

# BrainFacts

A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

A Companion Publication to *BrainFacts.org*



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*Brain Facts* is produced as part of SfN's commitment to advance public education and information about the brain and nervous system. For more information or to download a free copy, please go to [brainfacts.org/book](http://brainfacts.org/book).

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## Know Your Brain, Know Yourself

*Brain Facts* serves as the companion publication to *BrainFacts.org* — a public information initiative of The Kavli Foundation, the Gatsby Foundation, and the Society for Neuroscience.

Relaunched in the fall of 2017, the site affirms its continued commitment to neuroscience literacy and outreach to the public. The site's new design and structure is evidence of this renewed commitment to providing trusted content that tells the story of neuroscience.

Funding from the Wellcome Trust allowed *BrainFacts.org* to expand its capacity for multimedia through video animations and interactive puzzles that lead you through the Core Concepts — the eight ideas that people need to know about their brain and nervous system — as well as an interactive human brain model containing more than 50 neuroanatomical structures with descriptions.

Visit *BrainFacts.org* and engage in an exploratory journey behind the neuroscience of everyday life.

As much as *Brain Facts* aims to inspire future scientists, researchers, and innovators, its primary purpose is to help you understand your brain — because when you know your brain, you know yourself.

As you peruse this new edition of *Brain Facts*, you will notice that in addition to incorporating Core Concepts, we have expanded the book to include chapters on the teenage brain as well as on thinking and decision-making. There are more than 30 images from neuroscience that will enhance your understanding of everything from neurogenesis to neural networks. In addition, the glossary has been rewritten and reviewed to include nearly 80 new key terms.

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A companion to *BrainFacts.org*

A PUBLIC INFORMATION INITIATIVE OF:





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# INTRODUCTION

Neuroscience is rapidly advancing what we know about the brain, the nervous system, and ourselves. It's often difficult to keep up with every discovery. Just as we were producing this book, The Brain Prize for 2017 was awarded to neuroscientists whose research explains the brain's learning and reward system. That discovery helps us to understand the behaviors that trigger compulsive gambling and drug and alcohol addiction. Then, the 2017 Nobel Prize for Medicine or Physiology honored researchers who revealed the inner workings of circadian rhythms, our body's internal clock, and The Brain Prize for 2018 recognized discoveries about the underlying mechanisms of neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

Discovery doesn't happen overnight, but the field has generated significant eureka moments since our last edition. Here we can take a moment to slow down and explore the fundamentals behind the research and discoveries that have built neuroscience. This eighth edition of *Brain Facts* contains our most current understanding of what we know *today* about the brain while addressing emerging topics in the field.

Underpinning every new discovery are the concepts and principles that neuroscientists have established in more than a century of studying the brain. Members of the Society for Neuroscience articulated those concepts more than a decade ago as Core Concepts — the eight ideas that people need to know about their brain and nervous system. Here, Core Concepts provide touchstones for deepening your understanding of the material presented. For example, information about circadian rhythms fits into the context of the concept that the brain uses specific circuits to process information. The role of the learning and reward systems in behaviors such as compulsive gambling and addiction illustrates the concept that the brain uses inference, emotion, memory, and imagination to make predictions.

Core Concepts icons throughout the text offer you the opportunity to place information in the book into the wider context of neuroscience as a whole. They serve as a foundation upon which you can build more detailed knowledge. If you need a reference point, don't forget to use the extended cover flap to remind you of the Core Concepts along the way, or as a bookmark during your reading.

## NEUROSCIENCE CORE CONCEPTS



### Your Complex Brain

A human brain contains roughly 86 billion nerve cells, or neurons. Contrary to popular misconception, we use all of the neurons in our brains, not just some small fraction of them.

Each of those neurons exchanges electrical signals with thousands of other neurons to create the countless circuits that, along with the nerves throughout our bodies, form our nervous system. In the course of millions of years, our nervous systems have evolved from much simpler beginnings. Roundworms, fruit flies, zebrafish, salamanders, mice, and monkeys all possess nervous systems that share fundamental

similarities with the human nervous system. The nervous system keeps our bodies in sync by communicating with all other parts of our bodies, like the cardiovascular system, the gastrointestinal system, the immune system, etc. With so many interconnected parts, however, there are endless ways for things to go wrong. From Alzheimer's disease to depression, an estimated one in four people worldwide will face a neurological or psychiatric condition, causing enormous financial and social burdens. The promise of solving these problems lies in unraveling the mysteries of the brain and nervous system.



### How Neurons Communicate

Your brain can serve as your body's command center because neurons communicate with each other. They relay messages throughout your body and power all of your thoughts and actions. Neurons talk to each other using both electrical and chemical signals.

When you stub your toe, sensory neurons create electrical signals, called action potentials, which travel rapidly down a neuron. Those electrical signals, however, cannot cross the gap between two neurons.

In order to communicate, the action potential is transformed into a chemical

message, which crosses the gap, called a synapse. The release of chemical messengers can trigger a second action potential in the neuron on the other side of the synapse, conveying the message onward or, when the action potential triggers the release of a chemical messenger that blunts the transmission of a signal, quelling the message.

This happens over and over, and with repeated activity, the synapse grows stronger, so the next message is more likely to get through. That way, neurons learn to pass on important messages and ignore the rest. This is how our brains learn and adapt to an ever-changing world.





### How Your Brain Processes Information

Your nervous system is filled with circuits made up of neurons that relay messages around your brain and body. They're responsible for everything you think, do, say, and feel. Sensory circuits carry signals from sense receptors to your brain. Motor circuits send commands to your muscles. Simple circuits carry out your automatic reflexes.

Higher-level activities like memory, decision-making, and perceiving the world

around you require complex circuits.

All of these circuits arise before you're born, when genes direct neurons to assemble simple circuits in your developing brain. As your neurons and their connections change from new experiences and environments, those simple circuits become much more complex. These changes happen mostly in childhood but continue over your whole life — all a part of building a better brain.



### How Experience Shapes Your Brain

You've had most of the neurons in your brain since birth. Most of those will stick around for the rest of your life, yet your brain is constantly changing — neuroscientists call this plasticity. Learn a new skill or language and your brain reacts by strengthening or weakening the connections between neurons — even creating new ones. Each new experience shapes your brain to become uniquely yours.

That capacity to change is vital. A brain damaged by injury or disease may eventually

regain lost abilities — rerouting connections and sometimes even growing new neurons, but only quite slowly if at all. At the same time, in a healthy brain neurons die off, too. During development, the human brain grows an excess of neurons. Early in life, the brain eliminates those extra cells, keeping only those connections you need in a process called synaptic pruning. Later on, unused neurons can wither away. Physical and mental exercise preserves them, keeping your brain healthy.



### Reasoning, Planning & Solving Problems

Your brain's roughly 86 billion interconnected neurons endow it with the ability to understand the world, plan actions, and solve problems. Doing so requires the brain to incorporate all available information. By combining information from all of your body's senses, the brain paints a picture of the world around you. Then, using inference and instinct, the brain makes sense of the picture it assembles.

The brain both makes and uses emotions, which are value judgments that help the brain respond effectively to events. It

associates the pictures it assembles with feelings to form memories. Our brains store those memories, learn from them, and use that knowledge in the future. By combining all of these tools with imagination, your brain can predict future events, calculate your next move, and devise plans for future opportunities. Consciousness requires that all of these activities function normally. In other words, your brain's trillions of connections work together to understand the world, to think about the future, and to create ... you.



### The Power of Language

One thing that makes humans special is our talent for talking. Whether it's a professor's technical discourse or a late night comic's zingy one-liner, humans communicate in ways that are far more complex than those of other animals because our brains are amply wired for it.

Compared with other animals, the human brain possesses an enormous cerebral cortex that is brimming with neural circuits dedicated to language. Neurons in the temporal, parietal, and frontal lobes of

the cortex form circuits that interpret the sounds and symbols of language.

We use those circuits to generate words, turn them into sounds, and understand the sounds we hear back. From birth, our brains are primed to learn language. Language endows us with thoughts and creativity. With it, we can trade ideas and information, share our observations, and let others build on our discoveries. Over time, that has led to human culture and all of the inventions of modern society.





### The Source of Curiosity

Did you know that your brain runs on only 25 watts of electricity — enough to power an LED light bulb? Or that there are nearly 10,000 different types of neurons in your brain? The fact that we know these things — or even care — is due to a special ability that arises in our complex brains: curiosity.

From a very early age, curiosity drives us to understand our world, our communities, our bodies, and even our own brains. For the last two hundred years, the study of neuroscience has allowed us to do just that. We've learned how individual neurons work at a molecular level, and how billions

of them work together to let you talk, learn, and imagine. We are learning why sugar is so hard to avoid, how exercise helps the brain, and why the urge to scratch when we have an itch is so irresistible.

Along the way, this exploration has led to innumerable insights that have helped us to solve human problems. We have treatments for pain and Parkinson's disease, and more are on their way. Depression and Alzheimer's disease are divulging their secrets. Still, much remains to be learned about the brain, and there are many more discoveries to be made.



### How Research Benefits Human Health

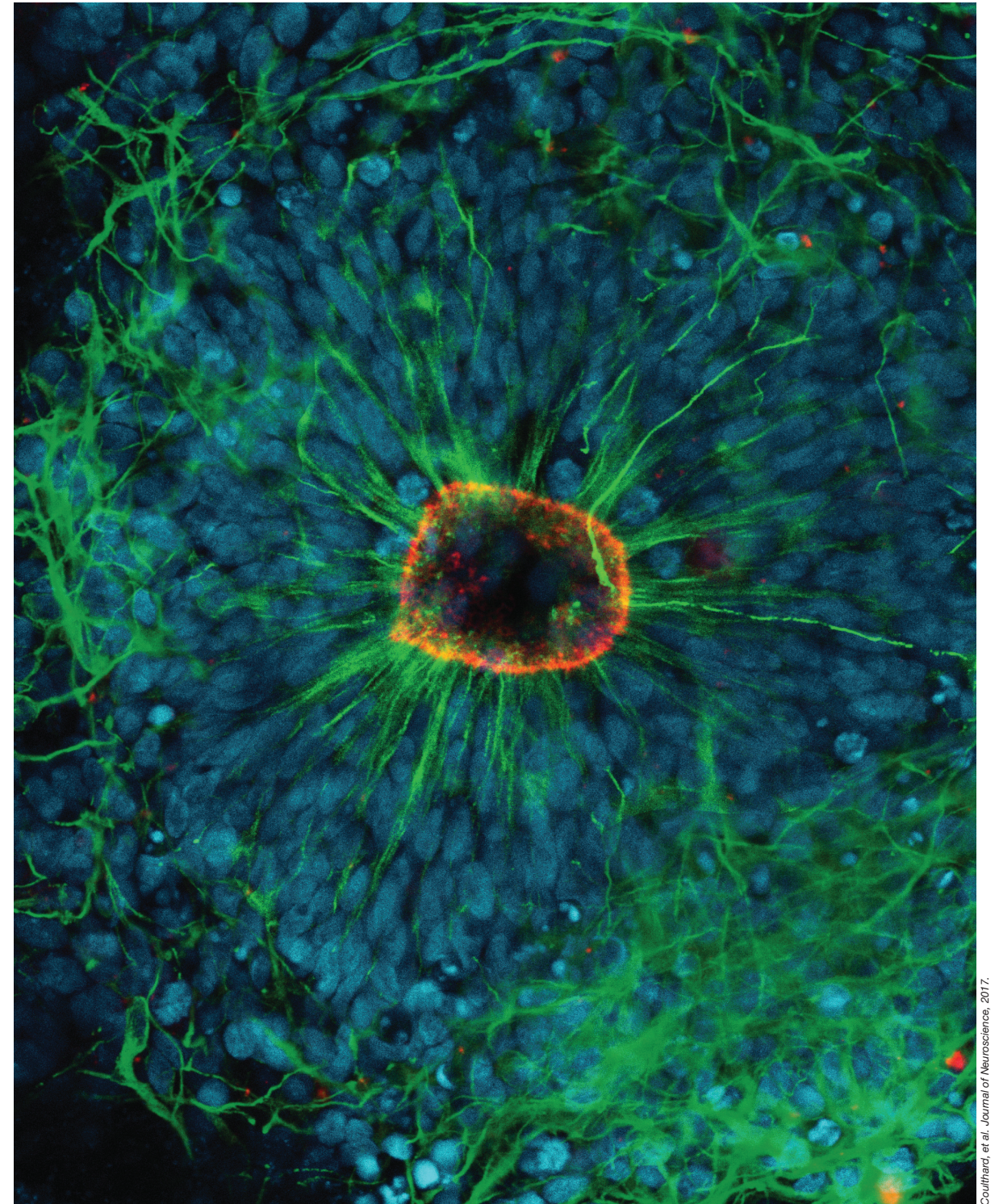
The United Nations estimates that neurological and psychiatric conditions like Alzheimer's disease, Parkinson's disease, and depression afflict one in four people worldwide. They cause more total disability than do heart attacks, cancers, or HIV/AIDS each year, inflicting profound suffering and robbing patients of health and independence. In doing so, they also leech an estimated \$1.5 trillion from the U.S. economy alone. Those numbers, and the human stories behind them, are among the driving forces behind neuroscience.

Neuroscientists study the biology of nerves and the brain, in both animals and humans, in order to understand these destructive conditions — and ultimately find a treatment or cure. When a promising treatment emerges, neuroscientists work with

other medical professionals to carefully test the remedy in animals and, eventually, in humans. If it proves safe and effective in those tests, the medicine is approved for patients nationwide. Researchers have been using that process to fight the devastation of neurological disorders and mental illness for decades.

In the 1950s and '60s, it led to the medication L-dopa, which has helped millions of patients to beat back symptoms of Parkinson's disease. In the 1990s, it yielded a class of drugs called Selective Serotonin Reuptake Inhibitors, like Prozac, to treat depression.

Today, neuroscience research is leading to promising advances for a host of conditions, from Alzheimer's disease to epilepsy to schizophrenia. In a field in which every advance has the chance to help ease suffering, research is more than a job: It's a human imperative.



To study the human brain, sometimes a petri dish is more useful than the real thing. This image shows a neural rosette, a model of the developing human brain that scientists use to study how new cells are born.

In the center of the rosette are precursor cells, specialized cells that create new neurons and glia by dividing themselves. The red ring is a visualization of the connections between these precursor cells. As they generate new neurons and glia, the newborn cells radiate out from the center of the rosette to the outer edge of the brain using the precursor cells as a scaffolding, marked in green. With this model, scientists can directly observe the processes behind the developing human brain from the earliest stages.



# Brain Basics

The brain is literally the “nerve center” of your body — it contains billions of neurons that transmit information from the body and the outside world, and then programs our responses — conscious and unconscious movements, thoughts, emotions, and memories. What’s more, your brain can do all these things simultaneously: You can throw a ball while talking to a friend, plan dinner while you’re shopping, or daydream about a balloon ride as you drive to work. Your brain can pull off these feats of multitasking because it is split into many distinct regions specialized for specific tasks and abilities.

## Major Brain Landmarks

The largest part of the human brain is the **cerebrum**. It is divided into two large, separate hemispheres, one on the left side, the other on the right. The hemispheres are connected by bundles of nerve fibers that carry information from one side of your brain to the other. The largest of these bundles forms a bridge between the cerebral hemispheres and is called the **corpus callosum**.

The surface of the cerebrum is a deeply folded layer of nerve tissue called the **cerebral cortex**. Its deep folds increase the area of the cerebral cortex, creating space in this surface layer for more neurons, which increase the brain’s processing power. Just as explorers use landmarks like rivers and mountain ranges to describe and map continents, neuroscientists use the deepest divisions of the cerebrum to identify regions of each hemisphere as separate lobes — distinct regions that have characteristic functions. This “brain map” will serve as a useful trail guide as you explore the brain in the chapters ahead.

The **frontal lobes** are at the front of the brain, immediately above the eyes. Parts of these lobes coordinate voluntary movements and speech, memory and emotion, higher cognitive skills like planning and problem-solving, and many aspects of personality.

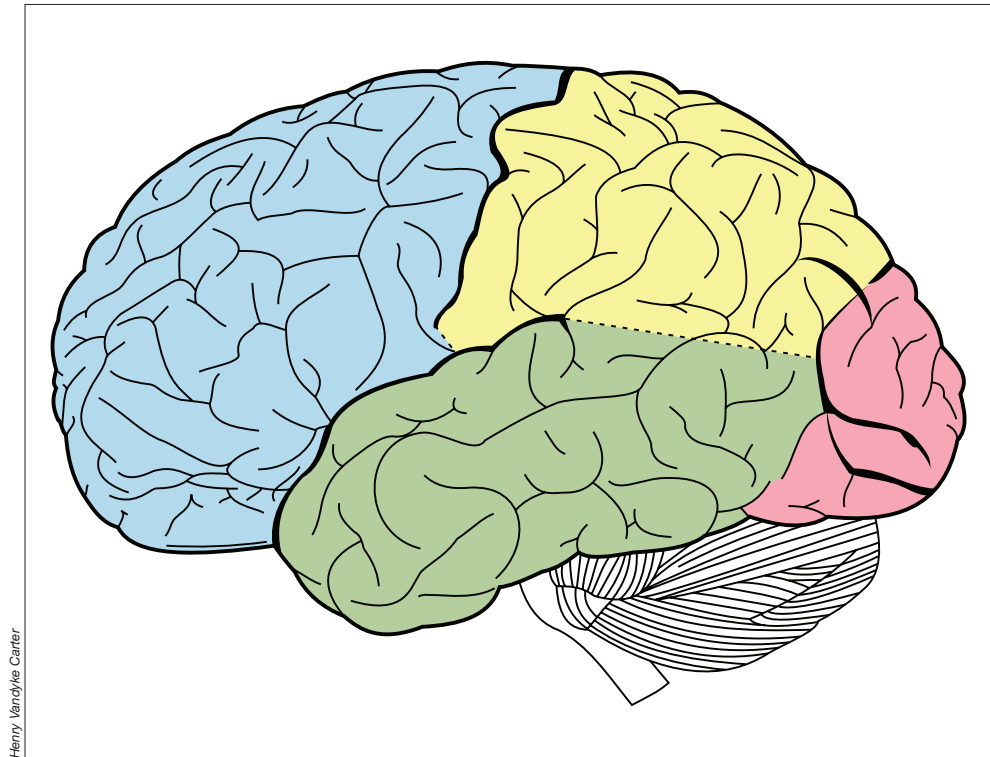
The **parietal lobes** are located at the top of the brain, immediately behind the frontal lobes. They integrate sensory signals from the skin, process taste, and process some types of visual information.

The back of the brain houses the **occipital lobes**. They process visual information and are responsible for recognizing colors and shapes and integrating them into complex visual understanding.

The **temporal lobes** lie on the sides of the brain, at and below the level of the eyes. They carry out some visual processing and interpret auditory information. The **hippocampus** consists of curved structures lying beneath the cerebral cortex; it is a region of the temporal lobes that encodes new memories. Another deep structure within each temporal lobe, the **amygdala**, integrates memory and emotion.

The hippocampus and amygdala are part of the **limbic system**, a group of structures deep within the brain that help regulate our emotion and motivation. Other parts of the limbic system include the **thalamus**, which integrates sensory information and relays it to other parts of the brain, and the **hypothalamus**, which sends hormonal signals to the rest of the body through the **pituitary gland**. These structures, together with the cerebral cortex, make up the **forebrain**.

The **midbrain** sits beneath the thalamus. It includes distinct groups of neurons that coordinate eye move-



Pictured are the brain’s four principal lobes. The frontal lobe, responsible for attention, planning, and decision-making, is labeled blue. The temporal lobe, associated with language, memory, and emotion, is labeled in green. The parietal lobe, which integrates information from the senses, is labeled in yellow. And the occipital lobe, responsible for vision, is labeled in pink.

ments like blinking and focusing, and trigger reflexes to sounds. An example is the startled jump when you are surprised by a loud noise. Other regions of the midbrain inhibit unwanted body movements and help coordinate sensory input and motor output to manage the fine motor control that enables you to write with a pen or play a musical instrument.

Some of these regions — along with parts of the forebrain — form a collection of structures called the **basal ganglia**, which helps regulate complex body movements.

The **hindbrain** plays roles in glucose regulation and sleep and includes several regions that help control movement. The **cerebellum**, tucked underneath the occipital lobe at the very back of the brain, is the second-largest part of the brain in volume, containing

over half the brain’s neurons. Like the cerebrum, the cerebellum is deeply folded, divided into two hemispheres, and carries out a variety of functions. For example, it coordinates voluntary movements and helps the brain learn new motor skills. It also has roles in spatial and temporal perception. A patient with cerebellar damage might have a jerky, arrhythmic gait or might be unable to accurately touch his finger to his nose.

Below the cerebellum is the **pons**, which influences breathing and posture. Another part of the hindbrain, the **medulla**, carries nerve pathways connecting the brain to the spinal cord and contains neural networks that help control basic functions like swallowing, heart rate, and breathing. Together, the midbrain, pons, and medulla make up the **brainstem**.

**Brain Evolution**

It's hard to believe that our complex human brain evolved from a simple tube. The earliest vertebrates probably had brains much like the one in the modern lancelet *Amphioxus* — little more than a wide spot in the hollow nerve cord running down its back. But while the lancelet's brain looks simple, it still contains specialized regions where neurons process specific kinds of information, like the presence of light or the chemicals drifting through the water. In its early development, the human brain began as a simple tube, and even today it is divided into the same kinds of regions as the brains of our ancestors.

In early vertebrates, the “brain” end of the nerve cord developed three distinct bulges as neurons were added, improving processing in sensory and motor reflex regions. These bulges became the forebrain, the midbrain, and the hindbrain. In the forebrain, the region able to detect chemicals expanded to form the olfactory bulbs, and with the evolution of image-producing eyes, light-sensing regions expanded and began processing more complex visual signals. The cerebellum appeared as the hindbrain and expanded the regions that control escape movements and orient the body in space. Both these functions are far more important to an actively swimming fish than to a sedentary lancelet buried in the sand.

Regions that could rapidly process visual and auditory information and trigger appropriate escape, feeding, or mating behaviors also expanded in vertebrates. Over time, those new types of neurons made the forebrain balloon out, forming the cerebral hemispheres. In early mammals, cortical tissues in the cerebrum and the cerebellum

expanded even further, packing new neurons into layers and folds generating more complex tissues with increased processing power.

**NEURAL NETWORKS**

Information moves from one region of your brain to another via chains of neurons that can transmit signals over long distances. When the nerve fibers of region-spanning neurons form distinct bundles, these are called nerve tracts. Examples of major nerve tracts include the corpus callosum (the thick bundle of neurons connecting your left and right cerebral hemispheres) and the smaller anterior commissure that transmits signals between the left and right temporal lobes.

A group of nerve tracts connecting a series of regions in the brain is called a neural network. Neural networks route signals through the brain along a linear pathway, analyzing and organizing different types of information within fractions of a second.

Have you ever wondered what happens in your brain when you watch a movie? Your brain turns a panoply of moving shapes into recognizable characters and scenery. The process begins with photoreceptors, cells in the retina that trigger electrical signals in response to specific wavelengths of light. Once those signals reach the optic nerve, they travel through the optic tract to the thalamus, where neurons respond to the shape, color, or movement of objects on the screen and pass their signals to the primary visual cortex in the occipital lobe, at the back of the brain. Neurons in the primary visual cortex, in turn, detect the edges of objects within the field of vision and integrate the signals from each eye, creating a three-dimensional

representation of the outside world. The image is even further refined as signals are sent down two parallel processing streams. In one stream, neurons in the temporal lobe recognize and identify objects; in the other, neurons in the parietal lobe detect the spatial location of those objects. And that's only the *visual* input from the film! New technologies that allow us to look with increasing detail at the brain regions being activated as we perform different functions are giving us increasing insight into the fine regions of the brain used for specific tasks.

**Network Activity Creates Brain Waves**

The visual cortex also sends signals back to the thalamus to become integrated with other sensory information; this is an example of a “thalamocortical loop,” a two-way circuit that connects the thalamus with parts of the cortex and back. As neuronal signals loop through the thalamus and cortex, they produce rhythmic, oscillating, electrical patterns that can be detected with an [electroencephalograph \(EEG\)](#). These signals are commonly called [brain waves](#). There are four distinct types, each recognized by its characteristic shape on an EEG display or printout.

Your awake brain typically produces alpha waves and beta waves. Alpha waves originate mainly in the parietal and occipital lobes when your brain is relaxed and eyes are closed, and are characterized by frequencies between 8 and 13 Hz. (The Hertz is a measure of frequency; 1 Hz = 1 cycle per second.) Beta waves are somewhat faster, with frequencies ranging from 14 to 30 Hz. Beta waves are typically produced by the frontal and parietal regions of your brain when it processes

sensory input or concentrates on a task. Theta waves and delta waves are typical of sleep. Theta waves are slower than alpha waves, ranging from 4 to 7 Hz, while delta waves, which occur during deep sleep, are very slow, with frequencies less than 3.5 Hz. Alpha and delta waves are typically of higher amplitude (stronger) than beta or theta waves but, when measured with elec-

works provide feedback that helps integrate sensory and motor signals. For example, the brain's basal ganglia are part of a feedback loop that takes information from cortical areas that elicit movement and produces signals that feed back to the cortex to excite or inhibit specific movements. Loops that connect the brainstem and the cerebellum also influence the timing

**NEURAL CIRCUITS**

Each region of your brain analyzes only a specialized subset of all the information that is received, but all regions use the same basic mechanism to process information. When signals arrive at a brain region, they engage local neural circuits — interconnected neurons that turn entering signals into output patterns that can be sent to other parts of the brain.

