or regional level, formats are often simpler. For example, the Boston University regional Brain Bee has described three rounds: a written exam of open-ended questions, an **oral round** where students answer aloud and are eliminated after two wrong answers, and a

final elimination round answered on whiteboards. It also notes that details may vary (BU Brain Bee). Other chapters run different mixes of written and oral questions.

At the IBB World Championship, the IBB lists several sections (IBB: Competition):

Section	What students do (as described by the IBB)
Neuroanatomy	Identify structures on real whole or sectioned human brains, or on detailed illustrations, and know their positions, connections, and functions.
Neurohistology	Identify structures in human tissue shown under microscopes, and/or describe what the tissue does.
Written test	Multiple-choice and short-answer questions.
Patient diagnosis	Watch videos of patients with a written history, choose three diagnostic tests (from groups such as neuroimaging, EEG and nerve conduction studies, cognitive measures, and blood or spinal fluid biomarkers), then name the diagnosis.
Live judging	An elimination round for top scorers. Students write short answers within a time limit, and two wrong answers mean elimination.

The IBB notes that aspects of the competition may vary from year to year (IBB: Competition). Treat the table as a picture of the *kinds* of skills that get tested, not a promise of this year's format.

Official study materials

Every Brain Bee chooses its own official study source, and **the questions usually come from that source**. According to the IBB, most local Brain Bees are based on either the Society for Neuroscience's free book ***Brain Facts*** or the book *Neuroscience: The Science of the Brain* (IBB: Competition). You can download *Brain Facts* from The Brain Facts Book page on BrainFacts.org. The current edition there is from 2018, and the BU regional Brain Bee, for example, says all three of its rounds draw from that edition (BU Brain Bee). Some chapters add other books, and students who reach the World Championship receive extended study materials from their national coordinators (IBB: Competition).

The most important advice in this appendix is simple: **find out exactly which source your chapter uses, and read it closely.** This book is a *complement*, not a replacement. It gives you the "why," the pictures in your head, the MicroSims, and the clinical reasoning that make facts stick. Your official source tells you which facts and wording the judges expect. If the two ever describe something differently (for example, rounding a number differently), learn your official source's version for the competition.

Why we never copy Brain Facts

Brain Facts is copyrighted by the Society for Neuroscience. This book used it only as a general map of which topics high school neuroscience covers. None of its text, figures, or questions appear here, and the mock exam was written from scratch.

A.2 How This Book Lines Up With Brain Bee Topics

Brain Bee questions usually come from a broad set of topics. The table below shows where each kind of topic lives in this book. Use it when your official source covers something and you want a deeper, more visual explanation.

Topic area	Chapters in this book
Neurons, glia, and electrical signals	1: Neurons and Glia, 2: The Action Potential
Synapses, neurotransmitters, and drugs	3: Synapses and Neurotransmitters
Neuroanatomy	4: A Tour of the Brain
Senses and pain	5: Vision, 6: Hearing, Touch, Taste, Smell, and Pain
Movement	7: Movement
Development across life	8: The Developing and Teenage Brain, 13: The Aging Brain
Learning, memory, sleep, emotion, and thinking	9, 10, 11, 12

Topic area	Chapters in this book
Brain disorders	13, 14, 15, plus every chapter's Bedside case
Diagnosis and tools	16: How Doctors Examine the Brain

Each chapter also ends with a **Brain Bee Practice** section of five short-answer questions, a ten-question quiz, and a list of key terms you can look up in the Glossary.

A.3 A 4-Week Study Plan

This plan is for the **final four weeks** before your competition. It assumes you have already read the chapters at least once, or are reading them alongside the plan. If you are starting from zero, give yourself more time: reading one chapter every two or three days, with its quiz, takes about five to seven weeks before you begin this plan.

The plan follows two research-backed rules you will meet in Section A.4: **space your studying out**, and **test yourself instead of rereading**. Notice that every week mixes in a little review of earlier weeks. That is on purpose.

Week	Main focus	What to do	Self-test checkpoint
1	Foundations: Chapters 1 to 8	Two chapters per day for four days. For each one, reread the Key Takeaways, redo the MicroSim, and answer the Brain Bee Practice questions **out loud before** opening the answers. Spend days 5 and 6 reading the matching parts of your official study source. Day 7: rest or light review.	Each chapter's quiz, closed book. Write every missed term on a flashcard.
2	Brain systems and disorders: Chapters 9 to 16	Same routine as Week 1. Each day, start with 10 minutes of flashcards from Week 1	**End of Week 2: take the full mock exam in Section A.6**, timed, closed book, about

Week	Main focus	What to do	Self-test checkpoint
		(spacing!). Read your official source alongside.	two weeks before the competition. Score it with Section A.7.
3	Fix weak spots and practice the rounds	Use the "What to review next" table (Section A.7) to pick your two or three weakest chapters and restudy them. Practice the oral round with a partner every other day (Section A.5). Start neuroanatomy ID practice: 15 minutes a day labeling brain views (Section A.5).	Redo every mock exam question you missed, *without* looking at the old answer, and explain why each wrong option is wrong.
4	Diagnosis, mixed review, and rest	Work through all 16 Bedside cases with the method in Section A.5. Mix flashcards from all chapters every day. Two days before: light review only. The night before: sleep.	Two days in a row of mixed flashcards from all chapters with almost no misses. Re-take only the mock questions you missed in Week 2.

If you only have one or two weeks

Skip straight to the mock exam. Use your score to choose the chapters that need the most work, then study those with self-testing. A focused plan beats trying to reread the whole book.

A.4 Study Techniques That Actually Work

How you study matters as much as how long. Brain science has a lot to say about this, and you learned the biology behind it in Chapter 9.

Retrieval practice: test yourself

Retrieval practice means pulling information *out* of your memory, for example by answering a question or explaining an idea without looking. It feels harder than rereading, and that effort is the point. In a classic experiment, students who took practice tests on a passage remembered more of it a week later than students who spent the same time restudying it (Roediger & Karpicke, 2006).

How to use it:

- Cover the answers and **say your answer out loud** before checking. This also trains you for oral rounds.
- Make flashcards with a question on the front, not just a word. "What does the hippocampus do?" is better than "hippocampus."
- After each chapter, do the Brain Bee Practice and the quiz *before* you reread anything.

Spacing: spread it out

Spaced practice means studying the same material in several shorter sessions spread over days, instead of in one long cram session. A large review of hundreds of experiments found that spacing study sessions apart reliably improves long-term memory (Cepeda et al., 2006). Chapter 9, Section 9.11 explains why at the level of synapses. Even in the sea slug *Aplysia*, spaced training builds long-term memory better than massed training, because long-term memory needs new proteins and new connections that take time to build.

What the evidence says about popular habits

In 2013, a team of learning scientists rated ten common study techniques. **Practice testing** and **distributed (spaced) practice** were the only two given the highest rating for usefulness. Some of students' favorite habits, including **highlighting, rereading, and summarizing**, were rated low (Association for Psychological Science, 2013; full review: Dunlosky et al., 2013).

That doesn't mean rereading is useless. It just means it should not be your main tool. A good rule: **for every minute you spend reading, spend at least a minute testing yourself.**

Make it mean something

Facts stick better when they connect to things you already know. When you learn that the hippocampus helps form new memories, link it to Patient H.M.'s story. When you learn

about dopamine, connect it to Parkinson's disease, the reward pathway, and reward prediction error. This book's chapters are built around those links on purpose, so use the "Prerequisites" lists and the Learning Graph to see them.

Study like a sea slug



Short, spaced sessions where you quiz yourself beat one long night of rereading. My synapses need time between lessons to build long-term memories, and so do yours!

Sleep is part of studying

Sleep helps your brain **consolidate** (stabilize) what you learned during the day (Chapter 10). The American Academy of Sleep Medicine recommends **8 to 10 hours** a night for teens aged 13 to 18, as Chapter 10 explains. Staying up late to cram trades away the very sleep that would have locked in your studying.

A.5 Strategy for Each Kind of Round

Written rounds

- **Read every option.** In multiple choice, the first option that "sounds right" is often a near-miss. Look for the *best* answer.
- **Use the clues in the question.** Words like "most likely," "first," and "best explains" matter.
- **Eliminate.** Cross out options you know are wrong. Even narrowing four choices to two doubles your odds.
- **Watch the clock.** Skip a hard question, mark it, and come back. Don't let one question eat five minutes.
- **Spelling may count.** For short-answer questions, practice writing terms correctly: *hippocampus*, *cerebellum*, *oligodendrocyte*, *acetylcholine*. Ask your chapter whether spelling is graded.

Oral rounds

In competitions that have one, the oral round can decide the winner. Often you hear a question, have a short time to think, and answer aloud. Common rules include elimination after a set number of misses, so check yours.