The cerebral cortex is packed with neural circuits. Neurons are organized into a stack of distinct layers that span the thickness of the cortex like shelves in a bookcase. Circuits are arranged in columns, as each neuron forms connections with cells in the layers above and below. The neurons in a column form a single chain, and signals that enter the circuit travel down that chain from one neuron to the next. Each time the signal is fed forward, it is transformed in some way, building outputs that encode complex information — so you can recognize your grandmother's face in a crowd or plan where to run to catch a thrown ball.

Neuroscientists think each column in the cortex is dedicated to one very specific processing task. But a column's final output can be influenced by the activity of nearby circuits. Every neuron in a circuit has other connections to neurons in neighboring columns. Since every neuron behaves like a microprocessor, summing all the signals it receives before sending one of its own, the strength of signals from neighboring circuits can dynamically shift a neuron's response. This dynamic organization may help the brain react flexibly to different situations.

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**N**eurons are organized into a stack of distinct layers that span the thickness of the cortex like shelves in a bookcase.

trodes on your scalp, all these signals are in the microvolt range: 20–200  $\mu\text{V}$  for alpha and delta waves, and 5–10  $\mu\text{V}$  for beta and theta waves.

**Neural Networks Organize and Integrate Information**

Your brain and spinal cord contain many distinct neural networks. These include spinal tracts — chains of neurons that pass signals through the brainstem and the spinal cord. Signals either travel upward from sensory receptors in skin and muscles to the thalamus and parts of the cortex that interpret touch and pressure; or they travel downward from brain regions that induce movement, passing through the medulla and spinal cord before projecting to the body's muscles. Other neural net-

and strength of motor signals; some of these loops incorporate tracts from the cerebral cortex that enable environmental and emotional context to influence your body's movements. Networks that loop the hippocampus into sensory cortex pathways help your brain analyze whether environmental signals are familiar or are part of a new situation. Related networks linking the hippocampus to the thalamus and hypothalamus allow your memory to influence conscious behavior as well as unconscious physiological responses. Reflex loops are circuits eliciting action well before thoughts; these actions are controlled locally by information going in and out of the spinal cord or subcortical regions of the brain, and never reach the cortex.

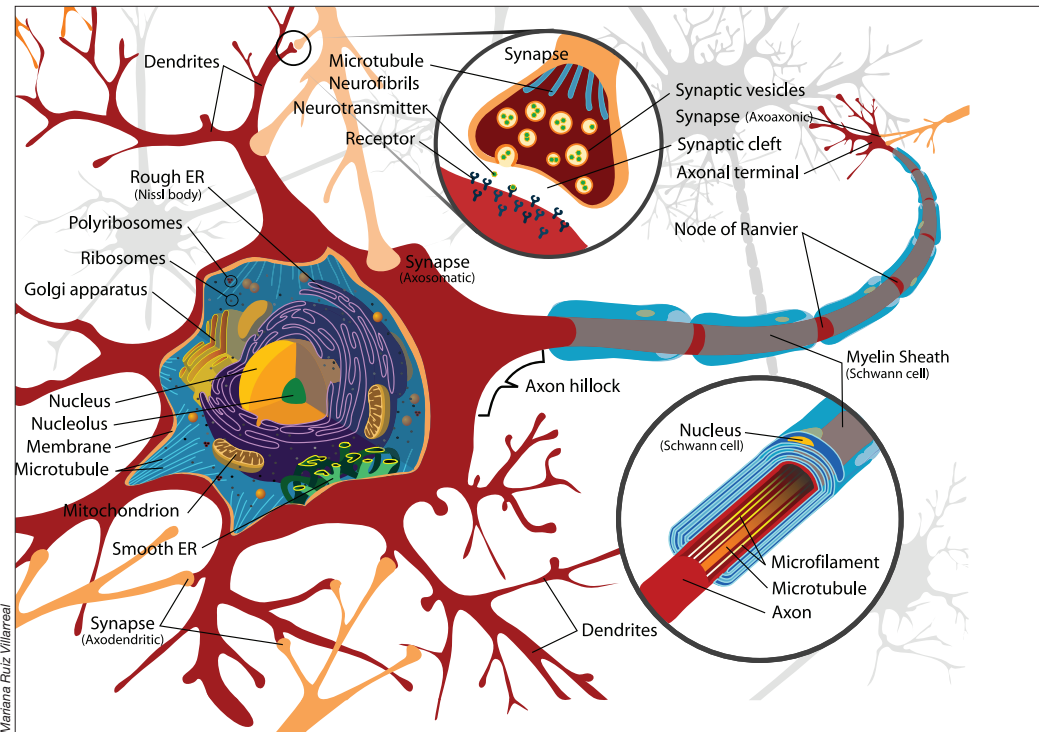


### Excitatory and Inhibitory Neurons

Individual neurons are either excitatory or inhibitory. The majority of neurons in your brain — about 80 percent of them — are **excitatory**, sending signals that push their neighbors toward firing. In many parts of the cerebral cortex, the most common type of excitatory neuron is the pyramidal cell, named for its cone-shaped cell body. Each pyramidal cell has two sets of branched dendrites — one set at the apex and another set of shorter dendrites at the base — that collect signals from neurons in every layer of the cortex. A multi-branched axon sends a single electrical signal to multiple destinations. The 20 percent of your brain's neurons that are **inhibitory** send signals that suppress the activity of neighboring neurons and regulate the activity of a circuit.

Every neural circuit contains both excitatory and inhibitory neurons. Neurons that pass signals forward through a circuit and eventually send outputs to other parts of the brain tend to be excitatory, while inhibitory neurons are typically local and often loop their responses back to earlier segments of a circuit. The interplay between these signals in a circuit seems to be important in learning, tuning and smoothing the signals sent to the body and other parts of the brain. Seizure disorders like epilepsy could be caused by imbalances in the activity of excitatory and inhibitory neurons.

Within circuits, neurons can be organized in a number of different input architectures, each affecting how a circuit manages information. In a feed-forward inhibitory circuit, inhibitory interneurons connect neighboring neural circuits in such a way that excitatory signals in one column



This is the neuron, the building block of the nervous system. Neurons come in many shapes and sizes, but most have some basic features. The cell body contains structures such as the nucleus. Dendrites, the arms extending from the cell body, receive signals from other neurons at junctions called synapses. The neuron sends signals via the axon, a long cable that ends with the axon terminals. The axon terminals release chemical messengers called neurotransmitters.

simultaneously send inhibitory signals to adjacent columns, reducing their activity. In feedback inhibition, however, neurons send signals to their downstream excitatory neighbors and to interneurons that reach back and inhibit preceding layers of the same circuit. Both are examples of recurrent neural networks, in which neurons inside interconnected circuits send feedback signals to one another.

### NEURONS AND GLIA

The functional unit of neural circuits and networks is the **neuron**, a specialized cell that can transmit electrical signals to other nerve cells, muscles, or glands. Neurons come in a broad range of shapes and sizes, but all of them have a **cell body**, **dendrites**, and an **axon**. The cell body, also called the soma, contains

the neuron's nucleus and most of its cytoplasm, along with molecular machinery for building and transporting proteins critical to the cell's function. Dendrites are branched projections that extend from the cell body and collect incoming signals from other neurons. The neuron's electrical signals travel down its axon — another extension from the cell body that may branch before ending in **axon terminals**, where the signal is passed across a synapse to other cells. In some neurons, axons are only a fraction of a centimeter long; in others, they may extend more than a meter.

Neurons are associated with support cells called **glia**. Neuroscientists have long believed that glia outnumber neurons by 10:1 (or more). However, recent investigations suggest that in some regions of the brains of humans

and other primates, that ratio is closer to 1:1. However, the ratio of glia to neuron from region to region varies considerably. The central nervous system contains four main types of glial cells: **astrocytes**, **microglia**, ependymal cells, and **oligodendrocytes**. Astrocytes form a network inside the brain that regulates ion concentrations around neurons, provides them with nutrients, and helps regulate the formation of new connections between neurons. Microglia are the main “immune cells” of the brain. They function mainly as phagocytes — helping protect the brain from infections and cellular damage — but can also regulate the formation of new neuronal connections. Ependymal cells make the cerebrospinal fluid that cushions the brain inside the skull, and oligodendrocytes improve neuron function by wrapping axons in a fatty sheath called myelin.

### Ion Channels and Action Potentials

Ions are electrically charged atoms that can only cross a neuron's cell membrane through tunnel-like proteins called **ion channels**. These tunnel-like proteins act like gates, allowing some ions to enter or leave the cell, but keeping others out. Ions that enter or leave the cell change the voltage difference across the membrane. This change in voltage influences the neuron's likelihood of generating an electrical signal.

In mammals, the voltage difference across the membrane of a resting neuron is around -70 millivolts (mV), more negative inside the cell than on its outer surface. That **membrane potential** is affected by signals arriving from other neurons in its circuit, which can make the membrane potential less negative (**depolarized**) or more negative

(**hyperpolarized**) by opening ion channels in the dendrites. If the sum of all the signals at the dendrites rises to match the membrane's threshold voltage, a series of voltage-sensitive ion channels opens automatically, triggering an electrical impulse called an **action potential**, which moves down the axon towards the next neuron in the circuit.

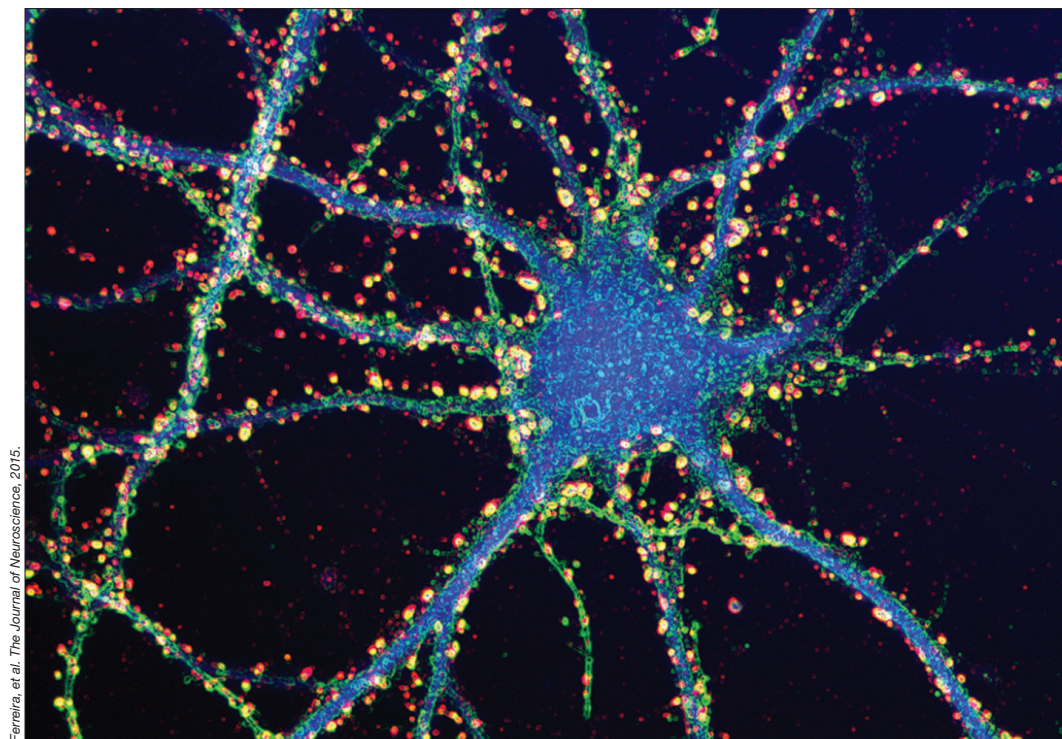
### SYNAPSES AND NEUROTRANSMISSION

Signals are passed from one neuron to the next at junctions called **synapses**. In most circuits, a synapse includes the end of an axon, the dendrite of an adjacent neuron, and a space between the two called the synaptic cleft. Amazingly, this separation between neurons was only verified (by electron microscopy) in the 1950s. The cleft is wide enough that electrical

signals can't directly impact the next neuron; rather, chemical signals called **neurotransmitters** cross the synapse. This process is called neurotransmission.

When an action potential arrives at the axon terminal, the voltage change triggers ion channels in the membrane to open, which lets calcium ions flow into the cell. When the calcium ions bind to packages of neurotransmitter molecules called synaptic vesicles, the vesicles fuse with the cell membrane at the axon terminal and empty their contents into the synaptic cleft. Afterwards, pieces of axon terminal membrane cycle back into the soma as new vesicles, which are refilled with neurotransmitter molecules.

Many substances act as neurotransmitters, including amino acids, gases, small organic chemicals, and short peptides. Neurons can synthesize



Dendrites — the arms extending from a neuron's cell body — receive information from other neurons at sites called synapses. Each dendrite can have thousands of synapses, which together form complex circuits that govern brain function. The synapses on this mouse neuron are labeled in yellow and red.

small *non*-peptides like dopamine or acetylcholine inside the axon terminal. But an axon terminal doesn't contain the molecular machinery for building proteins, so peptide-based neurotransmitters are built in the ribosome-rich space of the cell body. Vesicles containing neurotransmitter "cargos" bud off from the wall

channels, altering the voltage across the postsynaptic membrane. Local glial cells (astrocytes) mop up any excess neurotransmitters at the synapse. This process prevents them from continuously activating receptors.

There are two broad types of receptors on the postsynaptic membrane. In an ionotropic receptor, a

time. Once they detach, the ion channels return to their resting state and stop altering the charge across their membrane. The neurotransmitters are either broken down or reabsorbed by the axon terminal in a process called **reuptake**.

The excitatory and inhibitory neurons described above can be identified by the specific neurotransmitters that they make. Excitatory neurons make neurotransmitters that open ion channels that depolarize the dendrite's membrane; inhibitory neurons make neurotransmitters that hyperpolarize it. The brain's most common excitatory neurotransmitter is **glutamate**; the brain's most common inhibitory neurotransmitter is **gamma-aminobutyric acid (GABA)**.

Glutamate is an amino acid used as a neurotransmitter by approximately half the excitatory synapses in the brain. It can bind to several types of ionotropic receptors; the most important of these are AMPA receptors and NMDA receptors. When activated, the action of AMPA receptors is fast and brief; NMDA receptors activate more slowly, particularly in response to waves of multiple action potentials. Interactions between these receptors appear to be important in learning and memory.

GABA is the brain's most important inhibitory neurotransmitter. It binds to two groups of receptors; one group is ionotropic, the other metabotropic. Ionotropic GABA receptors have ion channels that let negatively charged chloride ions enter the cell. Metabotropic GABA receptors open ion channels that release potassium ions. In both instances, ion movement pushes membrane potential downward and inhibits a neuron from firing.

neurotransmitter binds directly to part of an ion channel. The channel is normally closed; the receptor protein changes its shape when the neurotransmitter attaches, widening the tunnel in the center of the ion channel so that ions can move through. Metabotropic receptors are more complex. The receptor and the ion channel are different proteins located at a distance from one another, but they are linked by a cascade of biochemical steps that are triggered when a neurotransmitter binds to the receptor. This response is less rapid and activates a series of events inside the postsynaptic cell. The result may be opening an ion channel some distance away or activating other intracellular molecules.

Neurotransmitter molecules only bind to their receptors for a short

**M**any different molecules act as neurotransmitters, and each one fits into specific receptors like a key fits a lock.

of the Golgi apparatus — the cell's protein-packaging organelle — then bind to proteins called kinesins that work their way down the axon along microtubules, filamentous parts of the cellular skeleton.

After neurotransmitters are released from an axon terminal, they drift across the synaptic cleft until they reach the outer surface of the dendrite, a region that looks thick or dense in highly magnified images. This region, the postsynaptic density, has a high concentration of neurotransmitter **receptors**. Many different molecules act as neurotransmitters, and each one fits into specific receptors like a key fits a lock. Receptors are linked to ion channels in such a way that, when neurotransmitter molecules dock on their receptors, they open those

## RECEPTORS AND MOLECULAR SIGNALING

Neurons have receptors for many molecules that can change the way they function. These molecules include **hormones**, which send the brain specific cues about the condition and activity of distant tissues in the body; **neuromodulators** such as the endocannabinoids, cannabis-like chemicals that seem to suppress neurotransmitter release; and **prostaglandins**, small lipids that change the brain's response (increasing pain sensitivity) to pain and inflammation.

Individual neurons have receptors for different subsets of hormones and neuromodulators. In each case, these molecules are signals that trigger a series of chemical reactions inside the cell. The process starts when one of these molecules binds to its specific receptor. If the receptor is on the surface of the cell, the bound molecule changes the receptor's shape across the cell membrane and starts a chain of intracellular reactions. This signal transduction pathway ultimately modifies neuronal function, either by shifting the cell's ion balance or by changing the activity of specific enzymes.

If a molecule can diffuse through the cell membrane — as occurs with steroid hormones like estradiol or cortisol — its receptor might be a protein inside the neuron's soma. When the hormone binds to its receptor, the complex can transform into a transcription factor that is capable of entering the cell nucleus, binding to specific genes and changing their activity.

## NEURONS, GENES, AND GENE EXPRESSION

By this point, it should be clear that neurons inside the brain can differ in appearance and function. They can produce different types of neurotransmitters, determining whether their signals have excitatory or inhibitory effects in their circuits. They can have different assortments of neurotransmitter receptors, determining the cells' sensitivity to the effects of specific neurotransmitters. And, in their cell membranes, neurons possess different combinations of receptors capable of detecting neuromodulators that influence neuronal behavior — for example, hormones such as vasopressin, estradiol, or cortisol.

All cells in your body, including neurons, contain the same DNA housing the same genes. Differences among your neurons result from differences in which genes direct cellular activities, a process called gene expression. Each cell (or cell type) builds proteins from a slightly different subset of genes in its genetic code, the same way different children will build different structures from the same starting set of Lego blocks.

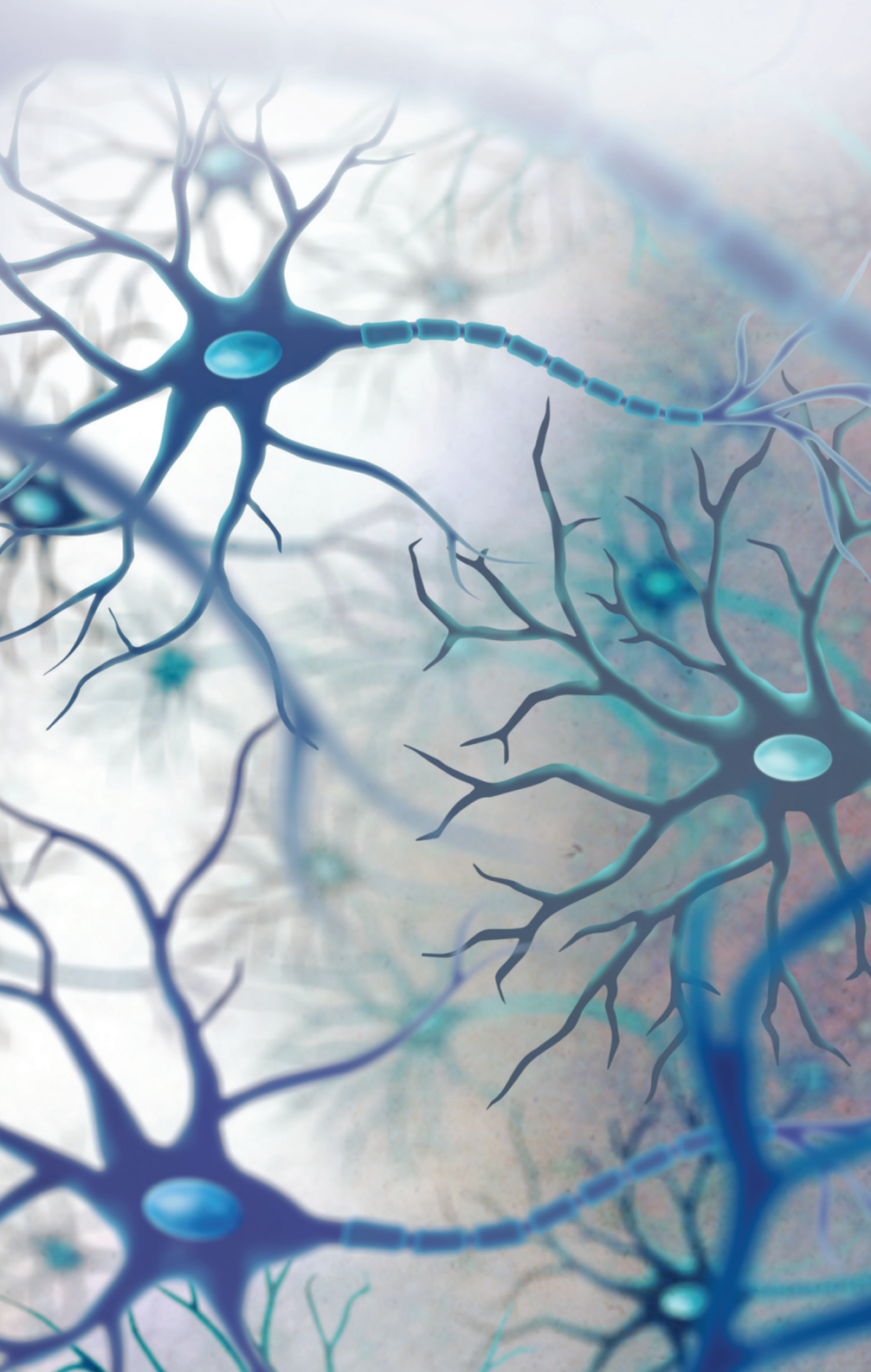
The mechanisms causing neurons to express some genes and not others are currently an area of intense research. Many of these mechanisms depend on chemical changes to chromatin, the complex of protein and DNA that compactly packages the long DNA molecule inside the nucleus. Genes that a cell is using to build proteins need to be accessible

and are associated with open, unfolded chromatin, while unexpressed genes are typically in tightly packed regions. Chemical changes that tighten or spread out chromatin complexes can, respectively, shut down or activate the genes on that segment of DNA. These changes are reversible, giving neurons flexibility to alter the genes they express in response to hormonal cues and environmental changes.

The genes that affect neuron structure and function can also differ between individuals. Gene variants or alleles reflect differences in the nucleotide sequences that make up a gene. While different alleles code for forms of the same protein, the variants can produce structural differences that affect their function. An allele might code for a version of an enzyme that is less effective than the usual version, and specific alleles of some genes can even cause neurological diseases. For example, Tay-Sachs disease, a fatal degenerative neurological condition, is caused by mutations in a gene that codes for part of a fat-metabolizing enzyme called beta-hexosaminidase A. Because the variant enzyme is poor at breaking down specific fats, these build up in neurons and become toxic. There are many cases where small changes in genetic sequence affect how our brain can function, and in the next 10 years — with our capacity to sequence a person's entire genome now possible — we will be able to move much closer to understanding the genetic basis of brain disorders. ■



# Senses & Perception



**Y**ou can think of your sense organs as the brain's windows on the external world. The world itself has no actual images, sounds, tastes, and smells. Instead, you are surrounded by different types of energy and molecules that must be translated into perceptions or sensations. For this extraordinary transformation to work, your sense organs turn stimuli such as light waves or food molecules into electrical signals through the process of transduction. These electrical messages are then carried through a network of cells and fibers to specialized areas of your brain where they are processed and integrated into a seamless perception of your surroundings.

## VISION

Vision is one of your most complicated senses, involving many processes that work simultaneously enabling you to see what is happening around you. It is no surprise, then, that the visual system involves about 30 percent of humans' cerebral cortex — more than any other sense does. Vision has been studied intensively, and we now know more about it than any other sensory system. Knowledge of how light energy is converted into electrical signals comes primarily from studies of fruit flies (*Drosophila*) and mice. Higher-level visual processing has mostly been studied in monkeys and cats.

In many ways, seeing with your eyes is similar to taking pictures with an old-fashioned camera. Light passes through the cornea and enters the eye through the pupil. The iris regulates how much light enters by changing the size of the pupil. The lens then bends the light so that it focuses on the inner surface of your eyeball, on a sheet of cells called the **retina**. The rigid cornea does the initial focusing,

but the lens can thicken or flatten to bring near or far objects into better focus on the retina. Much like a camera capturing images on film, visual input is mapped directly onto the retina as a two-dimensional reversed image. Objects to the right project images onto the left side of the retina and vice versa; objects above are imaged at the lower part and vice versa. After processing by specialized cells in several layers of the retina, signals travel via the **optic nerves** to other parts of your brain and undergo further integration and interpretation.

## The Three-Layered Retina

The retina is home to three types of neurons — **photoreceptors**, interneurons, and **ganglion cells** — which are organized into several layers. These cells communicate extensively with each other before sending information along to the brain. Counterintuitively, the light-sensitive photoreceptors — **rods** and **cones** — are located in the most peripheral layer of the retina. This means that after entering through the cornea and lens, light travels through the ganglion cells and interneurons before it reaches the photoreceptors. Ganglion cells and interneurons do not respond directly to light, but they process and relay information from the photoreceptors; the axons of ganglion cells exit the retina together, forming the optic nerve.

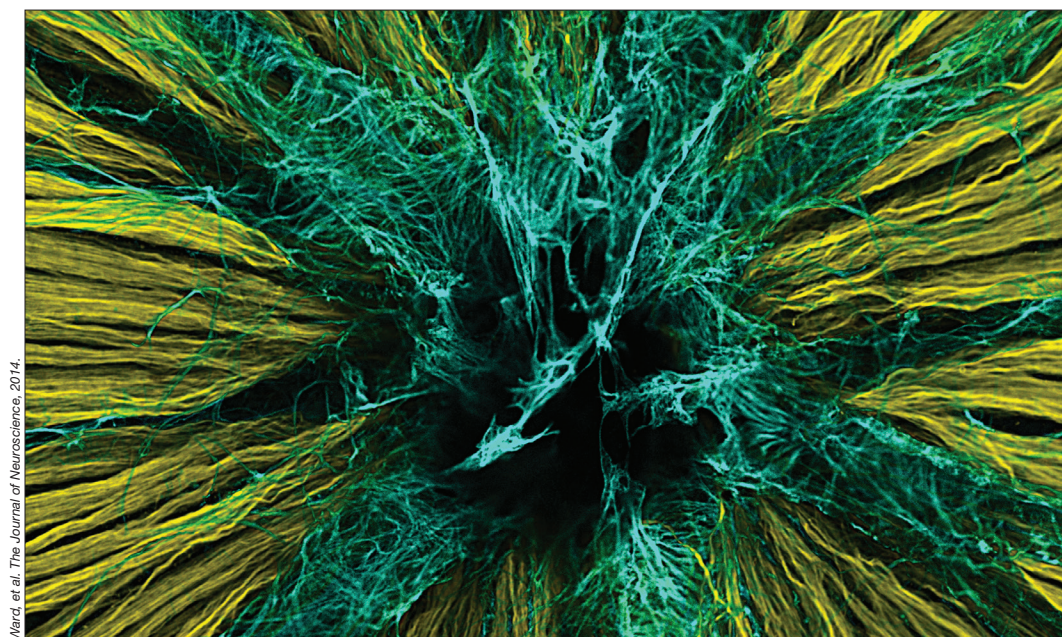
There are approximately 125 million photoreceptors in each human eye, and they turn light into electrical signals. The process of converting one form of energy into another occurs in most sensory systems and is known as transduction. Rods, which make up about 95 percent of photoreceptors in humans, are extremely sensitive, allowing you to see in dim light. Cones,

on the other hand, pick up fine detail and color, allowing you to engage in activities that require a great deal of visual acuity. The human eye contains three types of cones, each sensitive to a different range of colors (red, green, or blue). Because their sensitivities overlap, differing combinations of the three cones' activity convey information about every color, enabling you to see the familiar color spectrum. In that way, your eyes resemble computer monitors that mix red, green, and blue levels to generate millions of colors.

Because the center of the retina contains many more cones than other retinal areas, vision is sharper here than in the periphery. In the very center of the retina is the **fovea**, a small pitted area where cones are most densely packed. The fovea contains only red and green cones and can resolve very fine details. The area immediately around the fovea, the **macula**, is critical

for reading and driving. In the United States and other developed countries, death or degeneration of photoreceptors in the macula, called macular degeneration, is a leading cause of blindness in people older than 55.

Neurons in each of the three layers of the retina typically receive inputs from many cells in the preceding layer, but the total number of inputs varies widely across the retina. For example, in the macular region where visual acuity is highest, each ganglion cell receives input (via one or more interneurons) from just one or very few cones, allowing you to resolve very fine details. Near the margins of the retina, however, each ganglion cell receives signals from several photoreceptor cells. This convergence of inputs explains why your peripheral vision is less detailed. The portion of visual space providing input to a single ganglion cell is called its receptive field.



Here, in the back of the eye, is one of the first stops visual information makes on its way to the brain. In this image of a mouse retina, axons of nerve cells are labeled in yellow. They extend through a small opening in the back of the eye — labeled in black — through the optic nerve to higher vision centers. The axons must penetrate another layer of cells known as astrocytes, labeled in blue, that provide nutritional support to the retina.



### How Is Visual Information Processed?

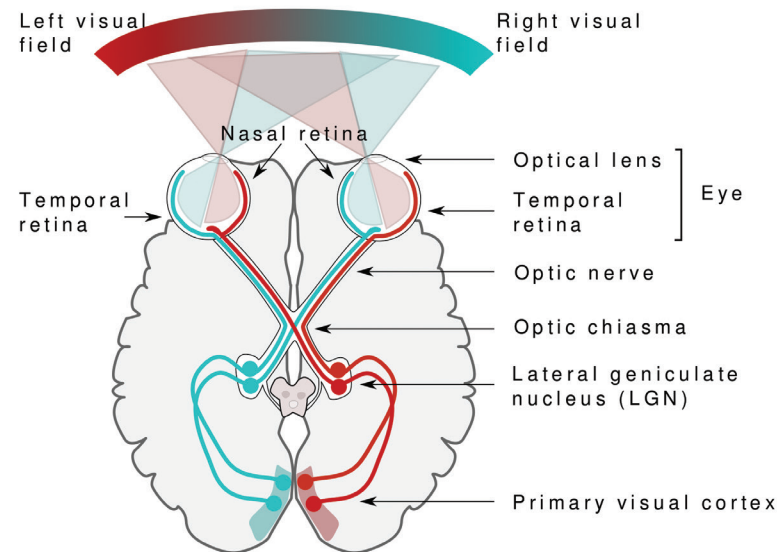


Every time you open your eyes, you distinguish shapes, colors, contrasts and the speed and direction of movements. You can easily distinguish your coffee mug from the peanut butter jar in front of you. You can also tell that the tree outside the window stands still and the squirrel is scurrying up the tree (not vice versa). But how is a simple two-dimensional retinal image processed to create such complex imagery?

Visual processing begins with comparing the amounts of light hitting small, adjacent areas on the retina. The receptive fields of ganglion cells “tile” the retina, providing a complete two-dimensional representation (or map) of the visual scene. The receptive field of a ganglion cell is activated when light hits a tiny region on the retina that corresponds to the center of its field; it is inhibited when light hits the donut-shaped area surrounding the center. If light strikes the entire receptive field — the donut *and* its hole — the ganglion cell responds only weakly. This center-surround antagonism is the first way our visual system maximizes the perception of contrast, which is key to object detection.

Neural activity in the axons of ganglion cells is transmitted via the optic nerves, which exit the back of each eye and travel toward the back of the brain. Because there are no photoreceptors at this site, the exit point of the optic nerve results in a small “blind spot” in each eye, which our brains fortuitously “fill in” using information from the other eye. On their way to the brain, signals travel along nerve fibers from both eyes which first converge at a crossover junction called the **optic chiasm**. Those fibers carrying

Miquel Pereñó Nieto.



**Vision begins with light. The light bouncing off an object passes through the optical lens and hits the retina at the back of the eye. Receptors in the retina transform light into electrical signals that carry information to the vision processing centers in the brain.**

information from the left side of the retinas of both eyes continue together on the left side of the brain; information from the right side of both retinas proceeds on the right side of the brain. Visual information is then relayed through the lateral geniculate nucleus, a region of the thalamus, and then to the primary visual cortex at the rear of the brain.

#### Visual Cortex: Layers, Angles, and Streams

The primary visual cortex, a thin sheet of neural tissue no larger than a half-dollar, is located in the occipital lobe at the back of your brain. Like the retina, this region consists of many layers with densely packed cells. The middle layer, which receives messages from the thalamus, has receptive fields similar to those in the retina and can preserve the retina’s visual map. Cells above and below the middle layer have more complex receptive fields, and they register stimuli shaped like bars or edges or with particular orientations. For example, specific cells can respond to edges at a certain angle or moving in a particular direction. From these layers

of cells, new processing streams pass the information along to other parts of the visual cortex. As visual information from the primary visual cortex is combined in other areas, receptive fields become increasingly complex and selective. Some neurons at higher levels of processing, for example, respond only to specific objects and faces.

Studies in monkeys suggest that visual signals are fed into several parallel but interacting processing streams. Two of these are the dorsal stream, which heads up toward the parietal lobe, and the ventral stream, which heads down to the temporal lobe. Traditionally, these streams were believed to carry out separate processing of unconscious vision, which guides behavior and conscious visual experiences. If you see a dog running out into the street, the ventral or “What” stream would integrate information about the dog’s shape and color with memories and experiences that let you recognize the dog as your neighbor’s. The dorsal or “Where” stream would combine various spatial relationships, motion, and timing to create an action plan, but without a need for conscious thought. You might

shout out “Stop!” without thinking. Ongoing research now questions this strict division of labor and suggests that crosstalk between streams may actually create a conscious experience. Clearly, in recognizing an image the brain extracts information at several stages, compares it with past experiences, and passes it to higher levels for processing.

#### Eyes Come in Pairs

Seeing with two eyes, called binocular vision, allows you to perceive depth or three dimensions, because each eye sees an object from a slightly different angle. This only works if the eyes’ visual fields overlap and if both eyes are equally active and properly aligned. A person with crossed eyes, a condition called strabismus, misses out on much depth perception. Information from the perspective of each eye is preserved all the way to the primary visual cortex where it is processed further. Two eyes also allow a much larger visual field to be mapped onto the primary visual cortex. Because some of the nerve fibers exiting each eye cross over at the optic chiasm, signals from the left visual field end up on the right side of the brain and vice versa, no matter which eye the information comes from. A similar arrangement applies to movement and touch. Each half of the cerebrum is responsible for processing information from the opposite side of the body.

#### Treating Visual Disorders



Many research studies using animals have provided insights into treatment of diseases that affect eyesight. Research with cats and monkeys has helped us find better therapies for strabismus. Children with strabismus initially have good vision in each eye but, because they cannot fuse the images coming from both eyes,

they start to favor one eye and often lose vision in the other. Vision can be restored in such cases, but only if the child is treated at a young age; beyond the age of 8 or so, the blindness becomes permanent. Until a few decades ago, ophthalmologists waited until children were 4 years old before operating to align the eyes, prescribing exercises or using an eye patch. Now strabismus is corrected well before age 4, when normal vision can still be restored.

Loss of function or death of photoreceptors appears to lie at the heart of various disorders that cause blindness. Unfortunately, many are difficult to treat. Extensive genetic studies and the use of model organisms have identified a variety of genetic defects that cause people to go blind, making it possible to design gene or stem cell therapies that can recover photoreceptors. Researchers are working on potential treatments for genetic blindness, and gene therapies have already enabled some patients with loss of central vision (macular degeneration) or other forms of blindness to see better. Work is also underway to send electrical signals directly to the brain via ganglion cells rather than attempting to restore lost photoreceptors, an approach very similar to the use of cochlear implants to treat deafness.

#### HEARING

Hearing is one of your most important senses, alerting you to an approaching car and telling you where it’s coming from long before it comes into sight. Hearing is also central to social interactions. It allows you to communicate with others by processing and interpreting complex messages in the form of speech sounds. Like the visual system, your hearing (auditory) system picks up several qualities of the signals it de-

tect, such as a sound’s pitch, loudness, duration, and location. Your auditory system analyzes complex sounds, breaking them into separate components or frequencies, as a result, you can follow particular voices in a conversation or instruments as you listen to music.

#### Can You Hear Me Now?

Whether it’s the dreaded alarm in the morning, the ringtone on your cell phone, or your favorite jogging music, hearing involves a series of steps that convert sound waves in the air into electrical signals that are carried to the brain by nerve cells. Sound in the form of air pressure waves reaches the pinnae of your ears, where the waves are funneled into each ear canal to reach the eardrum (tympanic membrane). The eardrum vibrates in response to these changes in air pressure, sending these vibrations to three tiny, sound-amplifying bones in the middle ear: the malleus (hammer), incus (anvil), and stapes (stirrup). The last bone in the chain (the stapes) acts like a tiny piston, pushing on the oval window, a membrane that separates the air-filled middle ear from the fluid-filled, snail-shell-shaped **cochlea** of the inner ear. The oval window converts the mechanical vibrations of the stapes into pressure waves in the fluid of the cochlea, where they are transduced into electrical signals by specialized receptor cells (**hair cells**).

#### From Pressure Wave to Electrical Signal



An elastic membrane, called the basilar membrane, runs along the inside of the cochlea like a winding ramp, spiraling from the outer coil, near the oval window, to the innermost coil. The basilar membrane is “tuned” along its length to

different frequencies (pitches). When fluid inside the cochlea ripples, the membrane moves, vibrating to higher-pitched sounds (like the screech of audio feedback) near the oval window and to lower-pitched sounds (like a bass drum) in the center.

Rows of small sensory hair cells are located on top of the vibrating basilar membrane. When the membrane moves up and down, microscopic hair-like stereocilia extending from the hair cells bend against an overlying structure called the tectorial membrane. This bending opens small channels in the stereocilia that allow ions in the surrounding fluid to rush in, converting the physical movement into an electrochemical signal. Hair cells stimulated in this way then excite the **auditory nerve**, which sends its electrical signals on to the brainstem.

The next stop for sound processing is the thalamus, the brain's relay station for incoming sensory information, which then sends the information into the auditory part of the cerebral cortex. Several thousand hair cells are positioned along the length of the basilar membrane. Each hair cell responds most strongly to just a narrow range of sound frequencies, depending on how far along the cochlea it is located. Thus, each nerve fiber connecting with the hair cells is tuned to very specific frequencies and carries this information into the brain.

### Making Sense of Sound

On the way to the cortex, the brainstem and thalamus use the information from both ears to compute a sound's direction and location. The frequency map of the basilar membrane is maintained throughout, even in the primary auditory cortex in the temporal lobe,

where different auditory neurons respond to different frequencies. Some cortical neurons, however, respond to sound qualities such as intensity, duration, or a change in frequency. Other neurons are selective for complex sounds, while still others specialize in various combinations of tones. At higher levels, beyond the primary auditory cortex, neurons are able to process harmony, rhythm, and melody, and combine the types of auditory information into a voice or instrument that you can recognize.

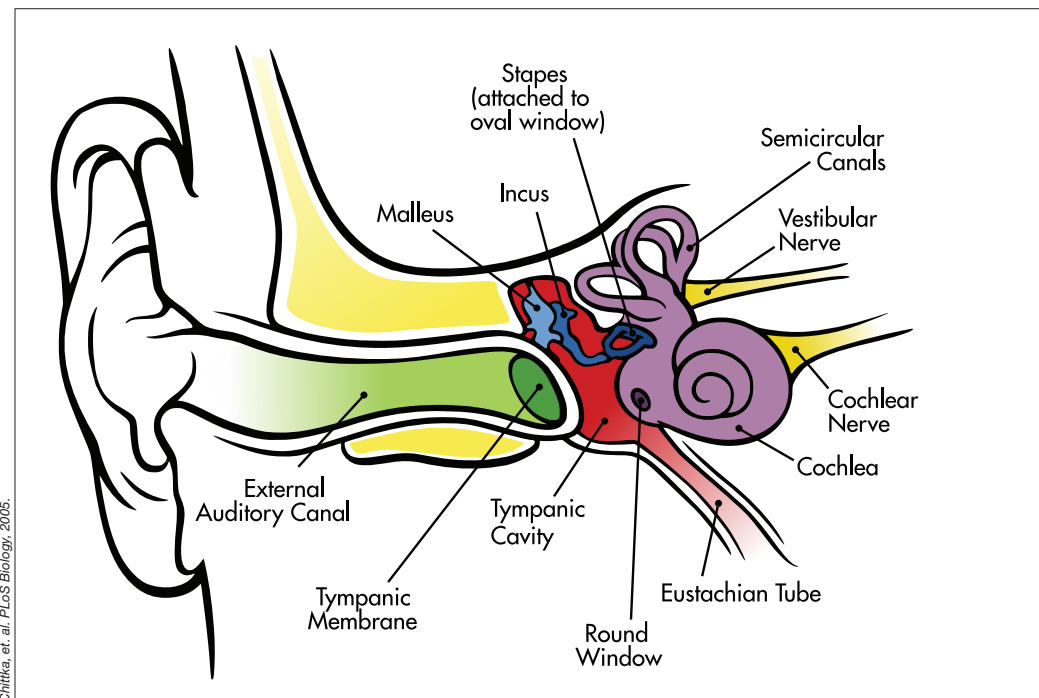
Although sound is processed on both sides of the brain, the left side is typically responsible for understanding and producing speech. Someone with damage to the left auditory cortex (particularly a region called **Wernicke's area**), as from a stroke, is able to hear a person speak but no longer understands what is being said.

### Treating Hearing Loss

Loss of hair cells is responsible for the majority of cases of hearing loss. Unfortunately, once they die, hair cells don't regrow. Current research is therefore focusing on how inner ear structures like hair cells develop and function, exploring new avenues for treatment that could eventually involve neurogenesis with the goal of replacing damaged hair cells.

### TASTE AND SMELL

The senses of taste (gustation) and smell (olfaction) are closely linked and help you navigate the chemical world. Just as sound is the perception of air pressure waves and sight is the perception of light, smell and taste are your perceptions of tiny molecules in the air and in your food. Both of these senses contribute to how food tastes, and both are important to survival, because



Sound waves — vibrations in the air caused by the sound's source — are picked up by the outer ear and funneled down the auditory canal to the ear drum. There, the malleus (hammer) transfers vibrations to the incus (anvil) and then onto the stapes. Hair cells in the cochlea convert the information in these vibrations to electrical signals, which are sent to the brain via the cochlear nerve.

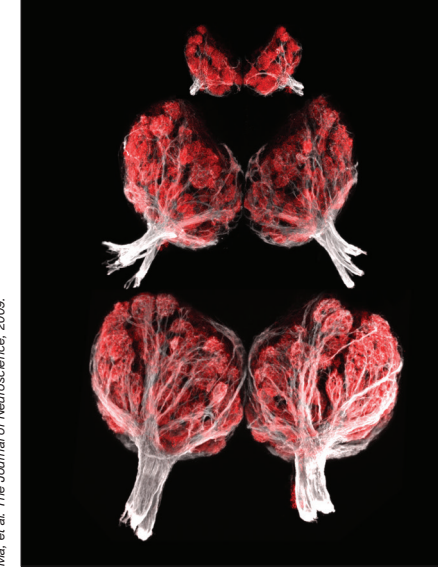


Your tongue's receptors, called taste buds, transform information about tastes and send them to the brain to be processed into your favorite flavors. In this image of a mouse tongue, the axons that connect to these receptors are highlighted in red.

they enable people to detect hazardous substances they might inhale or ingest. The cells processing taste and smell are exposed to the outside environment, leaving them vulnerable to damage. Because of this, taste receptor cells regularly regenerate, as do olfactory receptor neurons. In fact, olfactory neurons are the only sensory neurons that are continually replaced throughout our lives.

### From Molecules to Taste

Our ability to taste foods depends on the molecules set free when we chew or drink. These molecules are detected by taste (or gustatory) cells within **taste buds** located on the tongue and along the roof and back of the mouth. We have between 5,000 and 10,000 taste buds but start to lose them around age 50. Each taste bud consists of 50 to 100 sensory cells that are receptive to one of at least five basic taste qualities: sweet, sour, salty, bitter, and umami (Japanese for "savory"). Contrary to common belief, all tastes are detected across the tongue and are not limited to specific regions. When taste receptor cells are stimulated, they send signals through three **cranial nerves** — the facial,



The olfactory bulb is a structure in the forebrain responsible for processing smell information. This series of images shows the olfactory bulbs from a zebrafish at three stages of development.

glossopharyngeal, and **vagus nerves** — to taste regions in the brainstem. The impulses are then routed through the thalamus to the gustatory cortex in the frontal lobe, and insula where specific taste perceptions are identified.

### From Molecules to Smell

Odors enter the nose on air currents and bind to specialized olfactory cells on a small patch of mucus membrane high inside the nasal cavity. Axons of these sensory neurons enter the two **olfactory bulbs** (one for each nostril) after crossing through tiny holes in the skull. From there, the information travels to the olfactory cortex. Smell is the only sensory system that sends sensory information directly to the cerebral cortex without first passing through the thalamus.

We have around 1,000 different types of olfactory cells, but can identify about 20 times as many smells. The tips of olfactory cells are equipped with several hair-like cilia that are receptive to a number of different odor molecules, and many cells respond to the same molecules. A specific smell will therefore stimulate a unique combination of olfactory cells, cre-

ating a distinct activity pattern. This "signature" pattern of activity is then transmitted to the olfactory bulb and on to the primary olfactory cortex located on the anterior surface of the temporal lobe. Olfactory information then passes to nearby brain areas, where odor and taste information are mixed, creating the perception of flavor. Recent research suggests that people can identify odors as quickly as 110 milliseconds after their first sniff. Interestingly, the size of the olfactory bulbs and the way neurons are organized can change over time. As mentioned above, the olfactory bulbs in rodents and primates (including humans) are one of the few brain regions able to generate new neurons (**neurogenesis**) throughout life.

### Combining Taste and Smell

Taste and smell are separate senses with their own receptor organs. Yet, we notice their close relationship when our nose is stuffed up by a cold and everything we eat tastes bland. It seems like our sense of taste no longer works, but the actual problem is that we detect only the taste, not taste and smell combined. Taste sense itself is rather crude, distinguishing only five basic taste qualities, but our sense of smell adds great complexity to the flavors we perceive. Human studies have shown that taste perceptions are particularly enhanced when people are exposed to matching combinations of familiar tastes and smells. For example, sugar tastes sweeter when combined with the smell of strawberries, than when paired with the smell of peanut butter or no odor at all. Taste and smell information appear to converge in several central regions of the brain. There are also neurons in the inferior frontal lobe that respond selectively to



specific taste and smell combinations.

Some of our sensitivity to taste and smell is lost as we age, most likely because damaged receptors and sensory neurons are no longer replaced by new ones. Current research is getting closer to understanding how stem cells give rise to the neurons that mediate smell or taste. With this knowledge, stem cell therapies might one day be used to restore taste or smell to those who have lost it.

### TOUCH AND PAIN

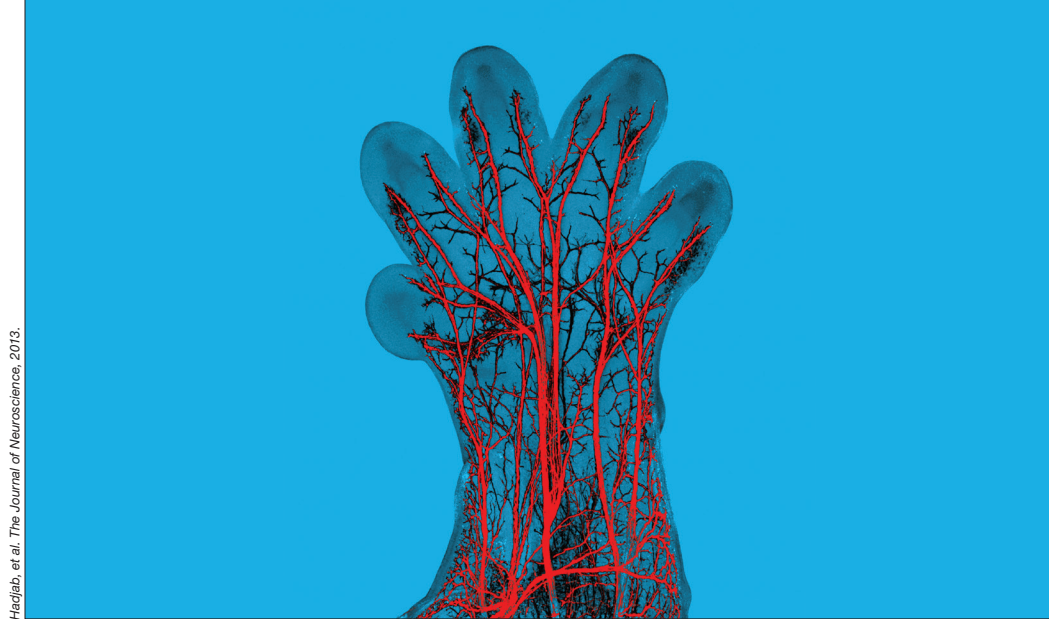


The somatosensory system is responsible for all the touch sensations we feel. These can include light touch, pressure, vibration, temperature, texture, itch, and pain. We perceive these sensations with various types of touch receptors whose nerve endings are located in different layers of our skin, the body's main sense organ for touch. In hairy skin areas, some particularly sensitive nerve cell endings wrap around the bases of hairs, responding to even the slightest hair movement.

Signals from touch receptors travel along sensory nerve fibers that connect to neurons in the spinal cord. From there, the signals move upward to the thalamus and on to the **somatosensory cortex**, where they are translated into a touch perception. Some touch information travels quickly along myelinated nerve fibers with thick axons (A-beta fibers), but other information is transmitted more slowly along thin, unmyelinated axons (C fibers).