- **Practice out loud, early.** Knowing something silently is different from saying it under pressure. Have a friend, parent, or teacher read you questions from each chapter's Brain Bee Practice section.
- **Answer short and exact.** Most oral questions want a word or short phrase. "The cerebellum" is better than a long explanation that might include a mistake.
- **Learn to pronounce terms.** Say tricky words out loud until they feel normal: *amygdala* (uh-MIG-duh-luh), *suprachiasmatic*, *oligodendrocyte*. A judge needs to understand you.
- **Pause before answering.** A two-second pause to think is fine. Rushing leads to careless misses.
- **Recover fast.** If you miss one, let it go. The next question is a fresh start.

Neuroanatomy identification

At higher levels, you may need to identify structures on real brains, brain slices, or detailed drawings. This is a visual skill, so you have to practice it visually.

- **Learn the directions and planes first.** Sagittal, coronal, and horizontal views look very different. Chapter 4, Section 4.2 explains them.
- **Use the Clickable Brain Atlas.** The Chapter 4 MicroSim lets you click structures and see their names and jobs.
- **Learn landmarks, then fill in.** Find the central sulcus, lateral sulcus, corpus callosum, ventricles, and brainstem first. Most other structures are easy to locate once you know these.
- **Pair every structure with a function and a disorder.** For example: *substantia nigra, dopamine, Parkinson's disease*. Judges often ask "what does this do?" right after "what is this?"
- **Draw it.** Sketching a midsagittal brain from memory, then checking it, is retrieval practice for your eyes.
- **Neurohistology** (tissue under a microscope) is only touched on in this book, mainly in Chapter 1 on neurons and glia. If your competition includes it, use the official materials

your chapter provides.

Patient diagnosis rounds

In a diagnosis round, you see a patient (in a video, a description, or an actor) and must name the condition, and sometimes choose the right tests. This is exactly what the **At the Bedside** sections of this book train you to do.

Use the doctor's method from Chapter 16:

1. **Where before what.** First ask *where* in the nervous system the problem is, then *what* the disease is.
2. **Look at the timing.** Sudden onset (seconds to minutes) suggests stroke or seizure. Hours to days suggests infection or inflammation. Months to years suggests a degenerative disease or a slowly growing tumor.
3. **Upper or lower motor neuron?** Stiffness, brisk reflexes, and a Babinski sign point to the brain or spinal cord. Floppy weakness, wasting, and twitching point to the motor neurons that leave the spinal cord or to the nerves.
4. **Which side? Which level?** A brain problem usually affects the opposite side of the body. A face droop that spares the forehead points to the brain, not the facial nerve.
5. **Pick tests that answer your question.** CT to look for bleeding fast, MRI for detail, EEG for seizures, a lumbar puncture for infection or inflammation, and nerve conduction studies for nerve problems. Chapter 16, Section 16.6 compares the imaging and recording tests, and Section 16.7 covers the lumbar puncture.

Then practice on every case in the book. Read only the "Meet the patient" box first, decide where and what, then read on to check:

Chapter	Bedside case
1	Blurry Vision and Tingling Legs
2	A Numb Lip at the Dentist
3	Eyelids That Droop by Evening

Chapter	Bedside case
4	Two Frontal Lobes, Nearly 180 Years Apart
5	The Driver Who Kept Bumping Door Frames
6	Pain in a Hand That Is No Longer There
7	The Slowing Teacher
8	A Second Grader Who Can't Keep Up
9	Patient H.M. and Anterograde Amnesia
10	The Student Who Collapsed When She Laughed
11	Nightmares After the Crash
12	Two Strokes, Two Kinds of Silence
13	Two Patients, Two Misfolded Proteins
14	Three Emergencies, Three Brains
15	An Overdose at a Dorm Party
16	Sudden Weakness on One Side

Also try each case's **"Your turn: diagnose a variation"** question. Changing one detail and asking "what would that change?" is how real diagnosticians think, and it prepares you for patients you have never seen before.

Test-day tips

- **Sleep well for the two nights before**, not just the last one. Nerves often cost people one night of good sleep, and that's fine if you slept well before it.

- **Eat a normal breakfast** and bring water and a snack if allowed.
- **Know the logistics:** the address, the start time, what to bring (ID, pencils, registration confirmation), and whether phones are allowed.
- **Arrive early** so you are not rushed. Rushing triggers the fast stress response you read about in Chapter 11.
- **Reframe the nerves.** A racing heart is your body getting ready to perform. Telling yourself "this energy will help me focus" is a form of reappraisal, a strategy described in Chapter 11.
- **Do not cram new material that morning.** Skim your flashcards of the most-missed terms, then stop.
- **Follow the rules exactly.** Recording or sharing questions is commonly forbidden. Your answers must be your own.
- **Enjoy it.** You will meet students who love the brain as much as you do, which the IBB describes as one of the rewards of competing (IBB FAQ).

A.6 The Mock Exam

Instructions. This is a 50-question multiple-choice exam that covers all 16 chapters. Set a timer for **60 minutes**, close the book, and put your phone away. Write your answers on paper first. Don't open any answer until you are done with all 50. Then check them and score yourself with Section A.7.

The questions mix **recall** (remembering a fact), **understanding** (explaining why), and **clinical reasoning** (applying ideas to a patient). They are grouped by chapter so you can find your weak spots. Real competitions usually mix topics together and may use different question styles.

You don't need a perfect score



This exam is a map, not a verdict. Every question you miss now shows you exactly where to study, and that is a win before the real competition!

Question 1

Which glial cells act as the central nervous system's resident immune cells, patrolling the brain and swallowing microbes and dead or damaged cells?

A. Astrocytes

B. Oligodendrocytes

C. Microglia

D. Schwann cells

Show Answer

The correct answer is **C**. Microglia are the brain's small immune cells: they patrol, detect trouble, and engulf invaders and debris. Astrocytes support neurons and help maintain the blood-brain barrier, while oligodendrocytes and Schwann cells make myelin.

Type: Recall **Chapter:** Chapter 1: Neurons, Glia, and the Nervous System

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Question 2

A classmate says, "Glial cells outnumber neurons ten to one." Which statement is best supported by modern cell counts?

A. The classmate is right: glia outnumber neurons about 10 to 1.

B. Overall, glia and neurons are roughly equal in number in the human brain.

C. Glia make up less than 1% of the cells in the brain.

D. Neurons outnumber glia about 10 to 1.

Show Answer

The correct answer is **B**. Careful counting studies have found that the human brain has roughly as many glia as neurons overall, so the "ten to one" figure is an old myth. Glia still do important work: they make myelin, support neurons, and defend the brain.

Type: Understanding **Chapter:** Chapter 1: Neurons, Glia, and the Nervous System

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Question 3

An antibiotic easily clears a bacterial infection from a patient's bloodstream, but it works poorly against the same bacteria inside the brain. Which explanation fits best?

A. The blood-brain barrier keeps many drugs from passing from the blood into brain tissue.

B. Myelin coats every brain cell and blocks drugs from reaching them.

C. Microglia destroy every drug that enters the brain.

D. The brain has no blood vessels, so drugs carried in the blood cannot reach it.

Show Answer

The correct answer is **A**. The tightly sealed capillaries of the blood-brain barrier, supported by astrocytes, block many substances, including many medicines. In fact, the brain has a dense blood supply (D is wrong), and myelin wraps axons, not every cell.

Type: Clinical reasoning **Chapter:** Chapter 1: Neurons, Glia, and the Nervous System

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Question 4

During the rising phase of an action potential, which ion movement mainly drives the membrane potential upward toward a positive value?

A. Potassium (K^+) flowing out of the cell

B. Chloride (Cl^-) flowing into the cell

C. Calcium (Ca^{2+}) being pumped out of the cell

D. Sodium (Na^+) flowing into the cell

Show Answer

The correct answer is **D**. When threshold is reached, voltage-gated sodium channels open and Na^+ rushes in, making the inside of the cell positive. Potassium flowing out (A) is what brings the voltage back down during the falling phase.

Type: Recall **Chapter:** Chapter 2: The Action Potential

Question 5

Right after an action potential, the membrane briefly dips to about −80 mV, more negative than the resting potential. What causes this undershoot?

A. Sodium channels stay open longer than usual.

B. Voltage-gated potassium channels are slow to close, so extra K^+ keeps leaving the cell.

C. Sodium channels reopen and let Na^+ flow back out.

D. The neuron's chloride ions all rush out at once.

Show Answer

The correct answer is **B**. Voltage-gated K^+ channels close slowly, so for a few milliseconds extra positive charge leaves the cell and the voltage overshoots below rest. Open sodium channels (A) would push the voltage up, not down.

Type: Understanding **Chapter:** Chapter 2: The Action Potential

Question 6

A signal travels along a myelinated motor axon at 100 meters per second. About how long does it take to travel 1 meter, roughly the distance from the lower spinal cord to the foot?

A. About 10 milliseconds (0.01 second)

B. About 1 millisecond (0.001 second)

C. About 100 milliseconds (0.1 second)

D. About 1 second

Show Answer

The correct answer is **A**. Time equals distance divided by speed: 1 m ÷ 100 m/s = 0.01 s, which is 10 milliseconds. A thin unmyelinated axon conducting at about 1 m/s would take a full second (D), which shows why myelin matters.

Type: Clinical reasoning (apply) **Chapter:** Chapter 2: The Action Potential

Question 7

Botulinum toxin causes muscle weakness and can cause paralysis. How does it act?

A. It blocks acetylcholine receptors on the muscle fiber.

B. It prevents motor nerve terminals from releasing acetylcholine.

C. It speeds up the enzyme that breaks down acetylcholine.

D. It blocks voltage-gated sodium channels in the muscle.

Show Answer

The correct answer is **B**. Botulinum toxin stops the release of acetylcholine from vesicles at the neuromuscular junction, so the muscle never receives the signal. Blocking the receptors (A) is how a different poison, curare, works.

Type: Recall **Chapter:** Chapter 3: Synapses and Neurotransmitters

Question 8

Acetylcholine makes skeletal muscles contract, but it slows the heartbeat. What best explains how one neurotransmitter can have opposite effects?

A. The heart uses a chemically different form of acetylcholine.

B. Acetylcholine is excitatory only in the brain and inhibitory everywhere else.

C. The heart breaks down acetylcholine before it can bind to anything.

D. The two tissues have different receptors: fast nicotinic channels on skeletal muscle and slower muscarinic (metabotropic) receptors on heart cells.

Show Answer

The correct answer is **D**. The receptor, not just the transmitter, decides the effect. The same acetylcholine molecule opens fast ion channels on skeletal muscle but acts through G proteins on heart cells, which slows the heart.

Type: Understanding **Chapter:** Chapter 3: Synapses and Neurotransmitters

Question 9

Maya drinks a cup of coffee and feels more alert. How does caffeine mainly produce this effect?

A. It makes neurons release more adenosine.

B. It activates adenosine receptors more strongly than adenosine does.

C. It fits into adenosine receptors without activating them, blocking adenosine's sleepiness signal.

D. It blocks dopamine reuptake, the same way cocaine does.

Show Answer

The correct answer is **C**. Caffeine is an adenosine receptor antagonist: it occupies the receptor but doesn't switch it on, so the adenosine that builds up while you're awake can't push neurons toward sleepiness. Option B describes an agonist, which would have the opposite effect.

Type: Understanding **Chapter:** Chapter 3: Synapses and Neurotransmitters

Question 10

Which tissue makes most of the cerebrospinal fluid (CSF)?

A. The dura mater

B. The pineal gland

C. The choroid plexus inside the ventricles

D. The gray matter of the cerebral cortex

Show Answer

The correct answer is **C**. The choroid plexus, a tissue rich in blood vessels inside the ventricles, makes most of the CSF. The dura mater (A) is the tough outer layer of the meninges, which protects the brain but does not produce CSF.

Type: Recall **Chapter:** Chapter 4: A Tour of the Brain: Neuroanatomy

Question 11

A brain slice that separates the front of the brain from the back is called a:

A. Coronal section

B. Sagittal section

C. Horizontal section

D. Midsagittal section

Show Answer

The correct answer is **A**. A coronal (frontal) section divides front from back, like slicing a loaf of bread. Sagittal and midsagittal sections divide left from right, and horizontal sections divide top from bottom.

Type: Recall **Chapter:** Chapter 4: A Tour of the Brain: Neuroanatomy

Question 12

Which structure helps keep body temperature, hunger, and thirst in balance and controls hormone release from the pituitary gland?

A. Thalamus

B. Hypothalamus

C. Cerebellum

D. Medulla

Show Answer

The correct answer is **B**. The hypothalamus maintains homeostasis and commands the pituitary, linking the nervous system to the hormone system. The thalamus (A) sits just above it but mainly relays sensory signals to the cortex.

Type: Recall **Chapter:** Chapter 4: A Tour of the Brain: Neuroanatomy

Question 13

A small stroke damages only the hand area of the **left postcentral gyrus**. Which problem is most likely?

A. Weakness of the left hand

B. Loss of vision in the right half of the visual field

C. Poor balance and clumsiness on the left side

D. Reduced touch sensation in the right hand

Show Answer

The correct answer is **D**. The postcentral gyrus is the primary somatosensory cortex ("feeling behind" the central sulcus), and each hemisphere receives sensation from the opposite side of the body. Weakness (A) would come from the precentral (motor) gyrus, and on the opposite side.

Type: Clinical reasoning **Chapter:** Chapter 4: A Tour of the Brain: Neuroanatomy

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Question 14

The fovea gives you your sharpest vision. Which cells is it packed with?

A. Cones

B. Rods

C. Ganglion cells stacked in thick layers

D. Blood vessels that nourish the photoreceptors

Show Answer

The correct answer is **A**. The fovea is a small pit in the center of the retina packed with cones, with the other retinal layers pushed aside so light reaches them directly. Rods (B) are far more common elsewhere in the retina and work best in dim light.

Type: Recall **Chapter:** Chapter 5: Vision

Question 15

Each eye has a blind spot where the optic nerve leaves. Why don't you notice it in daily life?

A. The blind spot has extra rods that make up for the missing cones.

B. The other eye covers that part of the scene, and the brain fills in the gap.

C. The blind spot only exists in dim light.

D. The lens bends light so that none of it ever lands on the optic disc.

Show Answer

The correct answer is **B**. The optic disc has no photoreceptors at all, but the two eyes' blind spots fall on different parts of the scene, and the brain fills in what's missing. Option A is wrong because the optic disc contains no rods or cones.

Type: Understanding **Chapter:** Chapter 5: Vision

Question 16

A tumor presses on the **left optic tract**, just behind the optic chiasm. Which visual problem is most likely?

A. Complete blindness in the left eye only

B. Loss of the outer (temporal) half of the visual field in both eyes

C. Loss of the right half of the visual field in both eyes

D. Loss of the left half of the visual field in both eyes

Show Answer

The correct answer is **C**. Behind the chiasm, the left optic tract carries fibers from both eyes about the right visual field, so damage causes right homonymous hemianopia. Option B (bitemporal hemianopia) comes from pressure on the chiasm itself, and option A from damage to one optic nerve.

Type: Clinical reasoning **Chapter:** Chapter 5: Vision

Question 17

Which receptors tell your brain how much a muscle is being stretched, helping you sense where your limbs are without looking?

A. Nociceptors

B. Pacinian corpuscles

C. Cochlear hair cells

D. Muscle spindles

Show Answer

The correct answer is **D**. Muscle spindles sense muscle stretch and are main receptors for proprioception, along with Golgi tendon organs. Nociceptors (A) detect damage or the threat of damage, and Pacinian corpuscles (B) are skin receptors best at sensing vibration.

Type: Recall **Chapter:** Chapter 6: Hearing, Touch, Taste, Smell, and Pain

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Question 18

Why is hearing loss from years of very loud music usually permanent?

A. Loud noise kills cochlear hair cells, and humans cannot regrow them.

B. Loud noise tears the eardrum, and eardrums can never heal.

C. Loud noise destroys the auditory cortex.

D. It isn't permanent; noise only ever causes temporary hearing loss.

Show Answer

The correct answer is **A**. Repeated loud noise kills the hair cells that turn sound vibrations into neural signals, and unlike birds and amphibians, humans can't replace them. A short blast of noise can cause temporary loss (D), but once hair cells die, the loss is permanent.

Type: Understanding **Chapter:** Chapter 6: Hearing, Touch, Taste, Smell, and Pain

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Question 19

Maya spins in a desk chair for 30 seconds, then stops suddenly. For a few seconds the room seems to keep turning. Which sense organs are mainly responsible?

A. The cochlea

B. The otolith organs

C. The semicircular canals

D. The olfactory bulbs

Show Answer

The correct answer is **C**. The semicircular canals sense head rotation through fluid that lags behind the head's motion. When Maya stops, the fluid keeps moving for a moment because of inertia, so her canals send a false "still turning" signal. The otolith organs (B) mainly sense gravity and straight-line acceleration.

Type: Clinical reasoning (apply) **Chapter:** Chapter 6: Hearing, Touch, Taste, Smell, and Pain

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Question 20

Maya lifts a pencil, then a heavy backpack, with the same arm. How does her nervous system mainly produce the extra force?