#### Cortical Maps and Sensitivity to Touch

Somatosensory information from all parts of your body is spread onto the cortex in the form of a topographic map that curls around the brain like head-



In this image, sensory nerve fibers, labeled in red, can be seen in the paw of a developing mouse embryo. These nerve fibers will become specialized to detect either pressure, pain, temperature, or itch.

phones. Very sensitive body areas like lips and fingertips stimulate much larger regions of the cortex than less sensitive parts of the body. The sensitivity of different body regions to tactile and painful stimuli depends largely on the number of receptors per unit area and the distance between them. In contrast to your lips and hands, which are the most sensitive to touch, touch receptors on your back are few and far apart, making your back much less sensitive.

Neurologists measure this sensitivity using two-point discrimination — the minimum distance between two points on the skin that a person can identify as distinct stimuli rather than a single one. Not surprisingly, acuity is greatest (and the two-point threshold is lowest) in the most densely nerve-packed areas of the body, like the fingers and lips. By contrast, you can distinguish two stimuli on your back only if they are several centimeters apart.

#### Pain and Itch Signals



Pain is both a sensory experience and an emotional experience. The sensory component signals tissue damage or the potential for damage, and the emotional component makes the experience unpleasant and

distressing. Pain is primarily a warning signal — a way your brain tells itself that something is wrong with the body. Pain occurs when special sensory fibers, called **nociceptors**, respond to stimuli that can cause tissue damage. Normally, nociceptors respond only to strong or high-threshold stimuli. This response helps us detect when something is truly dangerous. Different types of nociceptors are sensitive to different types of painful stimuli, such as thermal (heat or cold), mechanical (wounds), or chemical (toxins or venoms). Interestingly, these same receptors also respond to chemicals in spicy food, like the capsaicin in hot peppers, which might produce a burning pain, depending on your sensitivity. Some types of nociceptors respond only to chemical stimuli that cause itch. A well-known example is histamine receptors that are activated when skin irritation, bug bites, and allergies trigger the release of histamine inside your body. But scientists have recently identified other itch-specific receptors as well.

When tissue injury occurs, it triggers the release of various chemicals at the site of damage, causing inflammation. This inflammatory “soup” then triggers nerve impulses that cause

you to continue feeling pain, which helps you protect a damaged part of the body. Prostaglandins, for example, enhance the sensitivity of receptors to tissue damage, making you feel pain more intensely. They also contribute to a condition called allodynia, in which even soft touch can produce pain, as on badly sunburned skin. A long-lasting injury may lead to nervous system changes that enhance and prolong the perceived pain, even in the absence of pain stimuli. The resulting state of hypersensitivity to pain, called **neuropathic pain**, is caused by a malfunctioning nervous system rather than by an injury. An example of this condition is diabetic neuropathy, in which nerves in the hands or feet are damaged by prolonged exposure to high blood sugar and send signals of numbness, tingling, burning, or aching pain.

#### Sending and Receiving Messages

Pain and itch messages make their way to the spinal cord via small A-delta fibers and even smaller C fibers. The myelin sheath covering A-delta fibers helps nerve impulses travel faster, and these fibers evoke the immediate, sharp, and easily identified pain produced, for example, by a pinprick. The unmyelinated C fibers transmit pain messages more slowly; their nerve endings spread over a relatively large area and produce a dull and diffuse ache or pain sensation whose origin is harder to pinpoint. Pain and itch signals travel up the spinal cord through the brainstem and then to the thalamus (the ascending

pathway). From there, they are relayed to several areas of the cerebral cortex that monitor the state of the body and transform pain and itch messages into conscious experience. Once aware, the brain has the opportunity to change how it responds to these messages.

#### Pain Management



Why do different people, when exposed to the same pain stimulus, experience the pain differently? How itchy or painful something feels obviously depends on the strength of the stimulus, but also on a person's emotional state and the setting in which the injury occurs. When pain messages arrive in the cortex, the brain can process them in different ways. The cortex sends pain messages to a region of the brainstem called the **periaqueductal gray matter**. Through its connections with other brainstem nuclei, the periaqueductal gray matter activates descending pathways that modulate pain. These pathways also send messages to networks that release **endorphins** — opioids produced by the body that act like the **analgesic** morphine. Adrenaline produced in emotionally stressful situations like a car accident also works as an analgesic — a drug that relieves pain without a loss of consciousness. The body's release of these chemicals helps regulate and reduce pain by intercepting the pain signals ascending in the spinal cord and brainstem.

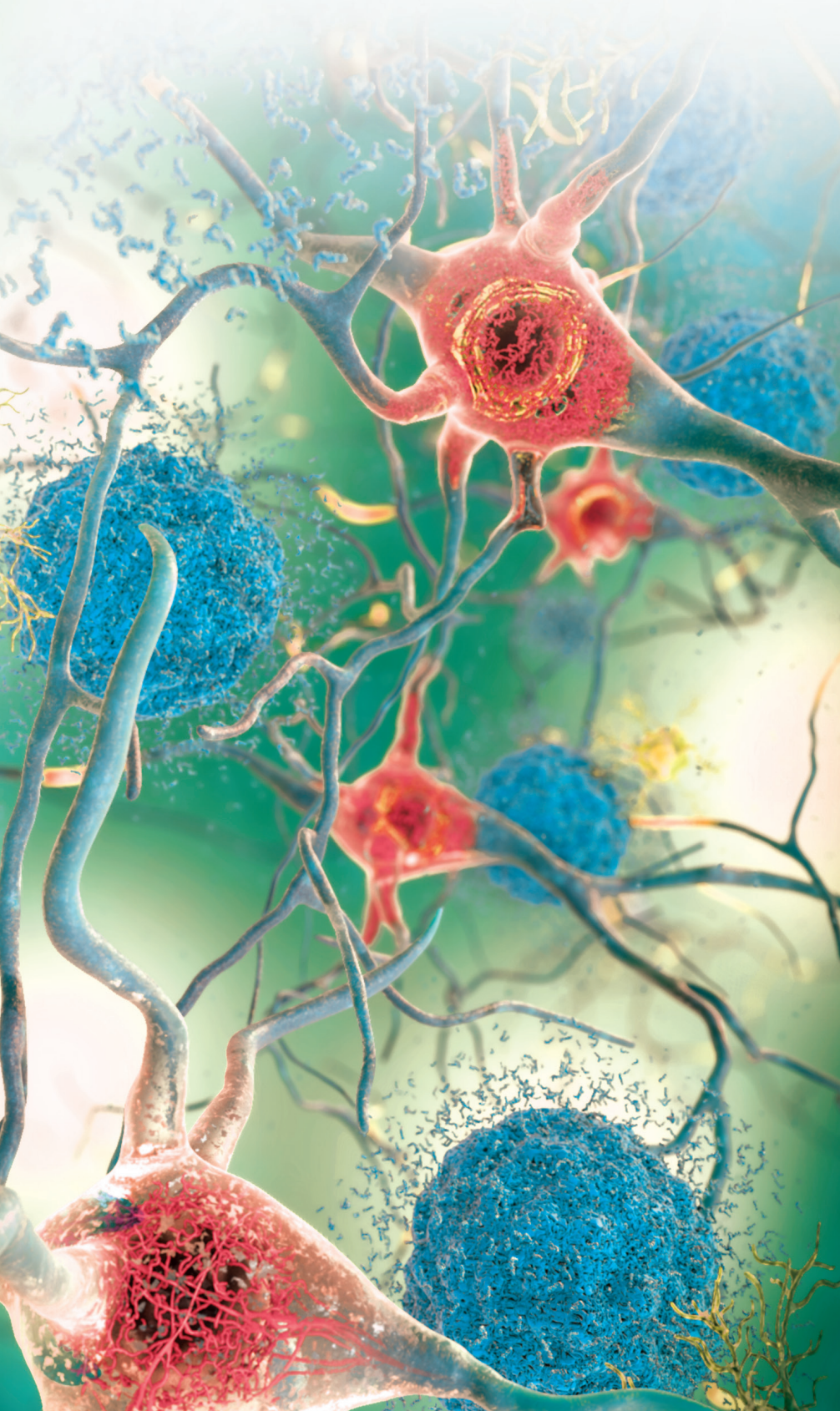
Although these brain circuits exist in everyone, their efficacy and sensitivity will influence how much pain

a person feels. They also explain why some people develop chronic pain that does not respond to regular treatment. Research shows that endorphins act at multiple types of opioid receptors in the brain and spinal cord, which has important implications for pain therapy, especially for people who suffer from intense chronic pain. For example, opioid drugs can now be delivered to the spinal cord before, during, and after surgery to reduce pain. And scientists are studying ways to electrically stimulate the spinal cord to relieve pain while avoiding the potentially harmful effects of long-term opioid use. Variations in people's perceptions of pain also suggest avenues of research for treatments that are tailored to individual patients.

It is now clear that no single brain area is responsible for the perception of pain and itch. Emotional and sensory components create a mosaic of activity that influences how we perceive pain. In fact, some treatment methods — such as meditation, hypnosis, massages, **cognitive behavioral therapy**, and the controlled use of cannabis — have successfully targeted the emotional component rather than stopping the painful stimulus itself. Patients with chronic pain still feel the pain, but it no longer “hurts” as much. We don't fully understand how these therapies work, but brain imaging tools have revealed that cannabis, for example, suppresses activity in only a few pain areas in the brain, primarily those that are part of the limbic system, the emotional center of the brain. ■



# Movement



**H**ave you ever marveled at the athleticism of a tennis player as she lands a perfect serve, or the virtuosity of a pianist whose fingers dance through a piece by Rachmaninoff? These are special and dramatic movements. Yet in our daily lives, each of us performs a suite of complex, skilled movements that are equally remarkable — from walking and talking, to signing our names, or sending a text. We even use our muscles to reveal our current mood: A smile and a wave are universally understood.

Movement is such an integral part of our day-to-day experience that we take for granted the sophisticated systems that make these actions possible. The **central nervous system** — brain and **spinal cord** — directs the coordinated actions of the hundreds of muscles that enable us to move. These actions are refined and strengthened as we make our way through the world, adapting to changing circumstances and practicing, sometimes even improving, our motor skills.

## VOLUNTARY MOVEMENTS

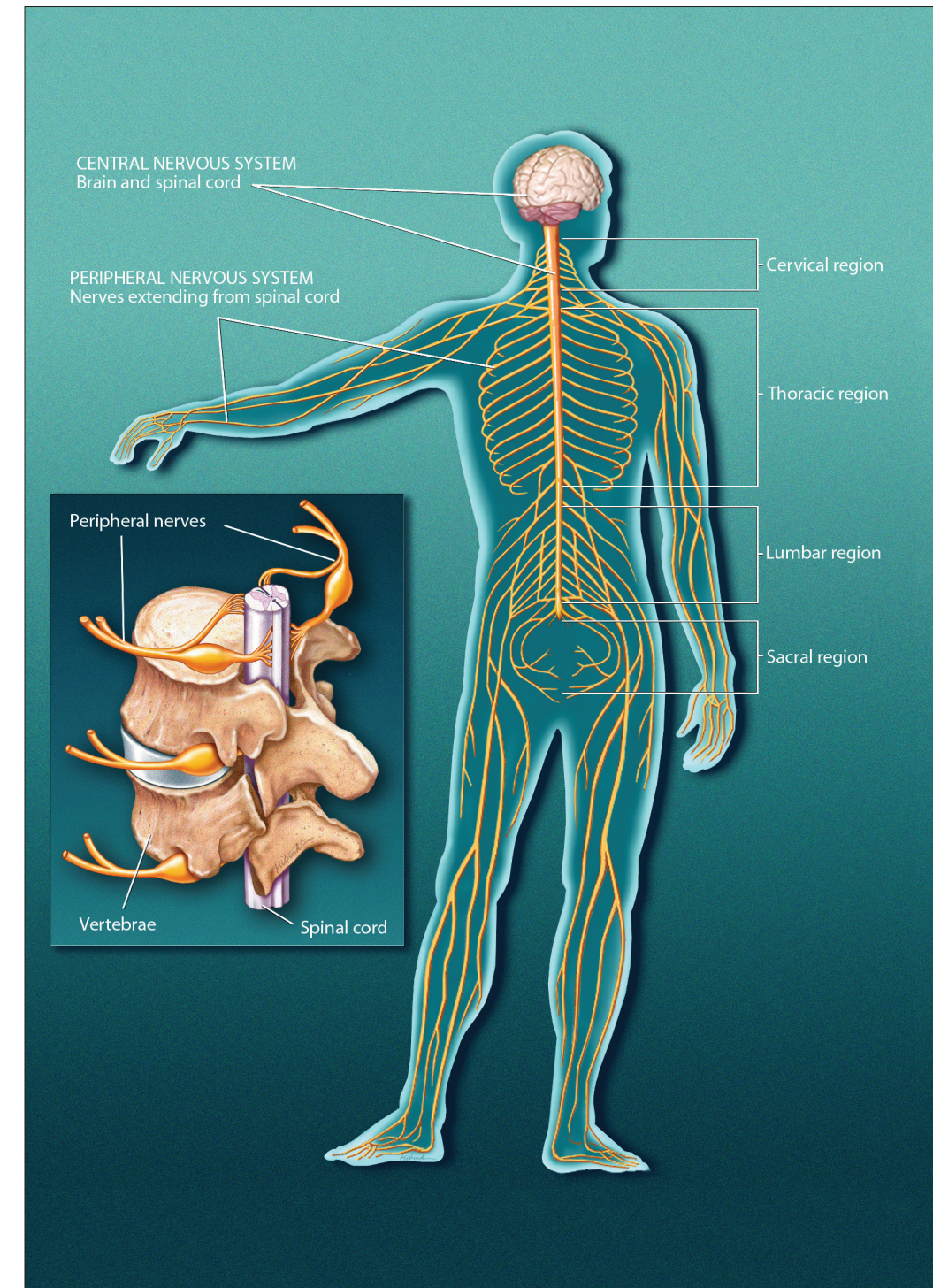


To understand how the nervous system governs motion, we begin with the muscles, the structures of the body that produce movement. Most muscles attach to the skeleton and span joints, the sites where two or more bones come together. The close relationship of these muscles to the skeleton gives them their name — skeletal muscles. Activating muscles can either flex or extend the joint that they span. Muscles that bend a joint, bringing the bones closer together, are called flexors; muscles that straighten the joint, increasing the angle between the bones, are

called extensors. Flexors and extensors work in opposition, so when one set of muscles contracts, the other relaxes. For example, bending the elbow requires contraction of the biceps (a flexor) and relaxation of the triceps (an extensor). For such motions, the muscles that promote the movement are called agonists, and those that oppose or inhibit the movement are antagonists. Skilled, rapid movements — like throwing a dart — are started by agonists and stopped by antagonists, allowing the limb to accelerate and halt with great speed and precision. For some movements, agonists and their opposing antagonists contract at the same time, which is called co-contraction. These simultaneous actions can stabilize or control a movement, such as holding an object at arm's length or stabilizing an immobile joint during isometric exercises.

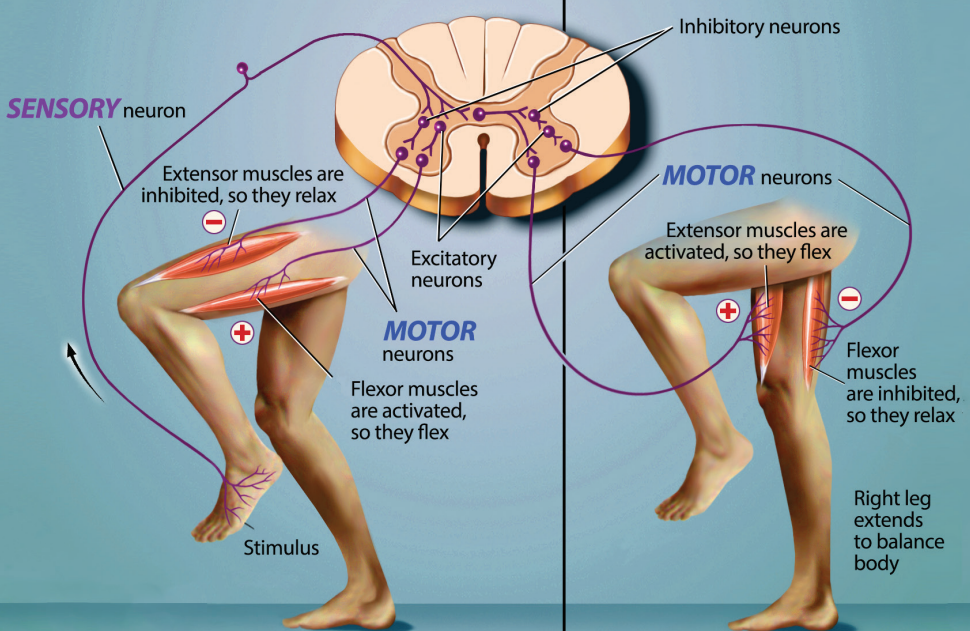
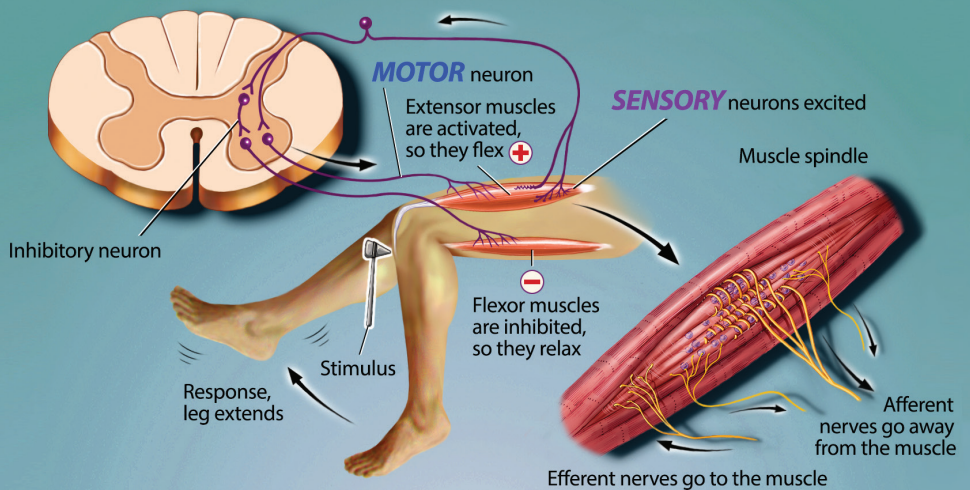
Whether flexion or extension, the movement of all skeletal muscles is controlled by the central nervous system. A skeletal muscle is made up of thousands of individual muscle cells, called muscle fibers. Each muscle fiber is controlled by a single alpha motor neuron that originates in the spinal cord or the brain. However, each of these alpha motor neurons can control multiple muscle fibers (from a few to 100 or more). An alpha motor neuron plus all the muscle fibers it controls form a functional unit known as a **motor unit**, the critical link between the central nervous system and skeletal muscles. When motor neurons die — as happens in diseases like **amyotrophic lateral sclerosis (ALS)** — people can lose their ability to move.

Some muscles act not on joints but on soft tissue. For example, muscles



The nervous system is divided in two. The central nervous system consists of the brain and spinal cord. The peripheral nervous system consists of nerves and small concentrations of gray matter called ganglia. The brain sends messages to the peripheral nerves, which control the muscles and internal organs.





The stretch reflex, as seen at top of the image, occurs when a doctor taps a muscle tendon to test your reflexes. This activates muscle spindle sensory fibers, which send a barrage of impulses to the spinal cord, activating motor neurons and triggering muscle contraction. Flexion withdrawal, shown on the bottom of this image, occurs when you step on a sharp object, and your leg is immediately lifted (flexion) from the source of potential injury. The opposite leg responds with increased extension so that you can maintain your balance, called the crossed extension reflex.

in the head and neck enable us to move our eyes, chew and swallow food, have conversations, and control our facial expressions. These muscles are also controlled by the central nervous system, and they operate in much the same way as those that attach to bones.

### INVOLUNTARY MOVEMENTS

Many types of movement take place without our conscious control. Among the simplest and most fundamental types of **involuntary movements** are the **reflexes**. Reflexes are relatively stereotyped, automatic muscle responses to particular stimuli — think of the rapid withdrawal of your hand after touching something hot. These reflexes involve the activation of sensory receptors in the skin, the joints, or even in the muscles themselves. The responses are rapid and occur without involvement of the brain or conscious attention. Instead, they depend on circuits of neurons located in or near the spinal cord itself.

One of the best-known reflexes is the “knee jerk” response, a stretch (myotatic) reflex that occurs when a physician strikes the tendon just below the knee with a small rubber hammer. This tap produces a slight stretch of the knee extensor muscle, which is “sensed” by receptors within the muscle called muscle spindles. The spindles sense the extent and speed of the stretch, and stimulate sensory neurons, which send a barrage of impulses into the spinal cord. There, the signals activate the alpha motor neurons that cause the stretched extensor muscle to contract, triggering the reflex. Of course, for the leg to kick forward, the antagonist

flexor muscle has to relax at the same time. In fact, the same sensory stimulus that directly activates the motor neurons controlling the extensor also indirectly inhibits the motor neurons controlling the antagonist flexor. This reciprocal inhibition is accomplished by connecting neurons that lie completely within the spinal cord. When these so-called inhibitory interneurons are activated by the original sensory stimulus, they send impulses that inhibit the motor neurons supplying the flexor.

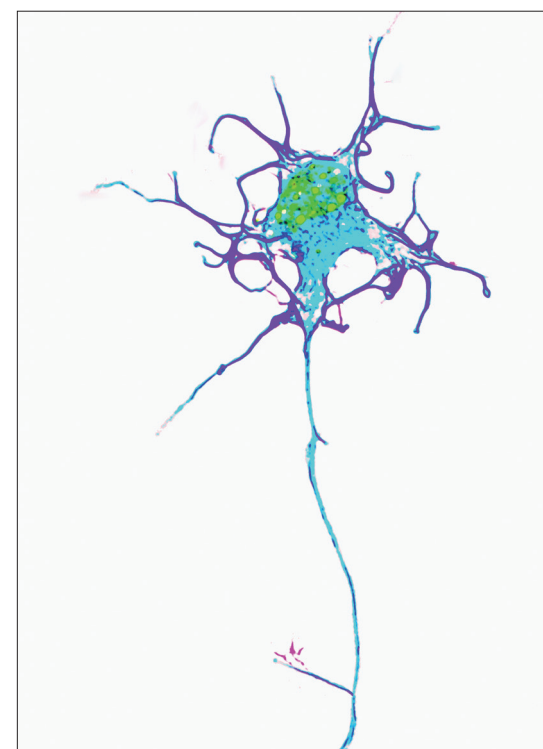
Thus, even the simplest of reflexes involves the synchronous activation (and inactivation) of multiple sets of motor neurons controlling both agonist and antagonist muscles.

Many reflexes protect you from

injury. When you’re seated in a doctor’s office, the “knee jerk” reflex simply makes your lower leg swing briefly forward. However, if you were to jump off a chair (or perform an even more dramatic gymnastic dismount) this same reflex would promote the contraction of the strong muscles that straighten your knees, helping you to “stick your landing” and remain upright. Another protective reflex is the flexion withdrawal reflex that occurs when your bare foot encounters a sharp object. In this case, pain receptors in the skin send a message to the spinal cord, alpha motor neurons are activated, and the leg is immediately lifted (flexion). At the same time, because your body weight is supported on both legs, the extensors of the

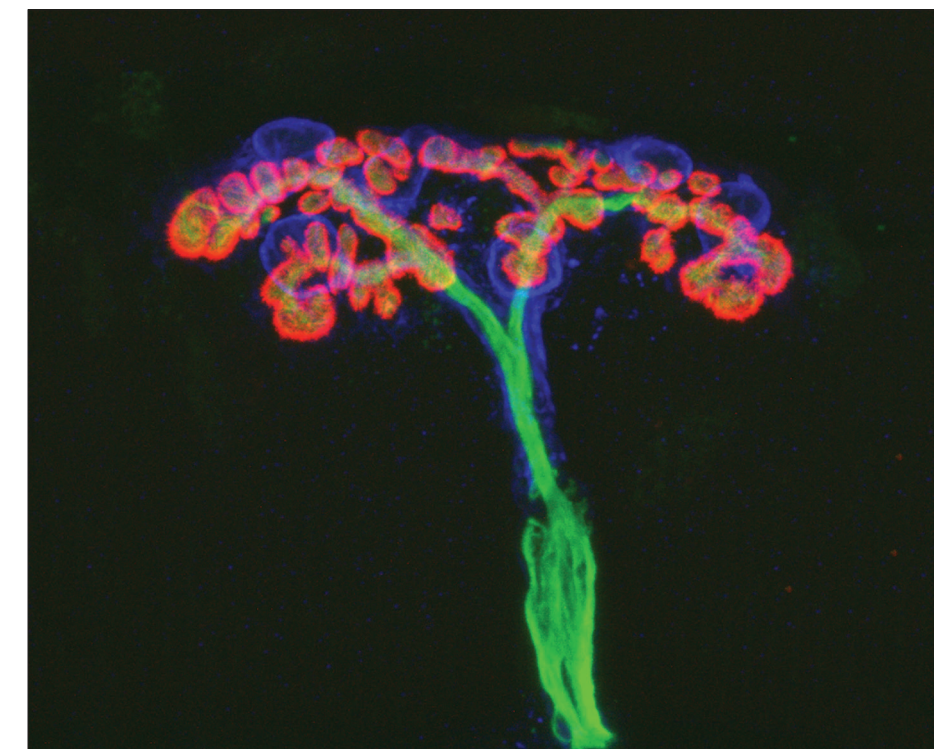
opposite leg must be activated. Without this additional reaction, called the flexion crossed extension reflex, you would lose your balance and fall over after stepping on a tack.