A. It makes each action potential in the motor neurons larger.

B. It recruits more motor units, adding larger ones, and fires them faster.

C. It hands control of the arm from the motor cortex to the cerebellum.

D. It grows new muscle fibers within a few seconds.

Show Answer

The correct answer is **B**. Force is graded by recruiting more motor units (small ones first, then larger ones, following the size principle) and by raising their firing rate. Action potentials are all-or-none, so they can't simply get bigger (A).

Type: Understanding **Chapter:** Chapter 7: Movement: Muscles, Reflexes, and Motor Control

Question 21

A 66-year-old man has a resting tremor in one hand, slow movements, and stiff muscles. His doctor diagnoses Parkinson's disease and starts a common medicine that the brain converts into the missing neurotransmitter. Which medicine is it?

A. Levodopa, which is converted into dopamine

B. Naloxone, which is converted into endorphins

C. Acetylcholine tablets, which replace lost acetylcholine

D. Melatonin, which is converted into serotonin

Show Answer

The correct answer is **A**. Parkinson's disease destroys dopamine neurons in the substantia nigra. Dopamine itself can't cross the blood-brain barrier, but levodopa can, and brain cells convert it into dopamine. Levodopa improves symptoms but doesn't cure the disease.

Type: Clinical reasoning **Chapter:** Chapter 7: Movement: Muscles, Reflexes, and Motor Control

Question 22

What is the role of ATP in skeletal muscle contraction?

A. It starts the action potential in the motor neuron.

B. It moves tropomyosin to uncover the binding sites on actin.

C. It lets each myosin head let go of actin and reset for the next pull.

D. It is the neurotransmitter released at the neuromuscular junction.

Show Answer

The correct answer is **C**. ATP is needed for myosin to release actin and re-cock. That's why muscles lock stiff after death (rigor mortis) when ATP runs out. Uncovering the binding sites on actin (B) is triggered by calcium, not ATP.

Type: Understanding **Chapter:** Chapter 7: Movement: Muscles, Reflexes, and Motor Control

Question 23

Spina bifida is a birth defect that happens when:

A. The corpus callosum fails to form.

B. The back (lower) end of the neural tube fails to close.

C. Too many synapses are pruned before birth.

D. Axons in the spinal cord fail to receive myelin.

Show Answer

The correct answer is **B**. The brain and spinal cord form from the neural tube, which closes early in pregnancy. If its lower end fails to close, part of the spinal cord can be left exposed (spina bifida). If the front end fails to close, the result is anencephaly.

Type: Recall **Chapter:** Chapter 8: The Developing and Teenage Brain

Question 24

Brain scans show that total white matter volume keeps increasing slowly until about the late twenties. What best explains this?

A. Myelination of axons continues for decades.

B. Large numbers of new neurons are produced every year until age 30.

C. Synapse formation (synaptogenesis) reaches its peak in the late twenties.

D. The skull keeps growing, which pulls the brain larger.

Show Answer

The correct answer is **A**. White matter is made mostly of myelinated axons, and myelination continues region by region well into adulthood. Most neurons are made before birth (B), and synapse numbers peak much earlier in childhood before pruning (C).

Type: Understanding **Chapter:** Chapter 8: The Developing and Teenage Brain

Question 25

Which statement about fetal alcohol spectrum disorders (FASD) matches CDC guidance?

A. Only heavy drinking in the last month of pregnancy can cause FASD.

B. Wine and beer are safe during pregnancy; only hard liquor is risky.

C. There is no known safe amount, time, or type of alcohol during pregnancy, and FASD is preventable if the baby is not exposed to alcohol.

D. The effects of FASD disappear by adulthood.

Show Answer

The correct answer is **C**. The CDC states that there is no known safe amount, time, or type of alcohol during pregnancy, and that FASDs are preventable if a developing baby is not exposed to alcohol. FASD effects are lifelong (D is wrong), and the brain develops throughout pregnancy, so no stage is safe (A is wrong).

Type: Understanding **Chapter:** Chapter 8: The Developing and Teenage Brain

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Question 26

Which structure is most needed to form new declarative memories (facts and events)?

A. Cerebellum

B. Hippocampus

C. Basal ganglia

D. Occipital lobe

Show Answer

The correct answer is **B**. The hippocampus and nearby medial temporal lobe are needed to form new declarative memories, as Patient H.M.'s case showed. The cerebellum and basal ganglia (A, C) matter more for procedural memory, the memory for skills.

Type: Recall **Chapter:** Chapter 9: Learning, Memory, and Neuroplasticity

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Question 27

Maya hasn't ridden a bike in three years, yet she hops on and rides smoothly without thinking about how. Which type of memory is she using?

A. Episodic memory

B. Semantic memory

C. Working memory

D. Procedural memory

Show Answer

The correct answer is **D**. Procedural memory stores skills and habits ("how" knowledge) and works without conscious recall. Episodic memory (A) would be remembering a specific event, such as the day she learned to ride.

Type: Clinical reasoning (apply) **Chapter:** Chapter 9: Learning, Memory, and Neuroplasticity

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Question 28

After a car crash with a head injury, a man cannot remember the hour before the crash. Since waking up in the hospital, he has formed new memories normally. What is this called?

A. Retrograde amnesia

B. Anterograde amnesia

C. Loss of procedural memory

D. A working memory disorder

Show Answer

The correct answer is **A**. Retrograde ("backward") amnesia is the loss of memories from before an injury. Anterograde amnesia (B), which Patient H.M. had severely, is trouble forming new memories after the injury, and this man forms new memories normally.

Type: Clinical reasoning **Chapter:** Chapter 9: Learning, Memory, and Neuroplasticity

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Question 29

Which sleep stage has bursts of rapid eye movements, an EEG that looks a lot like waking, and a near-total loss of muscle tone in the arms and legs?

A. N1

B. N2

C. REM

D. N3

Show Answer

The correct answer is **C**. REM sleep combines rapid eye movements, a wake-like EEG, vivid dreams, and muscle atonia, which keeps you from acting out dreams. N3 (D) is deep slow-wave sleep with large, slow delta waves.

Type: Recall **Chapter:** Chapter 10: Sleep and Brain States

Question 30

Why can bright light late at night, such as from room lights and screens, make it harder to fall asleep?

A. Light speeds up the breakdown of adenosine, so sleep pressure disappears.

B. Light signals reach the suprachiasmatic nucleus, which lowers melatonin release from the pineal gland.

C. Light switches off the orexin neurons that keep you awake.

D. Light makes the brain skip REM sleep for the whole night.

Show Answer

The correct answer is **B**. Special light-sensitive retinal cells (most sensitive to blue light) signal the SCN, the master clock, which then reduces the pineal gland's release of melatonin, the "darkness" signal. Orexin (C) promotes wakefulness, so switching it off would make you sleepier, not more alert.

Type: Understanding **Chapter:** Chapter 10: Sleep and Brain States

Question 31

An EEG recorded from a person who is awake and relaxed with eyes closed shows a rhythm of about 8 to 13 waves per second over the back of the head. What is this rhythm called?

A. Delta

B. Theta

C. Beta

D. Alpha

Show Answer

The correct answer is **D**. The alpha rhythm (about 8 to 13 Hz) appears during relaxed wakefulness with eyes closed. Beta (C) is faster and appears when you are alert with eyes open, while delta (A) is the slow wave of deep N3 sleep.

Type: Recall **Chapter:** Chapter 10: Sleep and Brain States

Question 32

Which part of the nervous system drives the "fight or flight" response within seconds of a scare?

A. The sympathetic nervous system

B. The parasympathetic nervous system

C. The somatic nervous system

D. The HPA axis

Show Answer

The correct answer is **A**. The sympathetic branch of the autonomic nervous system acts in seconds, raising heart rate and triggering adrenaline release from the adrenal medulla. The HPA axis (D) is also part of the stress response, but it works through hormones and takes minutes.

Type: Recall **Chapter:** Chapter 11: Emotion, Stress, and the Body

Question 33

In a fear conditioning experiment, a rat hears a tone that ends with a mild foot shock. After a few pairings, the tone alone makes the rat freeze. In this experiment, the **foot shock** is the:

A. Neutral stimulus

B. Conditioned stimulus

C. Unconditioned stimulus

D. Conditioned response

Show Answer

The correct answer is **C**. The shock causes fear without any learning, so it is the unconditioned stimulus. The tone starts out neutral (A) and becomes the conditioned stimulus (B) after it is paired with the shock.

Type: Understanding **Chapter:** Chapter 11: Emotion, Stress, and the Body

Question 34

A 19-year-old has had nightmares, avoidance of reminders, and constant jumpiness for several months after an assault, and is diagnosed with PTSD. Which treatment has the strongest research support?