As all these movements occur, the muscles involved provide feedback to the brain with information about where the various body parts are in space and how fast they are moving. The muscle spindles mentioned earlier supply information about changes in muscle length or stretch. The brain, in turn, adjusts the sensitivity of the system via a separate set of motor neurons, gamma motor neurons, which keep the muscle spindles taut. Other specialized receptors called Golgi tendon organs — located where the muscle fibers connect to the



Fallini, et al. The Journal of Neuroscience, 2016.

Specialized cells called motor neurons carry instructions from the brain along long axons that stretch from your spinal cord to the muscles in your hands and feet. These cells can be the longest in your body, stretching the length of your leg to control the muscles in your feet.



Wright, et al. The Journal of Neuroscience, 2009.

Neurons communicate with muscles at sites called neuromuscular junctions. This image shows a neuromuscular junction in a mouse, with a motor neuron labeled in green and neurotransmitter receptors on muscle cells labeled in red.



tendon — detect how much force or tension is applied to a muscle during ongoing movement, increasing the movement’s precision. These feedback systems are not unique to reflexes, but allow the brain to fine-tune how working muscles behave during a variety of movement tasks — from

occur in walking, flying, swimming, or breathing. Central pattern generators which evolved in primitive vertebrates, are being studied to determine the degree to which spinal circuitry can be co-opted to recover basic postural and locomotor function after severe **paralysis**.

ment of functionally related muscles in an individual body part, such as your hand or arm; such neurons are important for finely tuned motor skills. Other neurons in the motor cortex can direct the coordinated movement of a limb to a particular point in space — raising your arm in a defensive position or bringing a hand to your mouth to deliver a tasty morsel of food.

### Regions that Modulate Voluntary Movement



The motor cortex does not act alone in controlling complex or skilled voluntary movements. Several other brain regions participate in parallel circuits or “loops” to modulate motor control. These regions — including the basal ganglia, thalamus, cerebellum, and a large number of neuron groups located within the midbrain and brainstem — also influence the activity of motor neurons in the spinal cord. The basal ganglia themselves encompass two separate pathways. One appears to facilitate the desired motor program while the other suppresses unwanted, competing actions. Along with the thalamus, the basal ganglia share widespread connections with motor and sensory areas of the cerebral cortex, allowing these structures to monitor and adjust motor performance.

Dysfunction of the basal ganglia can lead to serious movement disorders. People with **Parkinson’s disease** experience degeneration of neurons in a brain region called the **substantia nigra**; these neurons relay signals to the basal ganglia using the neurotransmitter dopamine, a key chemical involved in motor control. Depletion of dopamine gives

The most complex movements that you perform, including those requiring conscious planning, involve input from the brain.

those that require a mastery of delicate positioning and coordination, such as sipping from a dangerously full teacup, to those that involve a targeted application of strength and speed, such as throwing a runner out at first base.

### VOLUNTARY AND COMPLEX MOVEMENTS

Spinal circuits also play a critical role in controlling more sophisticated, voluntary behaviors, such as the alternating action of the legs during walking. In fact, the rhythmic patterns of muscle activation that produce locomotion — not only in four-footed animals, but in humans — are generated by neurons within spinal cord and brainstem circuits. When these neuronal circuits (central pattern generators) are activated, they produce the rhythmic patterns that

The most complex movements that you perform, including those requiring conscious planning, involve input from the brain. These higher brain regions initiate voluntary motion, coordinate complex sequences of movement, and tailor behavioral output to suit a given situation. Successful execution of these programs requires your brain to relay commands to the appropriate spinal circuits.

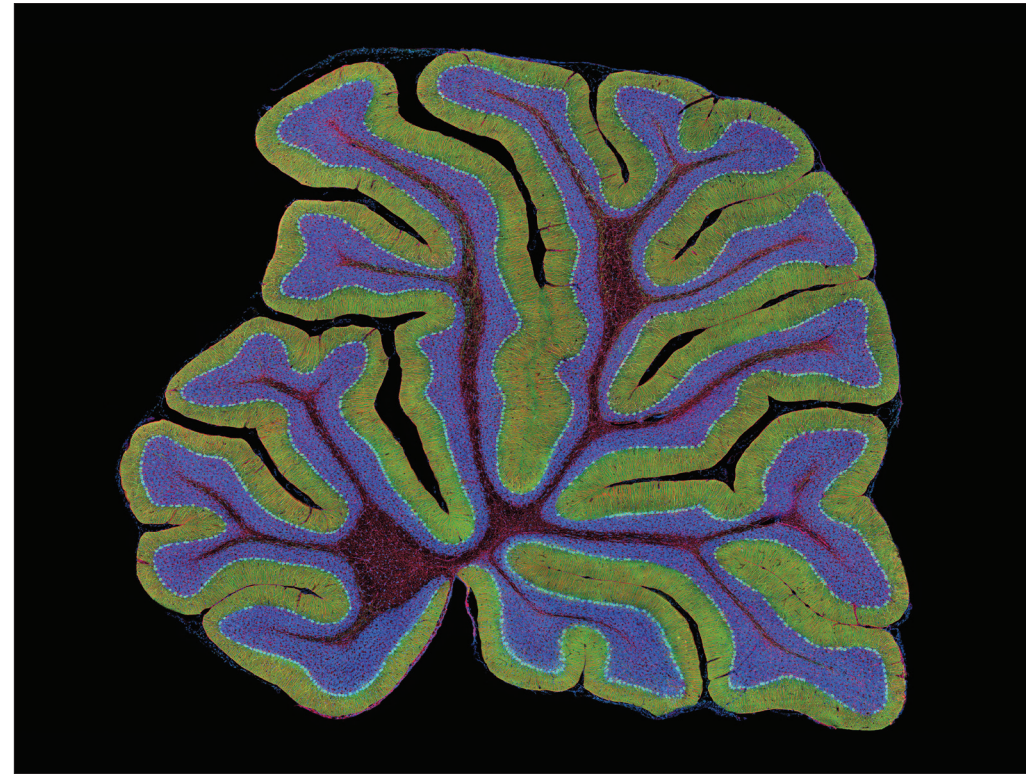
Through careful animal experiments, scientists are just beginning to understand the coordinated series of interactions that take place among different brain regions during voluntary movement. One brain area essential for voluntary movement is the **motor cortex**. Neurons in the motor cortex send signals that directly control the activation of alpha motor neurons in the spine. Some of these cortical neurons control the move-

from controlling limb movements to eye movement to grip force.

Disturbance of cerebellar function leads to poor coordination, disorders of balance, and even difficulties in speech, one of the most intricate forms of movement control. Long-term alcohol abuse is a common cause of acquired cerebellar degeneration. Typical symptoms are poor coordination, an unsteady walk or stumbling gait, changes in speech, and difficulty with fine motor skills including eating, writing, and dressing.

The cerebellum also allows you to adapt to the unexpected, adjusting your movements so that you can smoothly lift a box that you expected to be much heavier, for example. And, it plays a major role in motor learning. As you learned to walk or speak or practiced a musical instrument or a new dance routine, the cerebellum refined and sharpened the motor programs that allow you to perform these tasks with increasing accuracy and skill.

Considerable evidence also indicates that the cerebellum helps us recalibrate our movements as our own bodies change, as we grow taller, gain or lose weight or muscle mass, or cope with disease or disability. In that way, the cerebellum facilitates skillful movement through an ever-changing world as we grow up and we grow old. ■



The cerebellum, shown in this image of a mouse brain, is a region at the back of the brain associated with movement.

rise to the hallmark symptoms of Parkinson’s: tremor, rigidity, and in some cases, akinesia, an inability to move. In contrast, individuals with **Huntington’s disease** often display uncontrolled jerking or twitching movements, particularly in the face and extremities. These symptoms stem from a selective loss of inhibitory neurons in the basal ganglia, which eliminates the suppression of random involuntary movements.

Another brain region crucial for

coordinating and fine-tuning skilled movement is the cerebellum. The cerebellum receives direct input from sensory receptors in the limbs and head, as well as most areas of the cerebral cortex. Neurons in the cerebellum apparently integrate this sensory information ensuring the proper timing and integration of muscle action. This enables us to produce fluid movements more or less automatically. The cerebellum is essential to a wide range of motor learning and coordination,

Thomas Deerinck, National Center for Microscopy and Imaging Research, University of California, San Diego.



# Learning, Memory & Emotions

A patient known for most of five decades only by his initials, H.M., led to one of the most significant turning points in 20th century brain science: the understanding that complex functions such as learning and memory are tied to distinct biological processes and regions of the brain.

Following a childhood blow to the head, Henry Molaison developed severe seizures. Eighteen years later, still experiencing debilitating symptoms, he underwent an experimental procedure that removed sections of his medial temporal lobes — including most of his two hippocampi. The seizures abated, but Molaison was left with permanent **amnesia**. He could remember scenes from his childhood, some facts about his parents, and historical events that occurred before his surgery, but was unable to form new conscious memories.

For example, if Molaison met someone who then left the room, within minutes he had no recollection of the person or their meeting. He experienced every aspect of his daily life — eating a meal, taking a walk — as a first. Yet his intellect, personality, and perception were intact, and he was able to acquire new motor skills. Over time, he became more proficient at tasks such as tracing patterns while watching his hand movements in a mirror, despite the fact that he could never recall performing the task before.

Studied by neuroscientists for 50 years, until his death in 2008 at age 82, Molaison's intact abilities as well as his impairments provided evidence for the roles of the hippocampus and parahippocampal region in converting memories from short-term to long-term, paving the way for further exploration of brain networks encoding conscious and unconscious memories.

## LEARNING AND MEMORY

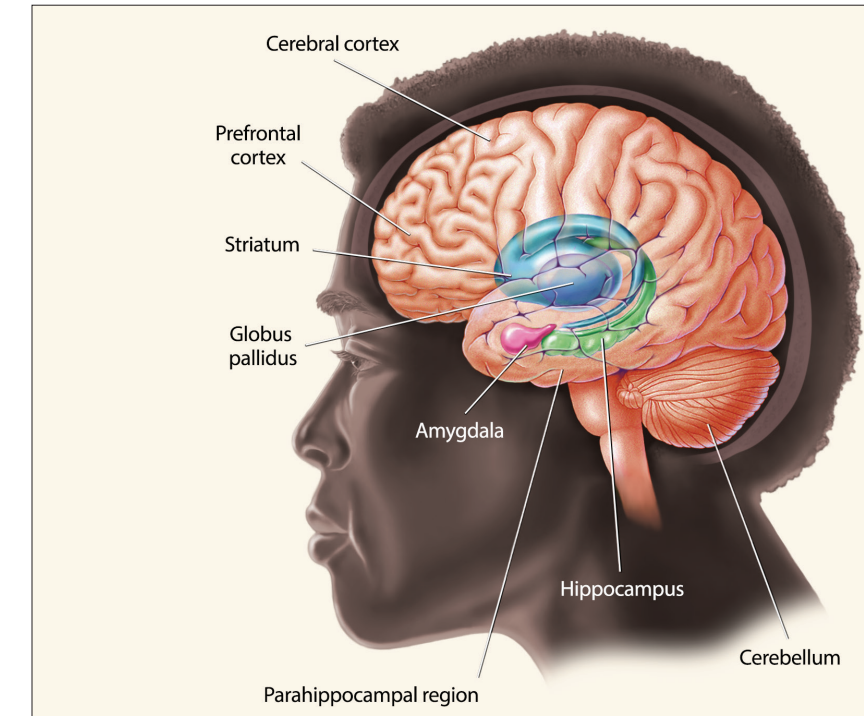
Our understanding of how humans learn and remember is far from complete, but researchers are uncovering intriguing new details about the mechanisms, limits, and architecture of memory formation.

Thanks in part to H.M., scientists now know that the medial temporal lobe, which includes the hippocampus and parahippocampal regions, works with other regions of the cerebral cortex, the brain's outermost layer, to form, organize, consolidate, and retrieve memories. The four major lobes of the cerebral cortex — frontal, parietal, temporal, and occipital — process sensory information such as smell, taste, sight, and sound. Associative regions in the cortex integrate these sensory inputs, enabling us to understand our environment and encode memories.

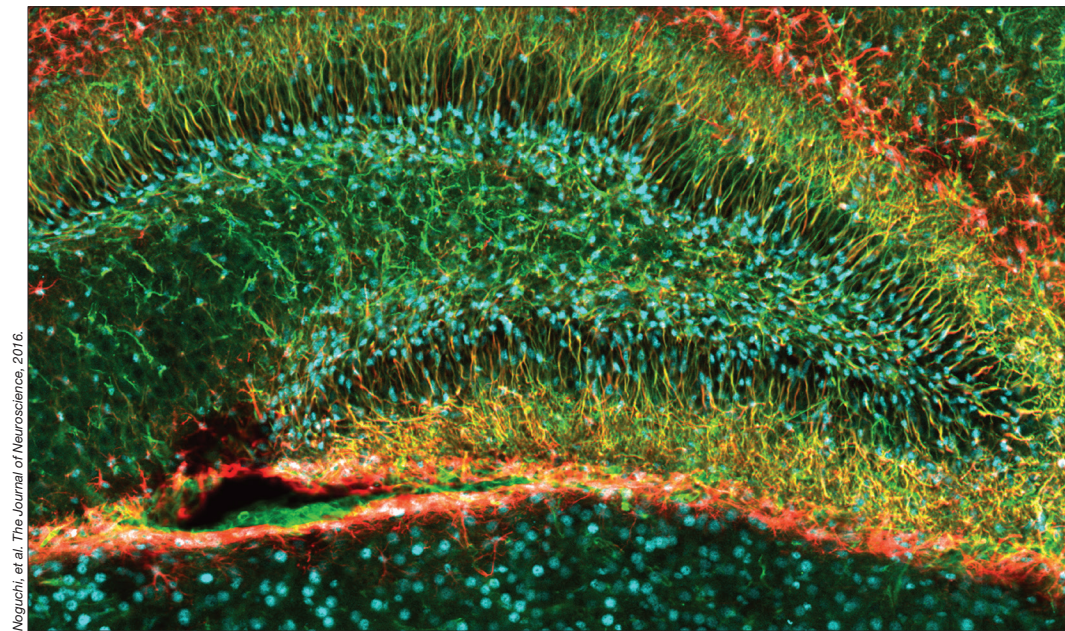
### Declarative Memory

**Declarative memory** is memory for facts, data, and events. Such conscious (explicit) memories are called declarative memories because you can consciously recall and describe the information. Declarative memories can be semantic or episodic. **Semantic memories** consist of the cultural knowledge, ideas, and concepts you've accumulated about the world — for example, names of state capitals, word definitions, how to add and subtract, or dates of historical events and their meaning. This type of memory involves cortical regions well beyond the hippocampus. **Episodic memories** are unique representations of your personal experiences. For example, mentally recalling the sights, sounds, time, space, and emotions associated with an experience involves episodic memory.

Interestingly, the emotional significance attached to memories of events and experiences is mediated by the



There are several different kinds of memory, and they are processed by different areas of the brain. The hippocampus, parahippocampal region, and areas of the cerebral cortex work in tandem to produce memories of facts and events. Other kinds of memories, such as emotional or behavioral memories, are handled by other parts of the brain, including the amygdala, striatum, and cerebellum.



The dentate gyrus, a portion of the hippocampus responsible for memories of events, is one of the few areas of the adult brain where neurogenesis takes place. This image of a mouse dentate gyrus shows newborn cells, labeled in blue, along with the support cells called glia, labeled in red, that will help them migrate to their final destinations. Some of these new cells will mature to become different types of neurons in the dentate gyrus, where they will play important roles in learning and memory.



amygdala. A paired structure consisting of two almond-shaped regions (amygdala comes from the Greek word for almond), the amygdala modulates “fight-or-flight” responses linked to survival. The parahippocampal region also aids the hippocampus in encoding the “what” of episodic memories, rather than the “where” or “when.”

The type of memory described so far is the **long-term** form of declarative

no longer be retrieved.

Some aspects of working memory are coordinated by the **prefrontal cortex (PFC)**, the “brain’s executive,” which also controls attention, decision-making, and long-term planning. Specific areas of the PFC monitor information from long-term memory as well as coordinating working memory from multiple brain regions. Brain imaging studies demonstrate the PFC

gating a maze display specific sequences of neuronal activity devoted to right or left turns. These patterns become increasingly distinct as the animals learn the maze. Studies have even shown that learning complex navigational routes causes changes in the hippocampus.

“Grid cells,” don’t represent particular locations. Located in the entorhinal cortex, an area near the hippocampus, they represent coordinates that allow the brain to track your position in space when landmarks or external cues are absent.

### Nondeclarative Memory

**Nondeclarative memory** — also known as implicit or procedural memory — is stored and retrieved without conscious effort. You use this type of memory when you perform learned motor skills like speaking or riding a bike. H.M. did *not* lose this type of memory, as evident in his ability to acquire new motor skills, even though he couldn’t remember doing them before.

The fact that H.M. (and other people with amnesia) show deficits in some types of memory but not others indicates that different types of memories are encoded in separate, but interacting, regions of the brain. Motor skill learning, for example, involves many areas of the brain, but three are especially important: the basal ganglia — the “habit center” of the brain — the prefrontal cortex, and the cerebellum, an area at the back of the brain involved in motor control and coordination.

### Storing Memories in Your Synapses



Your brain is able to form memories and rewire itself in response to experience because circuits in your brain change at synapses — the tiny gaps across

which neurons communicate via chemical and electrical signals. The ability of synapses to remodel themselves is called **synaptic plasticity**. Encoding a new long-term memory involves persistent changes in the number and shape of synapses, as well as the amount of neurotransmitter released and the number of receptors on the postsynaptic membrane.

In transmitting information from one neuron to another, a presynaptic (sending) neuron transforms an electrical signal into the release of chemical messengers called neurotransmitters that diffuse across the synaptic gap to the postsynaptic (receiving) neuron. The membrane of the postsynaptic neuron contains proteins called receptors that interact with neurotransmitters. Upon binding the neurotransmitters, the receptors unleash a cascade of molecular events that convert the message back into an electrical signal. The receptors then release the neurotransmitters, which are recycled back into the presynaptic terminal or broken down enzymatically, allowing postsynaptic receptors to receive new signals from the presynaptic neuron.

Scientists have learned a great deal about the ways presynaptic and postsynaptic neurons remodel themselves. The sea slug, *Aplysia californica*, was an important animal model for the first neuroscientists studying synaptic plasticity because its nerve cells are relatively few and easy to observe. Researchers identified chemical and structural changes in relevant nerve cells of *Aplysia* that correlated with simple forms of learning and memory. Studies in genetically modified mice have revealed that alterations in gene expression facilitate long-term changes in synaptic structure. Genes governing a type of glutamate receptor — N-methyl-d-aspartate (NMDA)

receptors — and a molecule called cAMP-response element binding protein (CREB) are especially important in the formation of long-term memories.

Two opposing but equal processes are key for synaptic plasticity: **long-term potentiation (LTP)** and **long-term depression (LTD)**. LTP is a long-lasting increase in synaptic strength, which occurs in many brain regions but especially in the hippocampus. LTD, conversely, decreases a synapse’s effectiveness. Experience physically changes our brains through LTP, shown in numerous animal and human studies to be essential for long-term memory consolidation.

While LTP has been identified throughout the brain, it has been studied extensively in the hippocampus, the brain region associated with encoding new memories. The precise mechanism of LTP varies depending on the type of neurons, but, in general, it involves an increase in the number of glutamate receptors on the postsynaptic neuron. Glutamate is the most prevalent neurotransmitter in the mammalian nervous system, and it binds to several different kinds of receptors. The NMDA and AMPA ( $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) classes of glutamate receptors are ion channels. Upon binding glutamate, they permit calcium and sodium ions, respectively, to flow into the cell. Increasing the number of receptors on the postsynaptic cell strengthens a synapse by allowing the entry of more electrically conductive ions.

Calcium ions also function as second messengers — signaling molecules that set off a chain of molecular events within cells. LTP boosts the concentration of calcium ions inside a postsynaptic cell, while LTD increases it to a lesser degree. The differing concentrations

of calcium activate different enzymes: kinase proteins in the case of LTP, or phosphatases for LTD. These enzymes modify the synapse, making it more or less efficient at relaying nerve impulses.

In LTP, a series of molecular events stabilizes the synaptic changes: The increase in calcium ions within the postsynaptic cell activates cyclic adenosine monophosphate (cAMP) molecules. This, in turn, activates several kinds of enzymes, some of which increase the number of synaptic receptors, making the synapse more sensitive to neurotransmitters. In addition, continued stimulation through repetitive experience activates CREB. CREB acts in the nucleus of the neuron to switch on a series of genes, many of which direct protein synthesis. Among the many proteins produced are neurotrophins, which stimulate the growth of the synapse and structural elements, stabilizing increased sensitivity to neurotransmitters.

The preceding molecular cascade is essential for memories to become long-term. The prevailing view is that declarative memories are encoded in the hippocampus, then transferred to the frontal lobes for long-term storage and consolidation. Research suggests that, over time, the hippocampus becomes less important for retrieving older memories as the frontal cortex assumes that task.

As researchers gain new insights into the molecular mechanisms underlying memory, pharmaceutical and technological advances may enable artificial manipulation of synaptic plasticity. New treatments could be developed for synapse-related neurological disorders — such as eradication of harmful memories tied to post-traumatic stress disorder (PTSD) — or for boosting our ability to learn and remember.

The brain seems to have unlimited capacity for long-term memories, but short-term memories are limited to small sums of data for a limited time.

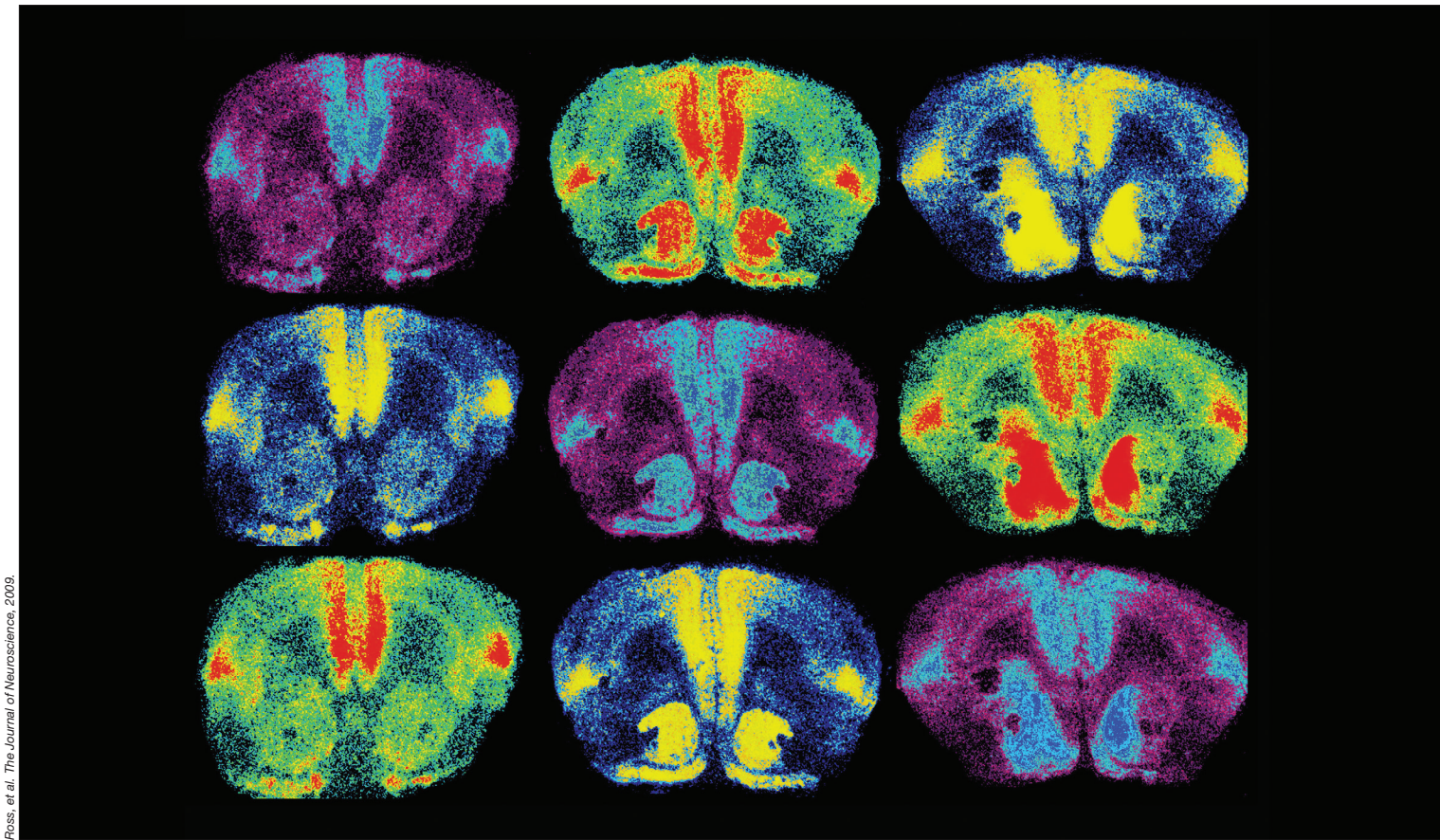
memory. Such memories are stored throughout a broad network of cortical areas. H.M. was able to retrieve his previous long-term memories, but not able to form new ones.