A. Avoiding every reminder of the event until the symptoms fade on their own

B. Trauma-focused talk therapy, such as cognitive processing therapy or prolonged exposure

C. Sleeping pills alone, to stop the nightmares

D. Waiting, because PTSD always goes away within a year

Show Answer

The correct answer is **B**. Trauma-focused psychotherapies are the most effective treatments for PTSD, and some medicines can also help. Avoidance (A) is one of the symptoms that keeps PTSD going, because it prevents new safety learning.

Type: Clinical reasoning **Chapter:** Chapter 11: Emotion, Stress, and the Body

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Question 35

In most people, where is Wernicke's area located?

A. Left frontal lobe

B. Right parietal lobe

C. Right occipital lobe

D. Left temporal lobe

Show Answer

The correct answer is **D**. Wernicke's area sits in the left temporal lobe and helps link speech sounds to meaning. The left frontal lobe (A) is home to Broca's area, which helps produce speech.

Type: Recall **Chapter:** Chapter 12: Language, Attention, and Decision-Making

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Question 36

A monkey learns that a light always comes one second before a sip of juice. Then, one day, the light turns on but **no juice arrives**. What do its midbrain dopamine neurons most likely do at the moment the juice was expected?

A. Their firing dips below the normal baseline.

B. They fire a strong burst.

C. They keep firing at their normal baseline rate.

D. They stop firing permanently.

Show Answer

The correct answer is **A**. Reward prediction error equals reward received minus reward predicted. Zero juice minus expected juice is negative, and dopamine neurons signal a negative error with a brief dip below baseline. A burst (B) signals a reward that is better than expected.

Type: Clinical reasoning (apply) **Chapter:** Chapter 12: Language, Attention, and Decision-Making

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Question 37

After a stroke, a 70-year-old man eats only the food on the right half of his plate and ignores people standing on his left. When someone points to the left side, he can see things there. His speech is normal. What is the most likely problem?

A. Broca's aphasia from a left frontal stroke

B. Wernicke's aphasia from a left temporal stroke

C. Left-sided neglect from a right parietal stroke

D. Complete blindness in his left eye

Show Answer

The correct answer is **C**. Neglect syndrome is a failure of attention to one side of space, most often the left side after right parietal damage. He can see the left side when cued, which separates neglect from a true loss of vision (D), and his normal speech rules out aphasia.

Type: Clinical reasoning **Chapter:** Chapter 12: Language, Attention, and Decision-Making

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Question 38

A 40-year-old man has jerky, dance-like movements he can't control, along with mood changes. His father had the same disease, and a genetic test shows an expanded CAG repeat in the *HTT* gene. Which brain region is damaged most?

A. Hippocampus

B. Striatum, part of the basal ganglia

C. Cerebellum

D. Occipital lobe

Show Answer

The correct answer is **B**. This is Huntington's disease, and the neurons it hits hardest are in the striatum, which normally helps put the brakes on unwanted movements. Losing that brake allows the involuntary movements. Early damage to the hippocampus (A) is typical of Alzheimer's disease instead.

Type: Clinical reasoning **Chapter:** Chapter 13: The Aging Brain and Neurodegeneration

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Question 39

Before a patient can start an anti-amyloid antibody such as lecanemab or donanemab, doctors confirm that amyloid is present, for example with an amyloid PET scan or a spinal fluid test. Why?

A. The drugs work by dissolving tau tangles, so tau must be measured first.

B. The test itself removes some amyloid and makes the drug work better.

C. The drugs are approved for any older adult with memory complaints, and the test is optional.

D. The drugs target amyloid and are approved for early Alzheimer's disease with confirmed amyloid, and memory problems can have other causes.

Show Answer

The correct answer is **D**. These antibodies clear amyloid plaques and are approved for mild cognitive impairment or mild dementia due to Alzheimer's with confirmed amyloid. Memory loss can come from many other conditions, and the drugs carry real risks such as ARIA, so treating someone without amyloid would bring risk without benefit.

Type: Understanding **Chapter:** Chapter 13: The Aging Brain and Neurodegeneration

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Question 40

Nusinersen, approved by the FDA in December 2016, is an antisense drug for which disease?

A. Spinal muscular atrophy (SMA)

B. Huntington's disease

C. Alzheimer's disease

D. Parkinson's disease

Show Answer

The correct answer is **A**. Nusinersen (Spinraza) treats SMA by changing how the mRNA from the backup gene *SMN2* is spliced (cut and joined), so cells make more full-length SMN protein. It is given into the spinal fluid by lumbar puncture.

Type: Recall **Chapter:** Chapter 13: The Aging Brain and Neurodegeneration

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Question 41

A rider's spinal cord is injured in the lower part of the chest (thoracic) region. Which pattern is most likely?

A. Weakness in all four limbs

B. Weakness of the face on one side

C. Weakness or paralysis of the legs, with normal arm strength

D. Loss of hearing in both ears

Show Answer

The correct answer is **C**. A spinal cord injury affects body parts below its level. Nerves to the arms leave the cord in the neck, above a chest-level injury, so the arms are spared and the legs are affected (paraplegia). Weakness in all four limbs (A) points to a higher, neck-level injury.

Type: Clinical reasoning (apply) **Chapter:** Chapter 14: Brain Injury, Stroke, and Epilepsy

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Question 42

Why do doctors say "time is brain" when someone may be having a stroke?

A. Most strokes get better on their own if the patient waits a few hours.

B. Brain tissue without blood flow starts dying within minutes, so faster treatment saves more of it.

C. All strokes are bleeds that keep growing until surgery.

D. Clot-busting medicines work best when given several days later.

Show Answer

The correct answer is **B**. Neurons have almost no energy reserve, so brain tissue starts dying quickly when blood flow stops. Treatments to reopen a blocked artery only work within limited time windows, so calling 911 right away matters. Most strokes are ischemic (blocked artery), not bleeds (C).

Type: Understanding **Chapter:** Chapter 14: Brain Injury, Stroke, and Epilepsy

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Question 43

During a soccer game, a 16-year-old heads the ball hard. Afterward he seems dazed, has a headache, and feels "foggy," but he never lost consciousness. A few minutes later he says he feels fine. What should happen?

A. He can return in 15 minutes if he answers a few memory questions correctly.

B. He can keep playing, because a concussion requires losing consciousness.

C. He should ice his head and return for the second half.

D. He should be removed from play for the rest of the day and not return until a health care provider clears him.

Show Answer

The correct answer is **D**. CDC guidance is to remove anyone with a suspected concussion from play right away and keep them out the same day and until a health care provider clears them. Most concussions happen without loss of consciousness, so option B is a dangerous myth.

Type: Clinical reasoning **Chapter:** Chapter 14: Brain Injury, Stroke, and Epilepsy

Question 44

In the United States, what number can you call or text to reach the Suicide & Crisis Lifeline?

A. 988

B. 1-800-662-4357

C. There is no national number; you have to find a local hotline.

D. 911 is the only option.

Show Answer

The correct answer is **A**. The 988 Suicide & Crisis Lifeline is free, confidential, and available 24/7 by call, text, or chat. 1-800-662-4357 (B) is a real line too, but it is SAMHSA's National Helpline for treatment referrals. If someone is in immediate danger, call 911.

Type: Recall **Chapter:** Chapter 15: Psychiatric Disorders, Developmental Disorders, and Addiction

Question 45

Stimulant medicines for ADHD, such as methylphenidate, are thought to help mainly by:

A. Blocking dopamine receptors so the brain calms down

B. Raising serotonin while lowering dopamine

C. Increasing dopamine and norepinephrine signaling, especially in the prefrontal cortex, which supports attention and impulse control

D. Shutting down the reward pathway completely

Show Answer

The correct answer is **C**. Stimulants boost dopamine and norepinephrine signaling, especially in the prefrontal cortex. Strengthening this "control center" can make it easier to filter distractions and hold back impulses, which is why a stimulant can help a person who is hyperactive.

Type: Understanding **Chapter:** Chapter 15: Psychiatric Disorders, Developmental Disorders, and Addiction

Question 46

For the past three weeks, a 15-year-old has felt sad most of the day, nearly every day. She has lost interest in soccer, sleeps poorly, and her grades are dropping. Which statement fits best?

A. This is normal teenage moodiness, so no one needs to do anything.

B. It can't be depression, because depression requires symptoms for at least a year.

C. Depression is a sign of a weak character, so she should try harder.

D. This matches the pattern of depression, so she should be evaluated by a doctor or mental health professional, because depression is treatable.

Show Answer

The correct answer is **D**. Depression involves a low mood or loss of interest for most of the day, nearly every day, for at least two weeks, with effects on daily life. It is a real, common, and treatable condition, not a weakness (C). A trusted adult can help her get evaluated.

Type: Clinical reasoning **Chapter:** Chapter 15: Psychiatric Disorders, Developmental Disorders, and Addiction

Question 47

During a neurological exam, the doctor asks the patient to raise her eyebrows, squeeze her eyes shut, and smile. Which cranial nerve is being tested?

A. Facial nerve (cranial nerve VII)

B. Trigeminal nerve (cranial nerve V)

C. Hypoglossal nerve (cranial nerve XII)

D. Oculomotor nerve (cranial nerve III)

Show Answer

The correct answer is **A**. The facial nerve controls the muscles of facial expression. The trigeminal nerve (B) is the one tested for facial sensation and chewing, and the hypoglossal nerve (C) moves the tongue.

Type: Recall **Chapter:** Chapter 16: How Doctors Examine the Brain

---

Question 48

Compared with CT, which is an advantage of MRI?

A. MRI is faster and is the usual first test for fresh bleeding in an emergency.

B. MRI is safe with any kind of metal implant.

C. MRI shows brain tissue in finer detail and uses no ionizing radiation.

D. MRI records the brain's electrical activity in real time.

Show Answer

The correct answer is **C**. MRI shows gray and white matter in fine detail without X-rays. CT is usually the faster first test in a suspected stroke because it quickly shows bleeding (A), and recording electrical activity in real time is the job of EEG (D).

Type: Understanding **Chapter:** Chapter 16: How Doctors Examine the Brain

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Question 49

A patient suddenly develops weakness of the left arm and leg. Her left-side reflexes are brisk, her left big toe goes up when the sole is stroked, and the lower left side of her face droops, but she can still wrinkle her forehead on both sides. Where is the lesion most likely?

A. Left cerebral hemisphere

B. Right cerebral hemisphere

C. Left facial nerve

D. Left side of the spinal cord in the neck

Show Answer

The correct answer is **B**. Brisk reflexes and a Babinski sign mean an upper motor neuron problem, the forehead-sparing face droop points to the brain rather than the facial nerve, and brain lesions affect the opposite side of the body. A spinal cord lesion (D) would not cause a face droop.

Type: Clinical reasoning **Chapter:** Chapter 16: How Doctors Examine the Brain

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Question 50

Over one day, a 19-year-old college student develops a fever, a severe headache, a stiff neck, and confusion. Doctors suspect an infection of the meninges. Which test samples the fluid around the brain and spinal cord to look for germs and white blood cells?

A. EEG

B. Functional MRI

C. Nerve conduction study

D. Lumbar puncture

Show Answer

The correct answer is **D**. A lumbar puncture collects cerebrospinal fluid from the lower back, below the end of the spinal cord, to check for signs of meningitis. Because bacterial meningitis is an emergency, doctors often start antibiotics right away rather than wait for every test result.

Type: Clinical reasoning **Chapter:** Chapter 16: How Doctors Examine the Brain

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A.7 Scoring Guide and What to Review Next

Score yourself

Give yourself 1 point for each correct answer, then find your range. These ranges are a rough guide for this mock exam only. They do not predict how you will place in a real competition, where questions, scoring, and the other competitors all vary.

Score	What it suggests	Next step
45 to 50	Excellent command of the book's content	Shift most of your time to your official study source, oral practice, and neuroanatomy ID.
38 to 44	Strong, with a few gaps	Restudy the chapters where you missed two or more questions, then retest yourself.
30 to 37	A solid base with clear weak areas	Use the table below to pick your three weakest chapters. Redo their quizzes and Brain Bee Practice.
Below 30	Many topics still need work	That's useful to know now. Go back to Chapters 1 to 4 first, since later chapters build on them, then work forward one chapter at a time.

Also look at the **type** of question you missed. If most misses are **Recall**, make more flashcards and test yourself daily. If most are **Understanding**, practice explaining ideas out loud in your own words. If most are **Clinical reasoning**, work through the Bedside cases with the method in Section A.5.

What to review next

Questions	Chapter to review
1 to 3	Chapter 1: Neurons, Glia, and the Nervous System
4 to 6	Chapter 2: The Action Potential
7 to 9	Chapter 3: Synapses and Neurotransmitters
10 to 13	Chapter 4: A Tour of the Brain: Neuroanatomy
14 to 16	Chapter 5: Vision
17 to 19	Chapter 6: Hearing, Touch, Taste, Smell, and Pain

Questions	Chapter to review
20 to 22	Chapter 7: Movement: Muscles, Reflexes, and Motor Control
23 to 25	Chapter 8: The Developing and Teenage Brain
26 to 28	Chapter 9: Learning, Memory, and Neuroplasticity
29 to 31	Chapter 10: Sleep and Brain States
32 to 34	Chapter 11: Emotion, Stress, and the Body
35 to 37	Chapter 12: Language, Attention, and Decision-Making
38 to 40	Chapter 13: The Aging Brain and Neurodegeneration
41 to 43	Chapter 14: Brain Injury, Stroke, and Epilepsy
44 to 46	Chapter 15: Psychiatric Disorders, Developmental Disorders, and Addiction
47 to 50	Chapter 16: How Doctors Examine the Brain

If you missed **two or more** questions from one chapter, put that chapter at the top of your Week 3 list. If you missed one, reread that chapter's Key Takeaways and redo its Brain Bee Practice questions. Then, a few days later, try the questions you missed again without looking at the answers. That second try is retrieval practice too.

Sources

- International Brain Bee. About, Competition, FAQ, and home page. Accessed October 12, 2026.
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- Dunlosky, J., Rawson, K. A., Marsh, E. J., Nathan, M. J., & Willingham, D. T. (2013). Improving students' learning with effective learning techniques. *Psychological Science in the Public Interest*, 14(1), 4-58. doi:10.1177/1529100612453266. Summary: Association for Psychological Science press release.

Appendix B: Careers in Neuroscience and Medicine

So, what do you want to be?



I'm a sea slug, so my career options are limited to "helping scientists win Nobel Prizes." Yours are much wider! This appendix maps out the many jobs that use what you learned in this book, and how people actually get there.

B.1 One Brain, Many Careers

Think about a single patient who has a stroke. A **neurologist** (a doctor who treats diseases of the brain and nerves) figures out where the damage is. A **neuroradiologist** reads the brain scans. A **neurosurgeon** may operate. A **neuroscience nurse** watches the patient around the clock. Then a **physical therapist**, an **occupational therapist**, and a **speech-language pathologist** help the patient walk, get dressed, and talk again. Behind them, **neuroscientists**, **engineers**, and **data scientists** built and tested the drugs, scanners, and tools everyone uses.

That is the big idea of this appendix: neuroscience is not one job. It is a field that connects to medicine, research, rehabilitation, engineering, computing, and teaching. Some take more than a decade of training after high school, and others take far less. Patients need all of them.

A quick note before we start. The training paths below describe the **United States** and are **typical**, not guaranteed. Rules change, and many people take detours. Always check the official sources linked in each section and in the Sources list.

B.2 Careers at a Glance

Here is a quick key for the table. A **residency** is paid, supervised on-the-job training that every new doctor completes after medical school. A **fellowship** is optional extra training in a narrower area after residency. A **license** is legal permission from a state to practice.

Career	What they do	Typical U.S. education and training path
Neurologist	Diagnoses and treats disorders of the brain, spinal cord, nerves, and muscles, such as stroke, epilepsy, migraine, multiple sclerosis, and Parkinson's disease. Does not usually operate.	4-year college degree → 4 years of medical school (MD or DO) → **4-year neurology residency**, which includes a first year of general internal medicine → optional fellowship (for example, stroke or epilepsy).
Neurosurgeon	Operates on the brain, spine, and nerves, for example to remove tumors, relieve pressure after injuries, or fix problems in the spine.	College → medical school → **7-year neurosurgery residency** (one of the longest in medicine) → optional fellowship.
Psychiatrist	A medical doctor who diagnoses and treats mental health conditions such as depression, anxiety, schizophrenia, and addiction. Can prescribe medicine and provide therapy.	College → medical school → **4-year psychiatry residency** → optional fellowship (for example, child and adolescent psychiatry).
Child neurologist	A neurologist for infants, children, and teens. Treats conditions such as childhood epilepsy, cerebral palsy, and genetic disorders of the nervous system.	College → medical school → typically **2 years of pediatrics** (or an approved mix of pediatrics plus another year) → **3 years of child neurology**, about 5 years in all.