In contrast, **working memory** is a temporary type of declarative memory, a form of **short-term memory** that lets you hold a phone number, a sum, a visual image, or other data point needed in the present and immediate future. While the brain seems to possess unlimited capacity for long-term memories, short-term memories are limited to relatively small amounts of data for a limited amount of time. These data are accessible while they’re being processed and manipulated but, unless transferred to long-term memory, they decay after only a few seconds and can

is particularly active when people concentrate on keeping something like a phone number in mind. Animal studies suggest that neurons in the PFC fire in spurts, keeping information active or “online” in working memory. H.M. did not lose this type of memory.

Spatial memory is another facet of declarative memory. This was identified in studies showing that discrete areas, and even individual neurons within the brain, are dedicated to processing specific types of information. For example, navigational memories involved in creating mental maps are tied to specific types of neurons. So-called “place cells” in the hippocampus light up as you move through a familiar house or room, or as a rat navigates a known maze. Studies have also shown that mice navi-





Ross, et al. The Journal of Neuroscience, 2009.

Oxytocin is a brain chemical closely associated with love. In order to study something as unique as love, researchers look at the brains of prairie voles, which mate for life. In this image, oxytocin receptors are labeled in light blue, red, and yellow. When researchers increased oxytocin receptor levels in the brain (right column), they found female voles formed partner preferences faster.

## EMOTIONS

In emotional memory, considered another type of nondeclarative memory, learned emotional responses become attached to stimuli over time after repeated exposure. In the 1970s, anthropologist Paul Ekman identified what he called the six basic emotions: anger, fear, surprise, disgust, joy, and sadness. While scientists have since disputed the exact number and attributes of human emotions, whether emotions are consistent across cultures, or even how to define an emotion, their research has linked some neural circuits to physiological responses that help us survive, interact, set goals, and initiate actions.

### Anatomy of Emotion

The brain structures most closely linked with emotions are the amygdala, the insula or insular cortex, and the periaqueductal gray, located in the midbrain. Neurons from the prefrontal cortex, the amygdala, and the insular cortex project to the periaqueductal gray, which in turn has reciprocal connections with the central nucleus of the amygdala and projections to the thalamus, hypothalamus, brainstem, and deep layers of the spinal cord.

The amygdala integrates emotions, emotional behavior, and motivation. It interprets fear, helps distinguish friends from foes, and identifies social rewards and how to

attain them. One very familiar type of learning is dependent on the amygdala: classical conditioning, which associates a stimulus with reward or punishment.

Through the insula, you experience disgust — a strong negative reaction to an unpleasant odor, for instance — that might protect you from ingesting poison or spoiled food. The insula has also been implicated in feeling and anticipating pain, although its exact function in this arena is not well understood. The insula is believed to take in system-wide inputs and generate subjective feelings about them; thus linking feelings, internal physiological states, social emotions, and conscious actions.

The periaqueductal gray, located in a region where incoming sensory information is acted on by higher brain centers, has been tied to pain perception as well as stress responses including defensive and reproductive behaviors, maternal attachment, and anxiety. Receptors for pain-reducing compounds such as morphine and oxycodone are clustered in the periaqueductal gray.

### Motivation: Affective Decision-Making

Human actions are driven by necessities — food, sleep, sex, avoidance of pain — and by rewards, but our responses and actions are not always logical. While little is known about exactly how the brain transforms feelings into decisions, researchers have developed theoretical models about decision-making. Affective decision-making involves choices under risky and uncertain conditions. An active area of neuroscience research is investigating how the brain balances reward and risk, and how emotional state affects this balance.

Emotionally centered decision-making changes with age — possibly because the lateral prefrontal cortex, responsible for self-regulation, matures gradually in adolescents. Teens' developing brains and high sensitivity to peer acceptance might be related to their increased tolerance for risky behaviors. Older adults might also make more risky decisions, as PFC function diminishes with age.

### Motivation: Dopamine and Reward Pathways

Although relatively few neurons in the mammalian central nervous system generate the neurotransmitter dopamine, these dopaminergic neurons influence multiple brain functions including voluntary movement and a variety of behavioral processes such as mood, reward, addiction, stress and memory.

When something is very rewarding, we are more likely to remember it. That is because dopamine influences the synapses in the entire reward pathway — the hippocampus, amygdala, and the prefrontal cortex — to create emotional associations with rewards. And the mesolimbic pathway, sometimes called the “reward pathway,” is a major pathway for dopamine, connecting the mid-brain's ventral tegmental area (VTA) to the **nucleus accumbens**. It is involved in cognitive processing of rewards and motivation. Neurons that release dopamine are activated in response to signals that a reward will be given.

Surprisingly, it's not the reward itself, but the expectation of a reward that most powerfully influences the emotional reaction. Reward learning occurs in response to something unexpected — when the actual reward differs from what was predicted. If a reward is greater than anticipated, dopamine signaling increases. If a reward is less than expected, dopamine signaling decreases. In contrast, a correctly predicted reward does not elicit changes in dopamine signaling,

and all remains the same.

Interestingly, recent research shows that dopaminergic responses vary among people. Some people's brains respond more strongly to rewards than punishments, while others respond more strongly to punishments. The amygdala has been implicated in various aspects of reward learning and motivation. Researchers at Vanderbilt University found that “go-getters” who are more willing to work hard have greater dopamine signaling in the striatum and prefrontal cortex — two areas known to impact motivation and reward.

While the brain's reward system typically reinforces behaviors associated with rewards and prevents behaviors leading to punishment, aberrant circuitry can lead to inappropriate aggression, a symptom of some neuropsychiatric disorders. For example, the lateral habenula, a major node in the reward circuitry, appears to encode punishment by inhibiting dopamine release, and dysfunction of the lateral habenula has been linked to disorders involving inappropriate aggression. The amygdala has also been associated with negative emotions. Stimulating some areas can trigger rage and aggression, while removing specific sections of the amygdala will make lab animals more docile. Recent studies in lab animals have also suggested that aggression can result from inappropriate activation of the brain's reward systems in response to violent social stimuli. ■



# Thinking, Planning & Language

**F**rom the moment you wake up, your brain is bombarded by stimuli: the sound of birds singing or the rumble of trucks, the smell of coffee, the brightness and warmth of sunlight streaming through your window. Fortunately, your brain is adept at filtering this flood of information and making a decision about what actions to take. Is it a workday or a weekend? What would taste good for breakfast? How warm a sweater do you need? Every moment you're conscious, you are thinking, planning, and making decisions.

But how do you think? What is happening in our brains when we reflect on last night's party or puzzle over what to wear today? Can other animals think the way that humans do? In order to think, your brain has to make sense of the noisy, chaotic world around you. The first filter for that information is your perception, which arises from the senses whose processing we considered in Chapter 2. The next step is interpreting those perceptions, which your brain does by comparing them to memories of past experiences and observations.

## Constructing Representations

Because your brain's capacity to store this information in short-term memory is limited, it builds fairly simple representations of people, places, objects, and events as references. To really make sense of our moment-to-moment perceptions, the brain relies on its complex network of associations assembled from prior experience. These connections enable your brain to deal with variable perceptions. For example, you can identify a dog even if it is a different breed or color than any you have seen before. A bicycle still registers as a bicycle, even if it is obscured so that only one wheel is visible.

Constructing these representations relies on semantic memory, a form of declarative knowledge that includes general facts and data. Scientists are just beginning to understand the nature and organization of cortical areas involved in semantic memory, but it appears that specific cortical networks are specialized for processing certain types of information. Studies using functional brain imaging have revealed regions of the cortex that selectively process different categories of information such as animals, faces, tools, or words.

Recordings of the electrical activity of individual brain cells show that specific, single cells may fire when someone looks at photographs of a particular person, but remain quiet when viewing photographs of other people, animals, or objects. So-called "concept cells" work together in assemblies. For example, the cells encoding the concepts of needle, thread, sewing, and button may be interconnected. Such cells, and their connections, form the basis of our semantic memory.

Concept cells reside in the temporal lobe, a brain area that specializes in object recognition. Scientists made great strides in understanding memory by studying H.M., a man with severe amnesia, who was discussed in Chapter 4. Similarly, our understanding of thinking and language has been informed by studying people with unique deficits caused by particular patterns of brain damage.

Consider the case of D.B.O., a 72-year old man who suffered multiple strokes. In tests run by researchers, D.B.O. could identify only 1 out of 20 different common objects by sight. He also struggled when he was asked to take a cup and fill it with water from the sink. He approached several different objects — a microwave, water

pitcher, garbage can, and roll of paper towels — saying "This is a sink ... Oh! This one could be a sink ... This is also a sink," before finally finding the real sink and filling the cup. But in striking contrast, he could easily identify objects when he closed his eyes and felt them; he could also name things that he heard, such as a rooster's "cock-a-doodle-doo."

Researchers concluded that D.B.O.'s strokes had damaged his brain in ways that prevented visual input from being conveyed to anterior temporal regions where semantic processing occurs. This blocked his access to the names of objects that he could see, but not his ability to name objects he could touch.

## Regional Specialization and Organization

Experts have learned from people like D.B.O. that damage to certain areas of the temporal lobes leads to problems with recognizing and identifying visual stimuli. This condition, called agnosia, occurs in several forms, depending on the exact location of the brain damage.

One such region is the fusiform face area (FFA). Located on the underside of the temporal lobe, the FFA is critical for recognizing faces. This distinct area responds more strongly to images with than without faces, and bilateral damage to this area results in prosopagnosia or "face blindness." Similarly, a nearby region called the parahippocampal place area responds to specific locations, such as pictures of buildings or particular scenes. Other areas are activated only by viewing certain inanimate objects, body parts, or sequences of letters.

Within these brain areas, information is organized into hierarchies,

as complex skills and representations are built up by integrating information from simpler inputs. One example of this organization is the way the brain represents words. Regions that encode words include the posterior parietal cortex, parts of the temporal lobe, and regions in the prefrontal cortex (PFC). Together, these areas form the semantic system, a constellation that responds more strongly to words than to other sounds, and even more strongly to natural speech than to artificially garbled speech. The semantic system occupies a significant portion of the human brain, especially compared to the brains of other primates. This difference might help explain humans' unique ability to use language.

Separate areas within this system encode representations of concrete or abstract concepts, action verbs, or social information. Words related to each other, such as "month" and "week," tend to activate the same areas, whereas unrelated words, such as "month" and "tall," are processed in separate areas of the brain. Many studies using a technique called **functional magnetic resonance imaging (fMRI)** to measure brain activity in response to words have found more extensive activation in the left hemisphere, compared to the right hemisphere. However, when words are presented in a narrative or other context, they elicit fMRI activity on both sides of the brain.

Written language involves additional brain areas. The visual word form area (VWFA) in the fusiform gyrus recognizes written letters and words — a finding that is remarkably consistent across speakers of different languages. Studies of the VWFA reveal connections between it and the brain areas that process visual information, bridges that help the brain link



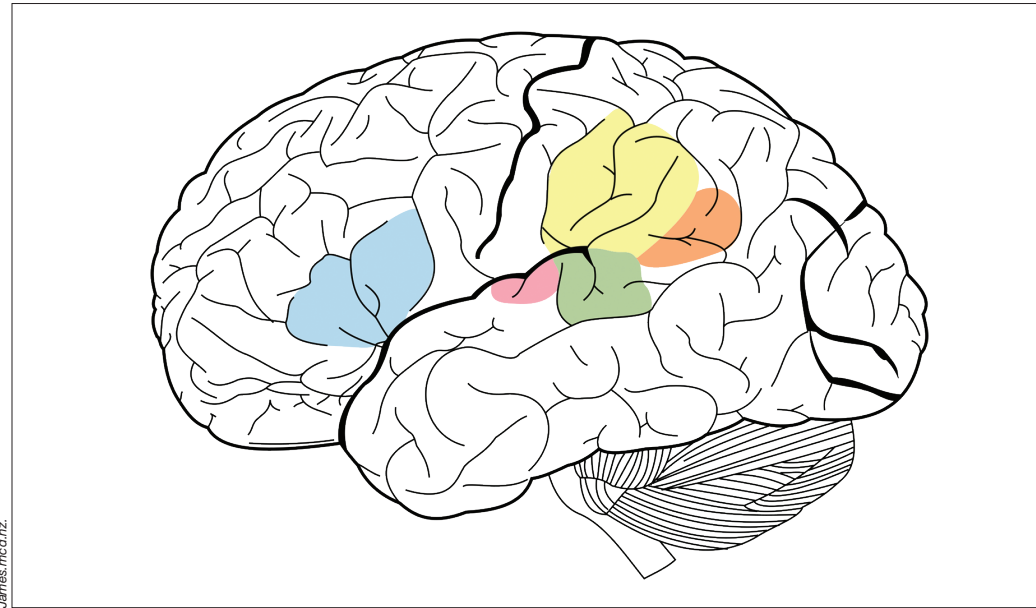
meaning to written language. Likewise, there are specific brain areas that represent numbers and their meaning. These concepts are represented in the parietal cortex with input from the occipitotemporal cortex, a region that participates in visual recognition and reading. These regions work together to identify the shape of a written number or symbol and connect it to its concept, which can be broad: For example, the number “3” is applied to sets of objects, the concept of trios, and the rhythm of a waltz.

Thus, through constructing hierarchical, connected representations of concepts, the brain is able to build meaning. All of these skills depend on the fluid and efficient retrieval and manipulation of semantic knowledge.

### LANGUAGE PROCESSING

In mid-19th century France, a young man named Louis Victor Leborgne came to live at the Bicêtre Hospital in the suburbs south of Paris. Oddly, the only word he could speak was a single syllable: “Tan.” In the last few days of his life, he met a physician named Pierre Paul Broca. Conversations with the young man, whom the world of neuroscience came to know as Patient Tan, led Broca to understand that Leborgne could comprehend others’ speech and was responding as best he could, but “tan” was the only expression he was capable of uttering.

After Leborgne died, Broca performed an autopsy and found a large damaged area, or lesion, in a portion of the frontal lobe. Since then, we have learned that damage to particular regions within the left hemisphere produces specific kinds of language disorders, or **aphasias**. The portion of the frontal lobe where Leborgne’s



Language is a complex cognitive ability, involving several areas of the brain. The blue area in this image is Broca’s area, which is vital for speech production. The green area is Wernicke’s area, which is responsible for understanding others’ speech. They and other areas work in tandem for many types of communication.

lesion was located is still called **Broca’s area**, and it is vital for speech production. Further studies of aphasia have greatly increased our knowledge about the neural basis of language.

Broca’s aphasia is also called “non-fluent” aphasia, because speech production is impaired but comprehension is mostly intact. Damage to the left frontal lobe can produce non-fluent aphasias, in which speech output is slow and halting, requires great effort, and often lacks complex word or sentence structure. But while their speaking is impaired, non-fluent aphasics still comprehend spoken language, although their understanding of complex sentences can be poor.

Shortly after Broca published his findings, a German physician, Carl Wernicke, wrote about a 59-year-old woman he referred to as S.A., who had lost her ability to understand speech.

Unlike patient Leborgne, S.A. could speak fluently, but her utterances made no sense: she offered absurd

answers to questions, used made-up words, and had difficulty naming familiar items. After her death, Wernicke determined that she had damage in her left temporal lobe. This caused her difficulty in comprehending speech, but not producing it, a deficit that is now known as “Wernicke’s aphasia,” or “fluent aphasia.” Fluent aphasic patients might understand short individual words, and their speech can sound normal in tone and speed, but it is often riddled with errors in sound and word selection and tends to be unintelligible.

Another type of aphasia is called “pure word deafness,” which is caused by damage to the superior temporal lobes in both hemispheres. Patients with this disorder are unable to comprehend heard speech on any level. But they are not deaf. They can hear speech, music, and other sounds, and can detect the tone, emotion, and even the gender of a speaker. But they cannot link the sound of words to their meaning. (They can, however, make

perfect sense of written language, because visual information bypasses the damaged auditory comprehension area of the temporal lobe.)

Although Broca and Wernicke’s work emphasized the role of the left hemisphere in speech and language ability, scientists now know that recognizing speech sounds and individual words actually involves both the left and right temporal lobes. Nonetheless, producing complex speech is strongly dependent on the left hemisphere, including the frontal lobe as well as posterior regions in the temporal lobe. These areas are critical for accessing appropriate words and speech sounds.

Reading and writing require the involvement of additional brain regions — those controlling vision and movement. Earlier, we mentioned that sensory processing of written words entails connections between the brain’s language areas and the areas that process visual perceptions. In the case of reading and writing, many of the same centers involved in speech comprehension and production are still essential, but require input from visual areas that analyze the shapes of letters and words, as well as output to the motor areas that control the hand.

### New Insights in Language Research

Although our understanding of how the brain processes language is far from complete, recent molecular genetic studies of inherited language disorders have provided important new insights. One language-associated gene, called FOXP2, codes for a special type of protein that switches other genes on and off in particular parts of the brain. Rare mutations in FOXP2 result in difficulty making mouth and jaw

movements in the sequences required for speech. The disability is also accompanied by difficulty with spoken and written language.

Remarkably, many insights into human speech have come from studies of birds, where it is possible to induce genetic mutations and study their effects on singing. Just as human babies learn language during a special developmental period, baby birds learn their songs by imitating a vocal model (a parent or other adult bird) during an early critical period. Like babies’ speech, birds’ song-learning also depends on auditory feedback — their ability to hear their own attempts at imitation. Interestingly, studies have also revealed that FOXP2 mutations can disrupt song development in young birds, much as they do in humans.

Imaging studies have revealed that disruption of FOXP2 can severely affect signaling in the dorsal striatum, part of the basal ganglia located deep in the brain. Specialized neurons in the dorsal striatum express high levels of the product of FOXP2. Mutations in FOXP2 interrupt the flow of information through the striatum and result in speech deficits. These findings show the gene’s importance in regulating signaling between motor and speech regions of the brain. Changes in the nucleotide sequence of FOXP2 might have influenced the development of spoken language in humans and explain why humans speak and chimpanzees do not.

Functional imaging studies have also identified brain structures not previously known to be involved in language. For example, portions of the middle and inferior temporal lobe participate in accessing the meaning of words. In addition, the anterior tem-

poral lobe is under intense investigation as a site that might participate in sentence-level comprehension. Recent work has also identified a sensory-motor circuit for speech in the left posterior temporal lobe, which is thought to help communication between the systems for speech recognition and speech production. This circuit is involved in speech development and is likely to support verbal short-term memory.

### COGNITION AND EXECUTIVE FUNCTION

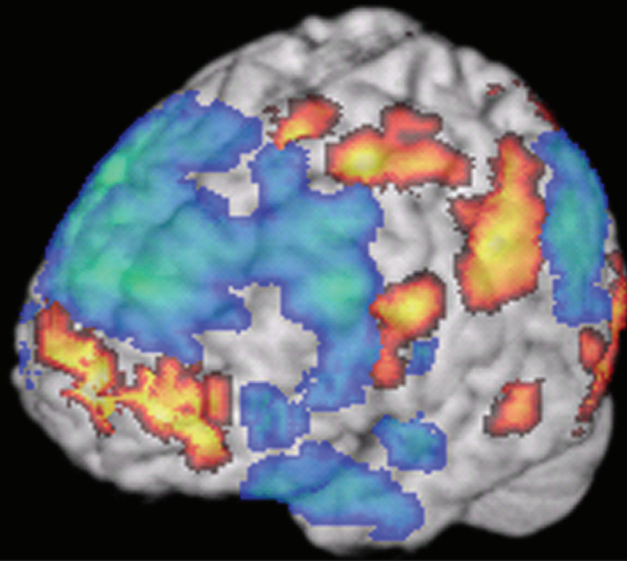
#### Executive Function

Some of the most complex processes in the brain occur in the prefrontal cortex (PFC), the outer, folded layers of the brain located just behind your forehead. The PFC is one of the last regions of the brain to develop, not reaching full maturity until adulthood. This is one reason why children’s brains function quite differently from those of adults. The processing that takes place in this area is known as executive function. Like the chief executive officer (CEO) of a company, the PFC supervises everything else the brain does, taking in sensory and emotional information and using this information to plan and execute decisions and actions.

Specific areas of the PFC support executive functions such as selecting, rehearsing, and monitoring information being retrieved from long-term memory. To serve these functions, the PFC also interacts with a large network of posterior cortical areas that encode specific types of information — for example, visual images, sounds, words, and the spatial location in which events occurred.

Although more fully evolved in humans, some aspects of executive function are displayed by other





National Institute on Deafness and Other Communication Disorders, National Institutes of Health.

Scientists can observe the brain activity underlying advanced cognitive functions, such as creativity. In this image, researchers were able to measure activity in the brains of jazz musicians while they improvised. This gave them a clue as to what brain regions are associated with creative thinking.

animals. Studies in nonhuman primates have shown that neurons in the PFC keep information active or “in mind” while the animal is carrying out a task that depends on it. This is analogous to working memory in humans, which is a form of executive function.

**Executive function** can be considered a blend of three core skills: inhibition, working memory, and shifting. Inhibition is the ability to suppress a behavior or action when it is inappropriate — such as calling out loudly when one is in an audience or classroom. Even toddlers demonstrate hints of a developing inhibition ability, as shown in their ability to delay (for at least a short period of time) eating a treat placed in front of them. By the time children reach preschool, they can tackle more complex inhibition tasks, such as “Lucia’s hand game,” in which they are told to make a fist when shown a finger and a finger when shown a fist. This test, which requires inhibiting their more

automatic imitation of adults, is very hard for three-year-olds, but four-year-olds perform significantly better. As people grow older, they wield this ability ever more skillfully.

In addition to inhibition, this hand game and similar tasks rely on working memory, which is the ability to hold a rule in mind while you decide how to act (in this case, opposite the demonstrator). When you have new experiences, information initially enters your working memory, a transient form of declarative or conscious memory. Working memory depends on both the PFC and the parietal lobe. It gives you the ability to maintain and manipulate information over a brief period of time without external aids or cues — such as remembering a phone number without writing it down. Most people can memorize and recite a string of numbers or words over a brief period of time, but if they are distracted or there is a time lag of many minutes or hours, they are likely to forget. This shows the duration of working memory, which

requires active rehearsal and conscious focus to maintain.

The third key component of executive function is shifting, or mental flexibility, which allows you to adjust your ongoing behavior when conditions require it. For example, in the card sorting task, people must figure out (from the examiner’s simple “yes/no” responses) that they must switch from sorting by one rule, such as suit, and begin sorting by another, such as number. People with damage to their PFC have great difficulty doing this and tend to stick with the first sorting rule. Children’s ability to shift successfully between tasks follows a developmental course through adolescence. It appears that preschool-aged children can handle shifts between simple task sets in a card-sorting task and later handle unexpected shifts between increasingly complex task sets. Both behavioral and physiological measures indicate that the ability to monitor one’s errors is evident during adolescence; by mid-adolescence, more complex task switching reaches adult-like levels. Because of its greater need for multiple cognitive processes, mature shifting likely involves a network of activity in many regions of the PFC.

Many of the changes in executive functioning ability are gradual, although the changes are more apparent in young children. The PFC is the main region implicated in executive functioning; however, the skills that fall under this umbrella use inputs from all over the brain. Interestingly, the activity level associated with executive function actually decreases as children and adolescents mature, reflecting the fact that these circuits become more fine-tuned and efficient as the neuron networks mature.

### Decision-Making



The fundamental skills of executive function — inhibition, working memory, and shifting — provide the basis for other skills. One of these is decision-making, which requires a person to weigh values, understand rules, plan for the future, and make predictions about the outcomes of choices.

You make many different types of decisions every day. Some of these rely primarily on logical reasoning — for example, when you compare the timetables for the bus and subway to determine the quickest way to get to a friend’s house. Other decisions have emotional consequences at stake, like when the person you’re trying to impress offers you a cigarette — your desire to be accepted might outweigh your rational consideration of smoking’s harms. This is an example of affective decision-making (Chapter 4).

Both types of decision-making involve the brain’s prefrontal cortex (PFC). In particular, activity in the lateral PFC is especially important in overriding emotional responses in decision-making. The area’s strong connections with brain regions related to motivation and emotion, such as the amygdala and nucleus accumbens, seem to exert a sort of top-down control over emotional and impulsive responses. For example, brain imaging studies have found the lateral PFC is more active in people declining a small monetary reward given immediately in favor of receiving a larger reward in the future. This is one of the last areas of the brain to mature — usually in a person’s late 20s — which explains why teens have trouble regulating emotions and controlling impulses.