Career	What they do	Typical U.S. education and training path
Neuroradiologist	A doctor who specializes in reading images of the brain, spine, head, and neck, such as MRI and CT scans. Some also do image-guided procedures.	College → medical school → **diagnostic radiology residency** (4 years of radiology, usually after a 1-year clinical year, so typically 5 years) → **neuroradiology fellowship**, which lasts 1 year (12 months) in ACGME-accredited programs.
Neuroscientist (PhD researcher)	Designs and runs experiments to discover how the nervous system works, in labs at universities, government agencies, or companies.	Bachelor's degree (often biology, psychology, neuroscience, chemistry, or engineering) → **PhD**, which averages about 6 years for biomedical fields → usually 1 or more years of postdoctoral research training.
Physician-scientist (MD/PhD)	Sees patients *and* runs a research lab, often turning lab discoveries into new treatments.	College → combined **MD-PhD program**, most often 7 to 8 years → residency → often a research-focused fellowship.
Clinical psychologist / neuropsychologist	Clinical psychologists assess and treat mental and behavioral health using therapy and testing (they usually do not prescribe medicine). **Neuropsychologists** study and test how brain damage or disease affects memory, attention, language, and behavior.	Bachelor's degree → **doctoral degree** in psychology (PhD or PsyD), including a 1-year internship → supervised experience for a state license. Neuropsychologists typically add a **2-year postdoctoral residency** in clinical neuropsychology, and many then seek board certification.
Neuroscience nurse	A registered nurse (RN) who cares for patients with stroke, brain injury, spinal cord injury, seizures, and other neurological	Nursing diploma, associate's degree, or bachelor's degree in nursing (BSN; many hospitals prefer a BSN) → pass the **NCLEX**

Career	What they do	Typical U.S. education and training path
	conditions, often in intensive care units or stroke units.	licensing exam → work as an RN. After at least 1 year (2,080 hours) of neuroscience nursing, nurses can seek the **CNRN** (Certified Neuroscience Registered Nurse) credential.
Physical therapist (PT)	Helps people regain movement, strength, and balance after strokes, spinal cord injuries, or other conditions.	Bachelor's degree with science prerequisites → **Doctor of Physical Therapy (DPT)**, typically about 3 years → state licensing exam. Optional residency later.
Occupational therapist (OT)	Helps people do everyday activities (dressing, cooking, writing, working) after injury or illness, often by retraining skills or adapting tools and spaces.	Bachelor's degree → **entry-level master's or doctoral degree** in occupational therapy (master's programs typically take 2 to 3 years) with supervised fieldwork → **NBCOT** certification exam → state license.
Speech-language pathologist (SLP)	Assesses and treats problems with speech, language, voice, fluency (such as stuttering), and swallowing. Many work with stroke survivors or with children in schools.	Bachelor's degree → **master's degree** in speech-language pathology (usually about 2 years) → supervised **clinical fellowship** (at least 36 weeks and 1,260 hours for ASHA certification) and a national exam → state license and the CCC-SLP certificate.
Neural / biomedical engineer	Designs medical devices and technology, such as brain-computer interfaces, deep brain stimulators, cochlear implants, prosthetic limbs, and imaging machines.	**Bachelor's degree** in biomedical engineering or a related engineering field. Some jobs require a graduate degree, and leading a research team usually does.

Career	What they do	Typical U.S. education and training path
Data scientist in neuroscience	Uses statistics, programming, and machine learning to find patterns in large data sets, such as brain scans, recordings from neurons, or clinical trial results.	**At least a bachelor's degree** (often math, statistics, computer science, or engineering). Some jobs require a master's or doctoral degree, and research roles in neuroscience often do.
Science teacher / science communicator	Teachers bring neuroscience into classrooms. Communicators explain science to the public as writers, journalists, video makers, museum educators, or podcasters.	**Teacher:** bachelor's degree → state teaching license, which includes student teaching and exams (every state also offers alternative routes). **Communicator:** no single path. Many have a science degree plus strong writing or media experience.

What about salaries?

This appendix does not list salaries. Pay changes every year and varies a lot by location and setting. If you want current numbers, the U.S. Bureau of Labor Statistics Occupational Outlook Handbook lists median pay for most of these jobs, with the year of the data.

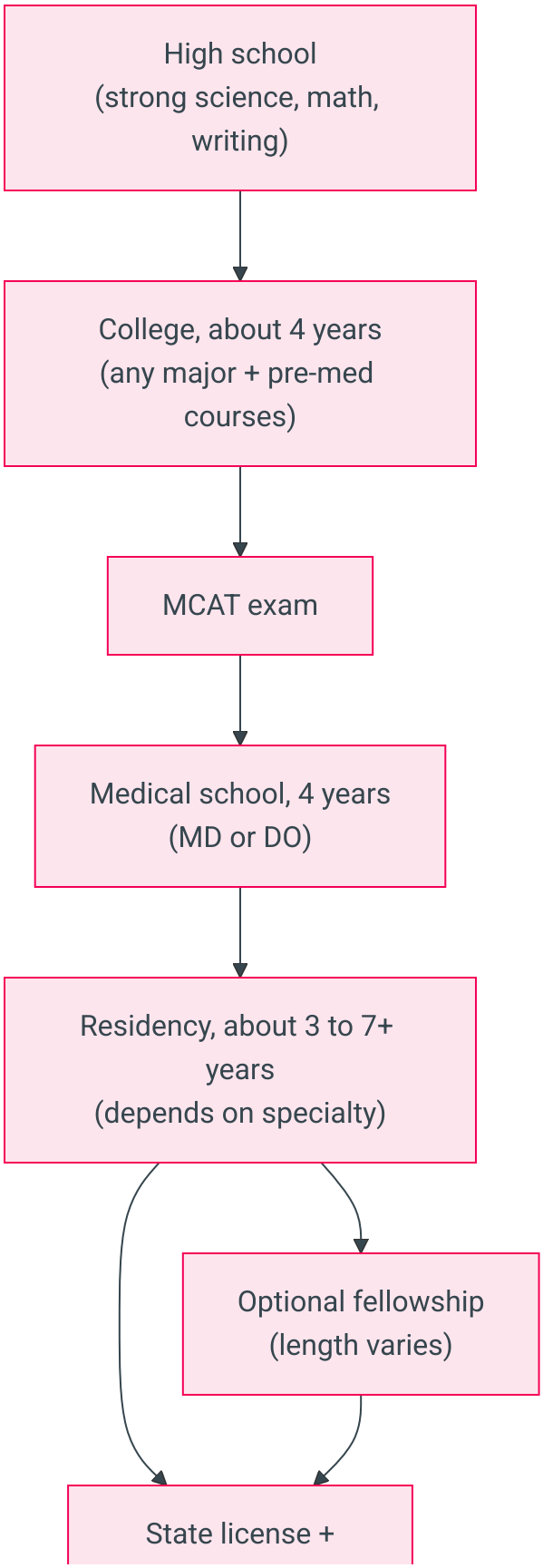
B.3 The Path to Becoming a Doctor (MD or DO)

In the U.S., there are two kinds of fully licensed physicians:

- **MD** (Doctor of Medicine), the more common degree.
- **DO** (Doctor of Osteopathic Medicine). DO schools teach the same core medicine plus required training in osteopathic manipulative medicine (OMM), which uses the hands to treat problems in the bones, joints, and muscles.

Both MDs and DOs can become neurologists, neurosurgeons, psychiatrists, or any other specialist. Since 2020, residencies for both MD and DO graduates have been accredited by

one organization, the Accreditation Council for Graduate Medical Education (ACGME). Here are the steps in plain language.


High school
(strong science, math, writing)
College, about 4 years
(any major + pre-med courses)
MCAT exam
Medical school, 4 years
(MD or DO)
Residency, about 3 to 7+ years
(depends on specialty)
Optional fellowship
(length varies)
State license +

board certification

Step 1: High school. Take the strongest science and math classes you can, and learn to write clearly. Explore what you enjoy (see Section B.5).

Step 2: College, with pre-med courses. You do **not** have to major in biology. The Association of American Medical Colleges (AAMC) says most medical schools have no preference about your major. You do need to take the courses that medical schools require and that the MCAT covers. At a minimum, the AAMC recommends a year each of biology, general chemistry, organic chemistry, and biochemistry. Many schools also want physics, math or statistics, English, and psychology or sociology. Requirements differ, so check each school.

Step 3: The MCAT. The Medical College Admission Test is a long, computer-based exam with four sections: chemistry and physics in living systems; biology and biochemistry; psychology, sociology, and biology of behavior; and critical reading and reasoning.

Step 4: Medical school (4 years). The first part is mostly classroom and lab science. The later part is mostly **clinical rotations**, where students work in hospitals and clinics in many specialties. Along the way, students take national licensing exams: the **USMLE** for MD students, and the **COMLEX-USA** for DO students (DO students may also take the USMLE).

Step 5: Residency (length depends on specialty). Most residencies last from about 3 to 7 years, depending on the specialty. For brain-related fields:

Specialty	Typical residency length (ACGME)
Neurology	4 years (48 months), including a first year of internal medicine (sometimes done as a separate preliminary year)
Psychiatry	4 years (48 months)
Child neurology	about 5 years (2 years of pediatrics or an approved alternative + 3 years of child neurology)
Diagnostic radiology	typically 5 years (1 clinical year + 4 years of radiology), then a 1-year neuroradiology fellowship

Specialty	Typical residency length (ACGME)
Neurosurgery	7 years (84 months)

Step 6: Optional fellowship. Many doctors add a fellowship to specialize further, for example in stroke, epilepsy, movement disorders, or neurocritical care. Fellowship length varies by field.

Step 7: Licensing and board certification. Every state requires physicians to be licensed. Most specialists also earn **board certification**, which the American Board of Medical Specialties describes as a higher standard than a license alone. It requires passing specialty exams and keeping skills current over a whole career.

Add it up and a neurologist typically trains for about 12 years after high school (4 + 4 + 4). A neurosurgeon trains for about 15 years, often more with a fellowship. That is a long road, but residents earn a salary (called a stipend), and every year you are learning by caring for real patients.

B.4 The Research Path: PhD and MD/PhD

Some people love the question "Why?" more than anything else. For them, a research career may be the best fit.

The PhD path. A **PhD** (Doctor of Philosophy) is a research degree. In neuroscience, PhD students take a year or two of advanced classes and then spend most of their time doing original experiments in a lab. They finish by writing and defending a **dissertation**, a long report on their new discoveries. The AAMC notes that the average biomedical PhD in the U.S. takes about six years. Many biomedical PhD students receive a **stipend** (a living allowance) and help with tuition, for example through NIH training grants that cover stipends, tuition, and fees. Funding differs from program to program, so ask each one how it supports students.

After the PhD, most researchers do one or more **postdoctoral** positions ("postdocs"). These are temporary research jobs where they build skills and publish their work before applying to lead their own lab, work in industry, teach, or move into science policy or communication.

The MD/PhD path. A **physician-scientist** earns both an MD (or DO) and a PhD. Most MD-PhD students finish both degrees in **7 to 8 years**, according to the AAMC. A common pattern is two years of medical school, then several years of PhD research, then a return to clinical rotations. After that comes residency, just like any other doctor.

Many MD-PhD programs are supported by the National Institutes of Health through the **Medical Scientist Training Program (MSTP)**, run by the National Institute of General Medical Sciences (NIGMS). MSTP training grants help pay trainees' tuition, fees, and stipends. Trainees must be U.S. citizens, noncitizen nationals, or permanent residents, and each institution can have only one MSTP. MD-PhD admission is very competitive, and applicants usually need significant research experience in college.

Research is for doctors, too



You don't need a PhD to do research. Many MDs, nurses, therapists, and engineers help run clinical trials or study better ways to care for patients. If you like both people *and* puzzles, you can have both.

B.5 What You Can Do in High School, Starting Now

You do not need to pick a career in ninth grade. The goal right now is to **explore**, build strong skills, and find out what you enjoy. Here are some concrete steps.

1. Take strong classes.

- **Biology and chemistry** are the base for almost every career in this appendix. Take physics too if you can.
- **AP Psychology** (if your school offers it) introduces brain and behavior topics, many of which also show up on the MCAT.
- **Statistics** matters more than most students expect. Doctors read studies, scientists analyze data, and data scientists live in it.
- **Math and computer science** help with engineering, data science, and research.
- **English and writing** matter for everyone. Doctors write notes, scientists write papers, and teachers explain ideas.

2. Join or start a neuroscience club. A club can read articles, invite local scientists or doctors to speak, and study for competitions together. If your school has no club, a teacher sponsor and a few friends are often all you need to start one.

3. Compete in the Brain Bee. The **International Brain Bee** is a neuroscience competition for students generally aged 13 to 19. Students compete in a **local** Brain Bee, and local winners advance to their **national** competition. National champions can then compete in the **IBB World Championship**. Formats, dates, and extra rules (such as grade or school requirements) differ by chapter, so **check your chapter's rules**. You can find chapters on the Brain Bee website. This textbook was built to help you prepare.

4. Take part in Brain Awareness Week. Every March, the **Dana Foundation** runs Brain Awareness Week, a global campaign to get the public excited about brain science. Schools, universities, hospitals, and labs host events. Your club could run a booth, a brain-themed lesson for younger students, or a display for your school.

5. Look for research experiences, carefully. Many universities and hospitals run summer research programs for high school students. One well-known federal option is the **NIH Summer Internship Program (SIP)**, where interns work full time in NIH research labs. It is **not** open to most high school students. In recent years, applicants have had to be U.S. citizens or permanent residents and **18 by September 30 of the internship year**. High school applicants must be **seniors** who will graduate before the internship starts, and a senior who is only 17 on June 1 of that year must live within 40 miles of an NIH campus. Interns should also plan ahead for housing near the lab. Rules can change each year, so always read the current SIP page.

> ⚠ **Be careful with pay-to-play programs**
>
> Some summer programs charge high fees and promise "research experience" or an edge in admissions. A high price does not mean a program is better. Many strong opportunities are free or even pay you. Before applying, ask a teacher or school counselor, find out who runs the program, and look for clear information about what you would actually do.

6. Read widely. Read science news, books about the brain, and articles from trustworthy sites. BrainFacts.org, from the Society for Neuroscience, is a good place to start.

7. Volunteer in healthcare settings. Hospitals, nursing homes, hospice programs, and clinics often have volunteer programs for teens. Most set a minimum age, so check with

each one. Volunteering shows you what healthcare is really like: the waiting, the kindness, and the hard moments. It also helps you learn whether you enjoy working with patients.

8. Shadow professionals. Shadowing means following a doctor, nurse, therapist, or scientist for a day or more to watch what they do. Ask family friends, your own doctor, or a teacher if they know someone. Shadowing different jobs is one of the best ways to compare them.

9. Take care of yourself. Sleep, friendships, hobbies, and sports matter. A long career is a marathon, not a sprint.

B.6 Ply's Advice

There is no single right path



Some of the best brain doctors and scientists started out as music majors, engineers, nurses, or late bloomers who found neuroscience in their twenties or thirties. Your path can bend and still get you somewhere great. Every big idea starts at a single synapse, and every big career starts with one small, curious step!

Here are a few last thoughts:

- **Many paths, one goal.** Doctors, nurses, therapists, engineers, scientists, data experts, and teachers all help people with brain conditions. Pick the work that fits *you*: how much time you want to spend with patients, in a lab, at a computer, or in a classroom.
- **Detours are normal.** People switch majors, take gap years, work before graduate school, or change careers. Admissions committees often value real-world experience.
- **Ask for help.** Counselors, teachers, college pre-health advisors, and professionals in the field are usually happy to answer questions.
- **Check the facts yourself.** Training rules and program details change. Use the official sources below to confirm anything before you make big decisions.

Sources

All links were opened and checked on October 12, 2026.

Medical training and specialties

1. Association of American Medical Colleges (AAMC). Applying to Medical School as a Nonscience Major.
2. AAMC. What's on the MCAT Exam?
3. AAMC. Education and Training in MD-PhD Programs.
4. AAMC. Is an MD-PhD Right for Me?
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7. United States Medical Licensing Examination. USMLE home page.
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3. BLS Occupational Outlook Handbook. Medical Scientists.

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1. BLS Occupational Outlook Handbook. Psychologists.
2. American Board of Professional Psychology. Clinical Neuropsychology: Specialty Specific Requirements.
3. BLS Occupational Outlook Handbook. Registered Nurses.
4. NCSBN. NCLEX: The Premier Nurse Licensure Exam.
5. American Board of Neuroscience Nursing. CNRN Eligibility.
6. BLS Occupational Outlook Handbook. Physical Therapists.
7. American Physical Therapy Association. Becoming a Physical Therapist.
8. BLS Occupational Outlook Handbook. Occupational Therapists.
9. American Occupational Therapy Association. Become an OT/OTA.
10. National Board for Certification in Occupational Therapy. NBCOT home page.
11. BLS Occupational Outlook Handbook. Speech-Language Pathologists.
12. American Speech-Language-Hearing Association (ASHA). Apply for Certification in Speech-Language Pathology.
13. ASHA. A Guide to the ASHA Clinical Fellowship Experience.
14. BLS Occupational Outlook Handbook. Bioengineers and Biomedical Engineers.
15. BLS Occupational Outlook Handbook. Data Scientists.
16. BLS Occupational Outlook Handbook. High School Teachers.
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