The orbitofrontal cortex, a region of the PFC located just behind the eyes, appears to be important in affective decision-making, especially in situations involving reward and punishment. The area has been implicated in addiction as well as social behavior.

### Social Neuroscience



Humans, like many other animals, are highly social creatures. Accordingly, large parts of our brain are dedicated to processing information about other people. Social neuroscience refers to the study of neural functions that underlie interpersonal behavior, such as reading social cues, understanding social rules, choosing socially-appropriate responses, and understanding oneself and others. The latter process is known as “**mentalizing**” — making sense of your own thought processes and those of others. The medial PFC, as well as some areas of the lateral PFC, are highly involved in these skills.

Mentalizing underlies some of our most complex and fascinating mental abilities. These include empathy and “theory of mind,” which is understanding the mental states of others and the reasons for their actions. Until recently, research devoted little emphasis to the social and emotional abilities needed for these higher-order mental functions, but now such topics are being avidly studied.

An obvious way that we understand the mental states of others is by observing their actions. This requires the brain to see and recognize others’ movements and facial expressions, and then draw inferences about the feelings and intentions that drive them. Scientists have learned how brain activity

drives these processes by scanning people’s brains with fMRI as subjects watch video clips of other people.

Several regions in the medial prefrontal cortex help us make judgments about ourselves and others. In addition, a specific region at the border of temporal and parietal lobes, the temporoparietal junction (TPJ), appears to focus on others and not on the self. The TPJ is also activated when we watch others engage in actions that seem at odds with their intentions or in actions intended to be deceptive.

A popular, though controversial, theory of social cognition centered on the discovery of “mirror neurons.” In the 1990’s, scientists identified neurons in the motor cortex of rhesus macaques that fired when the monkeys performed a specific action. They were astonished to find these neurons also fired when the monkeys simply *watched* another person or monkey perform that same action. The findings prompted speculation that mirror neurons underlie our ability to understand another person’s actions. Additional studies revealed humans also possessed mirror neurons, and in even wider brain networks.

Mirror neurons permeated popular media. Within a decade of their discovery, however, mirror neurons’ role in social cognition was called into question — many scientists argued that there was little direct evidence supporting mirror neurons’ purported roles in theory of mind, mentalizing, and empathy.

Researchers are continuing to investigate mirror neurons, as well as the complexities of the human brain that allow us understand and empathize with others. ■

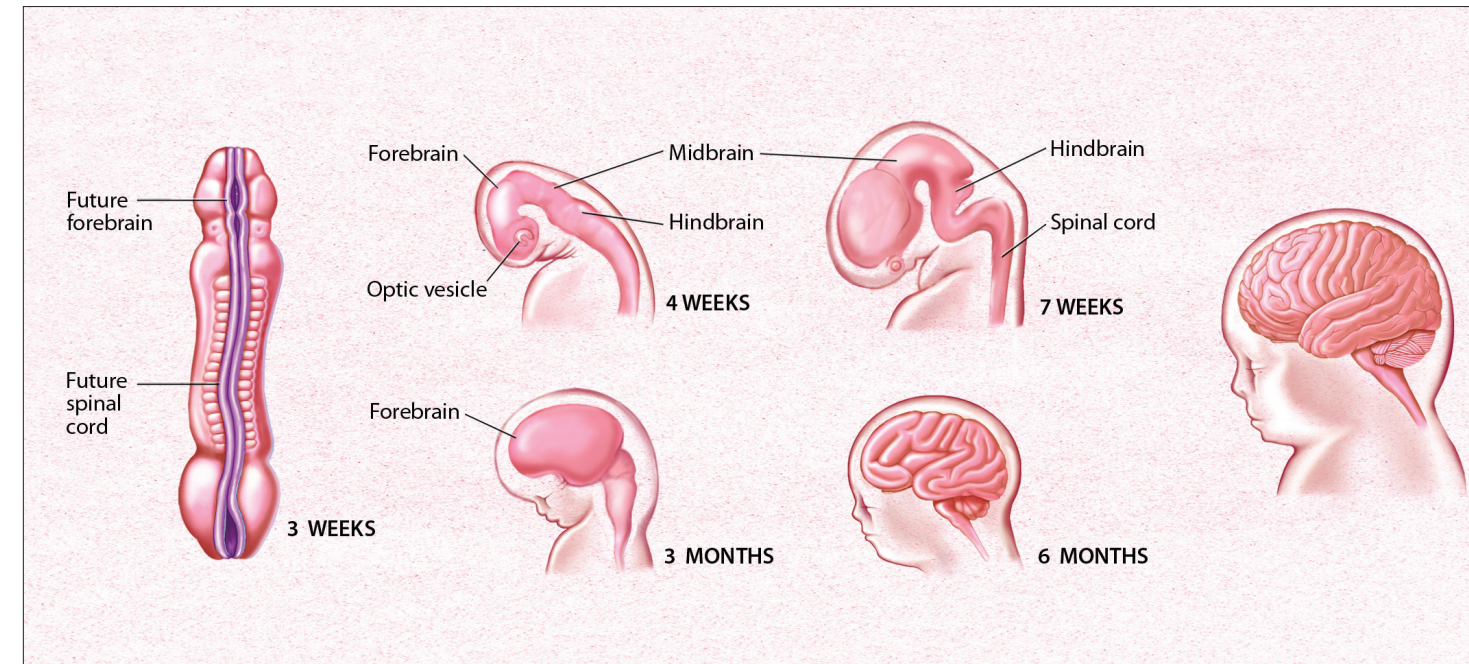


# The Developing Brain

Neurons develop through delicate and carefully choreographed processes that take place while an embryo grows. Signaling molecules “turn on” certain genes and “turn off” others, initiating the formation of immature nerve cells. During the next stage — cell division, also called proliferation — the pool of early-stage brain cells increases by billions. Finally, during migration, these newly formed neurons travel to their final destinations. The nervous system formed by these processes is active throughout life, making new connections and fine-tuning the way messages are sent and received. In this chapter, you will learn about the amazing early development of your ever-changing nervous system.

## THE JOURNEY OF NERVE CELLS Formation and Induction

During the very early stages of embryonic development, three layers emerge — the ectoderm (outer-most layer), mesoderm (middle layer), and endoderm (inner-most layer). Although the cells in each layer contain identical DNA instructions for development, these layers ultimately give rise to the rich variety of tissue types that make up the human body. The explanation for this diversity lies in signals produced by surrounding tissues. Those signals turn certain genes on and others off, thus inducing the development of specific cell types. Signals from the mesoderm trigger some ectoderm cells to become nerve tissue, a process called neural induction. Subsequent signaling interactions refine the nerve tissue into the basic categories of neurons or glia (support cells), and then into subclasses of each cell type.



After three week's gestation, the human brain begins to form. The first stage is the neural tube, pictured at left. By four weeks, the individual sections of the brain can be recognized. In 6 months, the ridges of the brain can be observed.

The fate of a developing cell is largely determined by its proximity to various sources of signaling molecules. The concentration of each type of signaling molecule decreases farther from its source, creating gradients throughout the brain. For example, a particular signaling molecule, called sonic hedgehog, is secreted from mesodermal tissue lying beneath the developing spinal cord. As a result of exposure to this signal, adjacent nerve cells are converted into a specialized class of glia. Cells that are farther away are exposed to lower concentrations of sonic hedgehog, so they become motor neurons that control the movement of muscles. An even lower concentration promotes the formation of interneurons, which don't relay messages to muscles but to other neurons. Interestingly, the mechanism of this molecular signaling is very similar in species as diverse as flies and humans.

## Proliferation

In the brain, neurons arise from a fairly small pool of neural stem and progenitor cells, special cells that can divide and become a variety of mature cell types. Before achieving their mature cell fate, this pool of cells undergoes a series of divisions — increasing the number of cells that will ultimately form the brain. Early divisions are symmetric — the split results in two identical daughter cells, both able to keep dividing. But as these divisions progress, the cells begin to divide asymmetrically, giving rise to only one daughter cell that keeps proliferating and a second that progresses towards its ultimate cell fate as a neural or glial cell (the exact sequences and ultimate fates vary by species).

This proliferative process permits rapid growth during early development of the brain, with billions of cells being produced in a matter of weeks. After that series of divisions is complete,

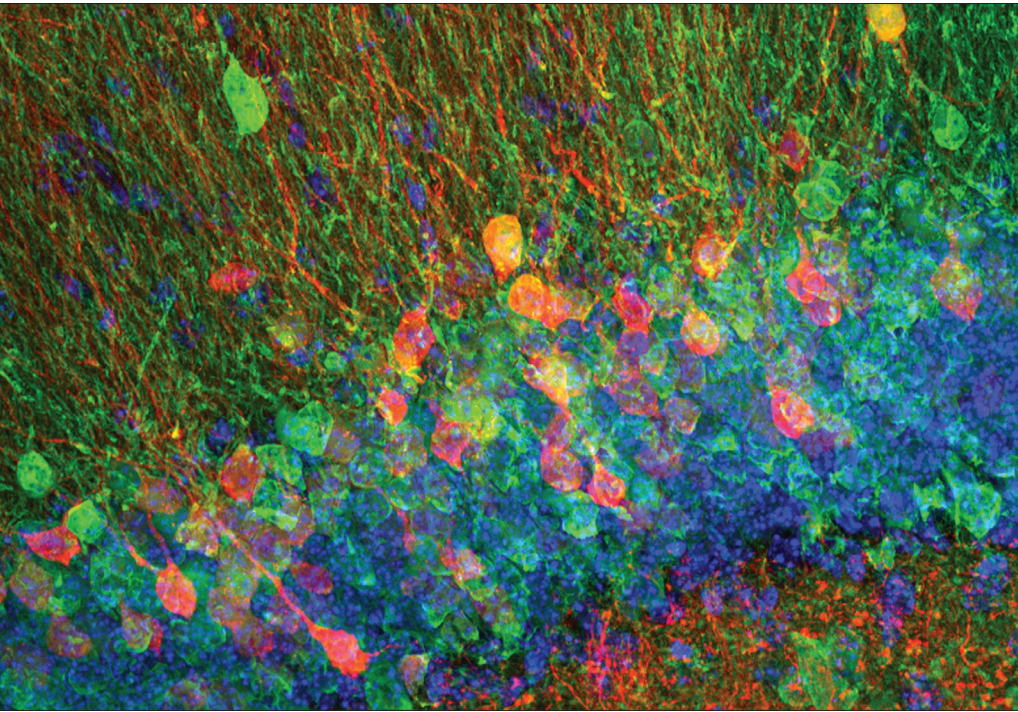
only a few neural stem and progenitor cells remain within the brain, and neurogenesis in adulthood is limited to a few regions of the brain, such as those involved with memory.

Scientists have proposed that protein defects causing a premature switch from symmetric to asymmetric divisions may be a cause of microcephaly. This disorder, characterized by a severe reduction in brain size, is associated with serious neurological disabilities and sometimes death in infancy. Similarly, excessive proliferation of brain cells can lead to a disorder called megalencephaly — a brain that is abnormally large and heavy — which is also associated with a variety of neurodevelopmental complications.

## Migration

After neural induction and proliferation occur, new neurons journey from the inner surface of the embryonic brain, where they formed, to their long-term locations in the brain. This





Winkler, et al. | The Journal of Neuroscience, 2016

New neurons, shown here in the mouse, are born throughout life in a specific region of the brain's hippocampus. This region, known as the dentate gyrus, is involved in pattern separation, the ability to discriminate between very similar memories.

process is called **migration**, and it begins three to four weeks after a human baby is conceived. At this time, the ectoderm starts to thicken and build up along the midline of the embryo. As the cells continue to divide, a flat neural plate grows, followed by the formation of parallel ridges, somewhat resembling the creases in a paper airplane, that rise along either side of the midline. These ridges extend from the “head end”, where the future brain will form, along the length of the embryo where the future spinal cord will develop. Within a few days, the ridges fold toward each other and fuse into a hollow neural tube. The head end of the tube thickens into three bulges that form the hindbrain, the midbrain, and the forebrain. Later in the process, at week 7 in humans, the first signs of the eyes and the brain's hemispheres appear. As new neurons are produced, they move from the neural tube's ven-

tricular zone, which lies along the inner surface of the tube, toward the border of the marginal zone, or outer surface. After neurons stop dividing, they form an intermediate zone where they gradually accumulate as the brain develops. A variety of guidance cue neurons to migrate to their final destinations.

The most common guidance mechanism, accounting for about 90 percent of migration in humans, is the radial glia, which project radially from the intermediate zone to the cortex. Neurons use these glia as scaffolding, inching along glial projections until they reach their final destinations. This process of radial migration occurs in an “inside-out” manner; that is, the cells that arrive the earliest (the oldest ones) form the deepest layer of the cortex, whereas the late-arriving (youngest) neurons form the outermost layer. Through a different mechanism, other neurons

migrate sideways, or tangentially (rather than radially), moving parallel to the brain's surface and across the radial cortical columns.

Migration is a finely tuned process that can be influenced by many factors. For example, exposure to alcohol, cocaine, or radiation, can prevent proper migration, resulting in misplacement of cells, which can lead to intellectual disability or epilepsy. Furthermore, mutations in the genes that regulate migration have been shown to cause rare genetic forms of intellectual disability and epilepsy in humans.

### Making Connections



After neurons reach their final locations, they begin making the connections that will determine how particular functions such as vision or hearing can occur. Induction, proliferation, and migration occur internally during fetal development, but the next phases of brain development depend increasingly on external experience. After birth, factors such as watching a mobile spin, listening to a voice, and even proper nutrition influence the connections formed by neurons.

Neurons become interconnected through their short branches called dendrites and long axons — two types of processes that extend from a neuron's cell body (soma). Axons produce and transmit signals to other neurons, and dendrites receive signals from the axons that contact them. To reach their targets, axons can span distances many times the size of their cell body, many crossing to the opposite side of the brain. The longest human axons are in the periphery, extending from the lower spinal cord all the way to muscles in the toes. Given the distance from spinal cord

to toes of a basketball player — a meter or more — such axons might be nearly a million times longer than their diameter!

A developing axon grows by the extension of its **growth cone**, an enlargement at the tip of the axon that actively explores the environment to seek out its precise destination. A growth cone is guided to that final destination by molecular cues in its environment. Some of these molecules stud the surfaces of cells, while others are secreted into areas near the growth cone. Receptors on the growth cone enable its responses to these environmental cues. Binding of environmental molecules tells the growth cone whether to move forward, stop, recoil, or change direction. Attractive cues lay a path growth cones follow, while repellent molecules funnel growth cones through precise corridors. Signaling molecules include families of proteins with names such as netrin, semaphorin, and ephrin.

One truly remarkable finding is that most of these proteins are common to many organisms — worms, insects, and mammals including humans. Each family of proteins is smaller in flies or worms than in mice or people, but its functions are very similar. As a result, simpler animals are highly useful experimental models for gaining knowledge that directly applies to humans. For example, netrin was first discovered in a worm, where it was found to guide neurons around the worm's “nerve ring.” Later, vertebrate netrins were found to guide axons around the mammalian spinal cord. When receptors for netrins were then discovered in worms, this knowledge proved invaluable in finding the corresponding, and related, receptors in humans.

### Synapse Formation



Once axons reach their targets, a specialized connection called a synapse begins to form. At the synapse, only a tiny space separates the signaling portion of the axon from the receiving portion of the dendrite. Electrical signals that travel down the axon trigger the release of chemical messages called neurotransmitters, which diffuse across this

Dendrites are also actively involved in initiating contact with axons, and both sides produce proteins that span the space between them and anchor the synapse together.

Once initial contact is established, a synapse continues to differentiate. On the presynaptic side, the tiny axon terminal that contacts the dendrite becomes specialized for releasing neurotransmitters, stocking itself with neu-

**A** human brain contains trillions of these synapses, which gives rise to the brain's astounding capacity for information processing.

space and are received by receptors on the target dendrite. Such chemical cues can either promote or hinder the generation of a new electrical signal in the receiving neuron. The combined effects of such cues from thousands of synapses ultimately determine how a receiving neuron responds. A human brain contains trillions of these synapses, which gives rise to the brain's astounding capacity for information processing.

For this processing to occur properly, the formation of synaptic connections must be highly specific. Some specificity is the result of the mechanisms that guide each axon to its proper target. Additional molecules mediate target recognition when the axon reaches the proper location.

rotransmitter packets, and proteins that enable those packets to be held in place and then released. On the dendritic — or postsynaptic — side, receptors that respond to those neurotransmitters begin to dot the membrane. Both processes ensure that a synapse can transmit signals quickly and effectively.

New evidence has implicated a third important player in the proper formation of a synapse. Astrocytes are a type of glial cell in the brain previously thought to simply provide scaffolding and passive support to neurons. They are now known to exert their own influence on synaptic development and function. Many synapses in the brain are contacted by astrocytes, and studies in rodents have found that a single astrocyte can



contact thousands of synapses across multiple neurons. The importance of astrocytes in synapse formation is also shown in other studies. Some neurons form only a few synapses when developing in a culture dish from which astrocytes are absent, and recent research has discovered that molecules secreted by astrocytes regulate aspects of synaptic development.

Scientists are learning that molecules from multiple sources work together to promote proper synapse formation. It is now thought that defects in such molecules could contribute to disorders such as autism. In addition, the loss of certain other molecules might underlie the degradation of synapses that occurs during aging.


An array of signals determines which type of neurotransmitter a neuron will use to communicate. For some cells, such as motor neurons, the type of neurotransmitter is fixed (acetylcholine), but for other neurons, it is not. Scientists have found that when certain immature neurons are maintained in a culture dish with no other cell types, they produce the neurotransmitter norepinephrine. In contrast, when the same neurons are cultured with specific cells, such as cardiac tissue, they produce the neurotransmitter acetylcholine. Just as genetic and environmental signals can modulate the development of specialized cells, a similar process leads to production of specific neurotransmitters. Many researchers believe that the signal to engage the gene, and therefore the final determination of the chemical messenger a neuron will produce, is

influenced by factors that come from the location of the synapse itself.

### Myelination

Insulation that covers wires preserves the strength of electrical signals that travel through them. The myelin sheath that covers axons serves a similar function. Myelination, the fatty wrapping of axons by extensions of glia, increases — by as much as 100 times — the speed at which signals can travel along axons. This increase is a function of how the sheath is wrapped, with somewhat regularly spaced gaps called **nodes of Ranvier** interrupting the sheath. The alternating pattern of insulation and nodes allows electrical signals to move down an axon faster, jumping from one node to the next. This phenomenon, called **saltatory conduction** (“saltatory” means “leaping”), is responsible for more rapid transmission of electrical signals. Formation of myelin occurs throughout the lifespan.

### Paring Back

 After its initial growth, the neural network is pared back, creating a more efficient system. In fact, only about half the neurons generated during development survive to function in an adult. Entire populations of neurons are removed through **apoptosis**, a process of programmed cell death initiated in the cells. Apoptosis is activated if a neuron fails to receive enough life-sustaining chemical signals called **trophic factors**, which are produced in limited quantities by target tissues. Each type of trophic factor supports the survival of a

distinct group of neurons. For example, **nerve growth factor** is important for the survival of sensory neurons. It has recently become clear that apoptosis is maintained into adulthood but constantly held in check. Based on this, researchers have found that injuries and some neurodegenerative diseases kill neurons not by directly inflicting damage but by activating the cells’ own death programs. This discovery — and its implication that death need not follow insult — have led to new avenues for therapy.

Just as too many brain cells develop early on, these cells initially form an excessive number of connections. In primates, for example, neural projections from the two eyes to the brain initially overlap; then, in some portions of the brain, they sort into separate territories devoted to one eye or the other. Furthermore, connections between neurons in a young primate’s cerebral cortex are more numerous and twice as concentrated as in an adult primate. The **pruning** of these excess connections is heavily dependent on the relative activity of each connection. Connections that are active and generating electrical currents survive, while those with relatively little activity are lost. Astrocytes and other glia also play an important role in this process. For example, astrocytes are known to aid the formation of eye-specific connections by engulfing and eliminating unnecessary synapses. Thus, at least to some extent, the circuits of the adult brain are formed by pruning away incorrect connections to leave only the correct ones. ■

# Infant, Child & Adolescent Brain

The amazing capabilities of the human brain arise from astoundingly intricate communication among billions of interacting cells. Understanding the processes by which brain cells form, become specialized, travel to their appropriate locations, and connect with each other in increasingly elaborate adaptive networks is the central challenge of developmental neurobiology.

Advances in the study of brain development have become increasingly relevant for medical treatments. For example, several diseases that scientists once thought were purely adult disorders are now being considered from a developmental perspective. Schizophrenia might actually occur because pathways in the brain and connections to it formed incorrectly in early life. Other research suggests that genes that influence brain development could also play a role in a person’s susceptibility to autism spectrum disorders. And regeneration following brain injury is now considered a realistic possibility, thanks to expanding knowledge of how neurons form connections during early development.

Knowing how the brain was first constructed is an essential step toward understanding its later ability to reorganize in response to external influences or injuries. As the brain develops from the embryo to the adult, unique attributes evolve during infancy and childhood that will influence people’s differences in learning ability as well as their vulnerability to specific brain disorders. Neuroscientists are starting to discover general principles that underlie these intricate developmental processes.

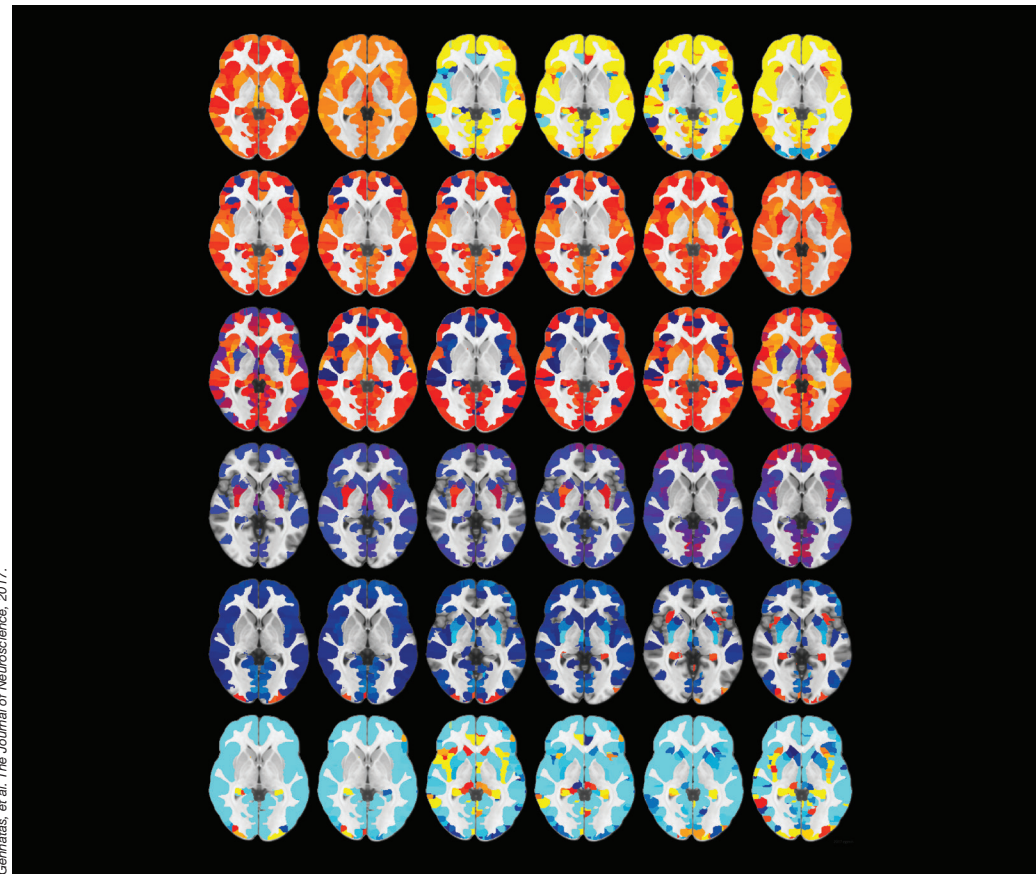
### THE FIRST YEARS OF LIFE

What does a human baby’s brain look like after its three trimesters of



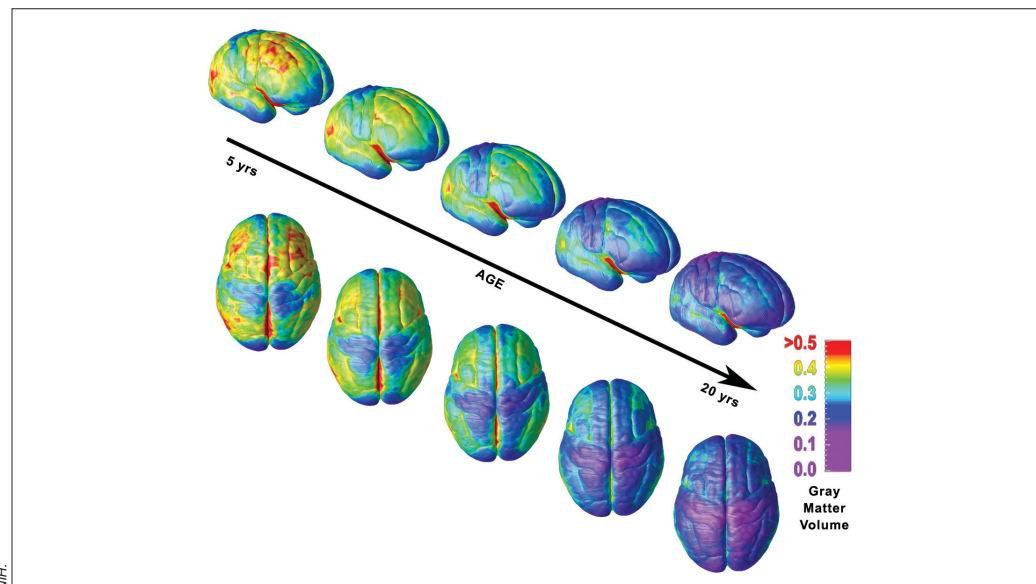
development in the womb? After birth, the baby's brain continues to grow and develop. The average brain-weight of a newborn human baby is about 370 grams (or 13 ounces), just slightly less than a pound. Compare that to the average weight of an adult brain: 3 pounds, with about 86 billion neurons. The newborn baby's brain is the product of 40 weeks of brain development, and its rapid development continues after birth.

How fast does an infant's brain grow? Immediately after birth, the growth rate of the whole brain is about 1 percent per day. The rate slows as the baby ages, reaching about 0.4 percent per day by 3 months after birth. By the time a baby is 90 days old, its overall brain volume is 64 percent larger than it was at birth, with the fastest-growing brain region, the cerebellum, more than double its volume at birth. Not only is the cerebellum the brain region with the most neurons, but it helps with learning motor skills and movements — highly important for babies learning to grab things and eat food. The overall increase in brain volume is the result of a large number of brain cells growing, multiplying (proliferating), maturing (differentiating), and migrating to different brain regions. During the first three months of life, the number of neurons in the cortex increases by 23–30 percent. The dendrites and axons of these neurons grow longer and make many connections, or synapses (synaptogenesis), which also makes the brain bigger. Adding even more to the brain volume, cells known as glia grow, multiply, and provide myelination (by oligodendrocytes) — in fact, the brain's white matter looks white due to all the myelin-wrapped nerve fibers in those areas. By the time a child is 5 years old, the brain has



Genovese, et al., The Journal of Neuroscience, 2017.

Researchers use MRI scans to study how your age and sex affect the size and shape of your brain. They found distinct differences in the density, volume, mass, and thickness of the gray matter in the brains of young people and adolescents.



MH.

The brain goes through many changes during adolescence, including the maturation of the cerebral cortex — the outer layer of the brain that is important for reasoning and abstract thinking. This image shows how this area develops during this time, with the blue color indicating areas that are more mature.

reached about 90 percent of its adult size, which still leaves plenty of room to grow during childhood, adolescence, and early adulthood.

The number of connections between neurons (synaptic density) increases rapidly during the first couple years of life, so that a 2-year-old's brain has 50 percent *more* synapses than an adult brain, although it is only about 80 percent the size of an adult brain. That's far too many synapses for the brain to maintain, as synapses use energy and resources. Therefore, during early childhood, the brain begins to reduce the number of synapses and fine-tune the connections — this **synaptic pruning** process is shaped by toddlers' experiences as they grow. Just as pruning rose bushes gets rid of the dying or weaker branches so that nutrients go to the newer branches and enable new roses to bloom and flourish, synaptic pruning allows weaker connections to diminish while stronger synapses that are activated more often will grow and stabilize.

### EXPERIENCE SHAPES THE BRAIN

Are the brains of human babies similar to the brains of other baby animals such as kittens and ducklings? Compared to other animals, humans are actually born with less developed brains, and human brains take longer to mature. Squirrel monkeys, for example, reach their adult brain size at 6 months old. Rather than developing more fully in the womb or egg, human brains grow and develop extensively after birth. One advantage is that our developing brains are more easily shaped by environment and experience, which helps us adapt appropriately to the surrounding environment.

A baby's early life experiences —

seeing parents' faces, hearing their voices, and being held in its parents' arms — provide important sensory inputs that shape connections between neurons. During these **critical periods** of development, inputs from sensory, motor, and even emotional aspects of life experiences affect how the brain develops and adapts to the given environment. Both genes and environment exert strong influences during critical periods, forming neural circuits that affect learning and behavior. Part of shaping these connections involves neuronal cell death and synaptic pruning, which occur in the embryo and in early postnatal life. Interestingly, changes in neural connections during critical periods coincide with high rates of learning, such as a toddler learning to run or to speak multiple languages.

### INTO ADOLESCENCE

What's going on in the typical teenage brain? It's no surprise that many changes are happening during adolescence, in the body as well as the brain. But what's amazing is the brain's capacity to learn during these teenage years. The teen brain is like a big ball of clay, ready to change and be molded by new experiences — but it is also very messy. During this time, more synaptic pruning occurs, with stronger connections beating out weaker ones in a process called competitive elimination. At the same time, the brain is improving its connections, with neurons extending their dendritic branches and myelination of axons increasing, especially in the frontal lobes.

In exploring how the brain changes during the aging process, scientists are particularly interested in longitudinal studies, which track human

subjects over extended periods of time. Longitudinal studies are especially important because they can reveal how early life events and environment can affect outcomes later in life, like education or risk for disease. These studies are also helpful for understanding how a healthy brain changes between early childhood and adolescence. Adolescence can be thought of as a second "critical period" as the more complex functions of the brain develop and can be influenced by environment and experience.

Images of the adolescent brain obtained by **magnetic resonance imaging (MRI)** show an increase in white matter volume, especially in the corpus callosum — a large bundle of myelinated fibers that connects the brain's right and left cerebral hemispheres. The growth of the corpus callosum may explain enhanced learning capacity in adolescence, due to the increasing connections. Enhanced connections, changes in the brain's reward systems, and changes in the balance between frontal and limbic brain regions can all contribute to teenage behaviors such as increased risk taking and sensation seeking — also aspects of an enhanced learning ability.

Unfortunately, this can be a double-edged sword, as the associated risk taking and sensation seeking also increase the risk of addiction. Some regard addiction as a type of acquired learning disorder, pointing to the overlap between brain regions involved in addiction and those supporting learning, memory, and reasoning. Frequent drug use during adolescence is associated with damage to brain regions important for cognitive functions such as memory, attention, and executive functioning. Studies using MRI to measure brain volume and a technique




called diffusion tensor imaging (DTI) to study quality of white matter show that alcohol and other drugs of abuse may cause significant changes in gray and white matter in adolescents. Compared to a healthy adolescent brain, adolescents who used alcohol had reduced gray matter volume and reduced white matter integrity. Another study used fMRI to measure brain activity and showed that binge drinking (alcohol) during adolescence was associated with lower brain activity, less sustained attention, and poorer performance on a working memory task.

When do we become adults? The definition of adulthood varies with the context — social, judicial, educational. Neuroscience research indicates that human brains continue to develop until we are about 30 years old. Different brain regions show different rates of growth and maturation. For example, MRI studies show that the gray matter density of most brain regions declines with age; however, gray matter density increases in the left temporal lobe (important for memory and language) until age 30. Brain development in 20-somethings also includes changes in where myelination occurs. Remember that myelination is important for efficiently conducting electrical signals along axons, and myelin protects axons from damage. Earlier in life, more myelination is found in the visual, auditory, and limbic cortices. Closer to 30, the frontal and parietal neocortices become more myelinated, which helps with working memory and higher cognitive functions.

These frontal lobe regions are the last brain regions to develop, gaining more myelin later in life. The frontal

lobe is important for executive functioning, which includes attention, response inhibition, emotion, organization, and long-range planning. The late maturation of the frontal lobe might explain characteristics of a “typical teenager,” such as a short attention span, blurting out whatever comes to mind, and forgetting to do homework. However, none of this means that the teenage brain is broken. It is simply experiencing a critical period of development that also opens the brain to millions of new learning opportunities.

### PLASTICITY

 **Plasticity** is the ability of the brain to modify itself and adapt to environmental challenges, including sensory inputs. Without plasticity, critical periods would not exist because the brain could not respond to environment and experience. Plasticity is not unique to humans, but our brains’ capacity to adapt is a defining attribute of human beings. Plasticity has been categorized as experience-expectant or experience-dependent.

Experience-expectant plasticity refers to integrating environmental stimuli into normal developmental patterns. Being exposed to certain common or universal environmental experiences — for example, hearing language, seeing faces, or being held — during limited critical, or sensitive, periods of development is essential for healthy brain maturation. An example comes from the bird world; finches that do not hear adult songs before sexual maturation will not learn to sing as well as other members of their species. In this case, the environmental

stimuli are the sounds of adult songs, which shape the normal development of the bird’s ability to sing accurately.


Experience-dependent plasticity describes continuing changes in the organization and specialization of a person’s brain regions as a result of life experiences that are not universal or anticipated. These include skills that develop throughout life, with no critical or optimal period for their acquisition. For example, not everyone will play the violin, but violinists often show greater cortical development in the brain region associated with the fingers of their left hand. Using an exciting technology called two-photon imaging, scientists can observe living neurons in animals with a microscope and track their growth after various experiences. The results of these studies indicate that experience-dependent plasticity occurs not only during critical periods but also during adulthood — apparently, our brains are always changing in response to our experiences.

Recent insights into brain development hold considerable promise for new treatments of neurological disorders, traumatic brain injury, and learning disabilities, and could help us understand aging as well. If scientists can design an approach to manipulating adult plasticity — whether with drugs or with therapies that involve rewiring neural circuits — it might be possible to correct problems that result from mistimed critical periods or similar dysfunctions. A better understanding of normal brain function during each developmental stage could be the key to finding age-specific therapies for many brain disorders. ■

# Adult & Aging Brain

The previous chapter described how your brain changes as you grow — in overall size, number of cells, myelination, and synapse formation — even continuing to develop well beyond your teenage years. In fact, recent research suggests that maturation is still occurring in the third decade of your life. So when does a human brain finally reach maturity? What is the structure of a fully-formed adult brain? And what can it do that a developing brain cannot?

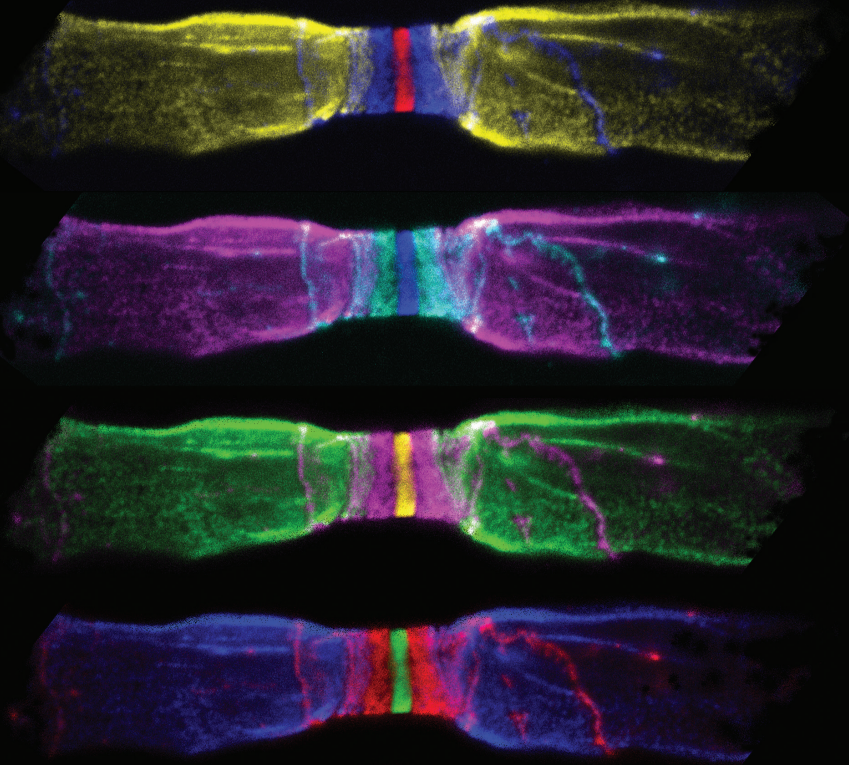
### THE ADULT BRAIN

 An adult brain differs from an adolescent brain in many ways. Between childhood and adulthood, a human brain loses **gray matter** as excess neurons and synapses are pruned away, although the rate of loss slows down by a person’s late 20s. At the same time, some brain regions strengthen their connections with each other, and the major nerve tracts become wrapped in insulating myelin, which increases the brain’s **white matter**. Around age 40, the white matter in the human brain has reached its peak volume.

Much of the added white matter represents increased connections between widely separated brain areas. During childhood and adolescence, most brain networks are locally organized, with areas near each other working together to accomplish a cognitive task. In adulthood, the brain’s organization is more widely distributed, with distant areas connected and working together.

The most important brain area to become fully “wired up” in adulthood is the prefrontal cortex (PFC) — the front (anterior) portion of the frontal lobe. This area handles many of our higher-level cognitive abilities such





As the brain matures, a fatty substance called myelin wraps around axons to speed up electrical transmission. This image shows axons wrapped in myelin, with exposed areas in the middle called nodes of Ranvier.

Desmazieres, et al. Journal of Neuroscience, 2014

as planning, solving problems, and making decisions. It is also important for cognitive control — the ability to suppress impulses in favor of more appropriate responses. Adult brains are better “wired up” for cognitive control than are adolescent brains, in which decision-making is more highly influenced by emotions, rewards, and social influences.

Intelligence also peaks during early to middle adulthood, roughly ages 25 to 60. However, different cognitive abilities have distinctive patterns of maturation. Fluid intelligence, which includes abilities like solving problems and identifying patterns, peaks around age 30. By contrast, crystallized intel-

ligence, which deals with vocabulary and knowledge of facts, increases until about age 50. Some scientists speculate that there is no single age at which all (or even most) of our cognitive functions are at their peak.

### WHAT IS AGING?

#### Normal vs. Pathological Aging

Aging is a dynamic, gradual process. While it can be characterized by resilience in both physical and neurological health, too often aging increases the risk of injury and disease. One such risk is **dementia**, a decline in cognitive ability that interferes with a person’s day-to-day functioning. While aging is inevitable, dementia

and disability are not. In fact, neuroscientists believe our brains can remain relatively healthy as we age. Pronounced decline in memory and cognitive ability, once thought to be part of normal aging, are now recognized as separate disease processes in the aging brain. Although the brain loses some neurons as we age, a widespread and profound loss of neurons is not part of normal aging.

Nonetheless, some mental decline is normal. The continuous process of aging involves subtle changes in brain structure, chemistry, and function that commonly begin in midlife. Some studies suggest that cognition starts declining as early as the 20s and

30s, while other studies indicate that cognition improves into the 50s or 60s, before declining. A growing area of neuroscientific research focuses on understanding “healthy aging,” which includes lifestyle choices, such as diet and exercise, which support cognitive health throughout life.

### HOW THE BRAIN CHANGES

#### Cognitive Changes

Subtle changes in cognition are a normal part of the aging process, with memory decline being the most common. However, not all types of memory are affected; declarative memory declines with age, but nondeclarative memory remains largely intact.

As you learned in Chapter 4, declarative memory includes autobiographical memory of life events, called episodic memory, and memory of learned knowledge, or semantic memory. Nondeclarative memory includes procedural memory like remembering how to ride a bike or tie a shoe.

Working memory — the ability to hold a piece of information in mind and manipulate it (for example, looking up a phone number and reciting it as you dial) — also declines with age. Some studies suggest that a slow decline starts as early as age 30. Working memory, an example of the fluid intelligence mentioned above, is a set of cognitive skills that depend on rapid processing of new information rather than on stored knowledge. Other aspects of fluid intelligence, such as processing speed and problem-solving, also decrease with age.

Certain aspects of attention can also become more difficult as our brains age. For example, it might be harder to focus on what friends are saying when we’re in a noisy restaurant. The ability to focus on a particular stimulus and

filter out distractions is called selective attention. Another type of attention, divided attention, refers to the ability to focus on two tasks at the same time. Activities that require this type of split focus — such as holding a conversation while driving — also become more challenging with age.

#### Structural Changes

All of these alterations in cognitive ability reflect changes in the brain’s structure and chemistry. As we enter midlife, our brains change in subtle but measurable ways. Studies using brain imaging techniques have revealed that total brain volume begins to decline when people are in their 30s or 40s, and starts declining at a greater rate around age 60. However, studies of individual brain regions suggest that the volume loss is not uniform throughout the brain. Some areas appear to shrink more, and faster, than other areas. The prefrontal cortex, cerebellum, and hippocampus show the biggest losses, which worsen in advanced age.

Several changes at the level of individual neurons can also contribute to the decreased volume seen in aging brains. The changes in aging are due to shrinking neurons, retraction and decreased complexity of dendrites, and loss of myelin. In contrast, the volume loss in adolescence is primarily driven by synaptic pruning and the death of excess cells.

Our cerebral cortex, the wrinkled outer layer of the brain containing neuron cell bodies, also thins as we age. Cortical thinning follows a pattern similar to volume loss, with some regions of the brain affected more than others. Thinning is especially pronounced in the frontal lobes and parts of the temporal lobes.

The temporal and frontal lobes

are among the areas that demonstrate the most pronounced declines in both volume and cortical thickness. These are the areas that took longest to reach maturity. This finding has led to a “last in, first out” theory of brain aging, which holds that the last parts of the brain to develop are the first to deteriorate. Interestingly, studies of age-related changes in white matter support this hypothesis. The first of the brain’s long-distance fibers to develop are the projection fibers that connect the cortex to lower parts of the brain and spinal cord. Fibers connecting diffuse areas within a single hemisphere — association fibers — are the last to reach maturity, and show the steepest functional declines with age.

#### Neuronal Changes

The aging brain also undergoes numerous changes at synapses. Although the synaptic changes are selective and subtle, their effect on cognitive decline is believed to be greater than the effects of structural and chemical changes. In the prefrontal cortex and hippocampus, scientists have observed alterations in dendrites, the branching processes that receive signals from other neurons. With increasing age, the dendrites shrink, their branches become less complex, and they lose dendritic spines, the tiny protuberances that receive chemical signals.

A study in rhesus monkeys observed that the aging process targets a certain class of spines called thin spines. These small, slender protuberances are also highly plastic structures, extending and retracting much more rapidly than the larger “mushroom” class of spines. This has led scientists to speculate that thin spines might be involved in working



memory, which requires a high degree of synaptic plasticity. The loss of thin dendritic spines could impair neuronal communication and contribute to cognitive decline. So far, direct evidence of their role in cognitive decline is lacking, and more studies are needed.

Finally, the formation of new neurons also declines with age. Although neurogenesis was once believed to halt after birth, we now know of two brain regions that continue to add new neurons through-

less dopamine is synthesized in the aged brain, and there are fewer receptors to bind the neurotransmitter. Less robust evidence indicates that the amount of serotonin might also decline with age.

#### WHY DOES THE BRAIN AGE?



From cortical thinning to the loss of dendritic spines, you've seen how the brain ages. But what causes these changes? Many different theories have been advanced to explain why neurons, and cells in

your body contains organelles called **mitochondria**, which function a bit like cellular power plants, carrying out chemical reactions that provide energy for cell use. Some of these metabolic reactions produce harmful byproducts called free radicals, highly reactive molecules which, if left unchecked, can destroy fats and proteins vital to normal cell function and can damage DNA as well.

Your body has natural defense mechanisms to neutralize free radicals. Unfortunately, these mechanisms decline with age, leaving aging tissues more vulnerable to oxidative damage by the free radicals. Studies of brain cells have shown that damage to their mitochondrial DNA accumulates with age. In addition, the brains of people with mild cognitive impairment and Alzheimer's disease show more signs of oxidative damage than the brains of healthy people. Studies in rodents also link increased oxidative damage to memory impairments.

Your brain is one of the most metabolically active organs, demanding around 20 percent of the body's fuel. Its enormous energy requirements might make the brain even more vulnerable than other tissues to the metabolic changes that occur in aging. While the brain's energy demands remain high, its energy supply can no longer keep pace; the brain's ability to take up and use glucose diminishes and mitochondrial metabolism declines.

#### Immune Dysfunction

Immune dysfunction often occurs in conjunction with the metabolic changes seen in aging. Microglia, the brain's resident immune cells, perform many important jobs: defending against pathogens, cleaning up cellular

general, age. One possibility is that changes in gene expression play a role. Researchers have found that genes important for synaptic plasticity are expressed less in the brains of older people than in the brains of younger adults. The underexpressed genes also showed more signs of damage.

#### Oxidative Stress and DNA Damage

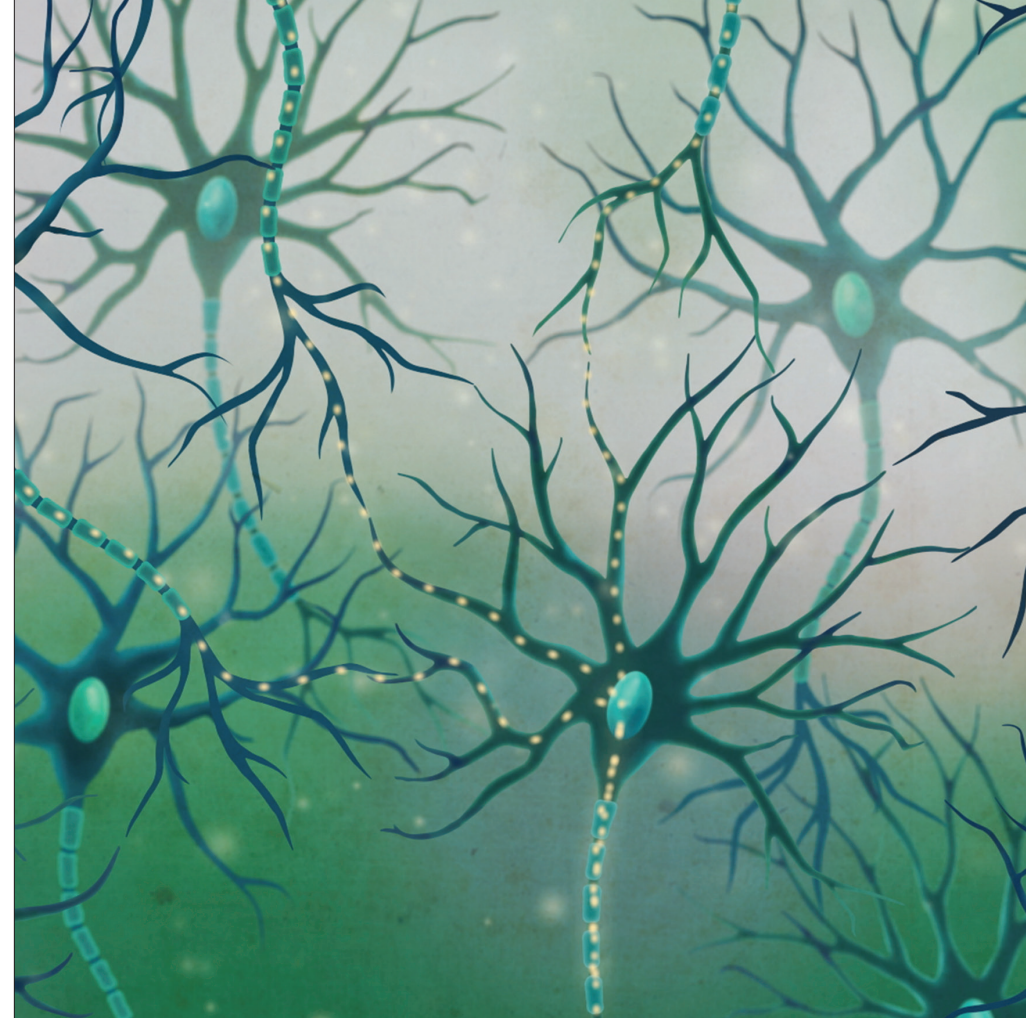
DNA damage that accumulates over a lifetime could contribute to aging processes throughout the brain and body, and DNA damage due to oxidative stress has received a great deal of attention. Every cell in

## Many different theories have been advanced to explain why neurons, and cells in general, age.

out life: the olfactory bulbs and the dentate gyrus of the hippocampus. Studies suggest that the rate of neurogenesis plummets with age in mice, but recent human studies suggest a more modest decline. It is not yet clear whether neurogenesis appreciably affects cognition in the aging human brain, but mouse studies indicate that strategies that boost neurogenesis can enhance cognitive function.

#### Chemical Changes

The amount of neurotransmitters and the number of their receptors might also decline with age. Several studies have reported that



Synapses begin to weaken as a person ages, which can contribute to normal cognitive decline.

debris, and helping maintain and remodel synapses. These inflammatory responses are protective, but a prolonged inflammatory state is harmful to brain health. Microglia become more reactive with age, increasing the inflammatory response in the brain while also damping production of helpful anti-inflammatory molecules. Mouse studies suggest that excessive microglial activity also contributes to cognitive impairments.

#### Impaired Protein Recycling

We know that excessive buildup of abnormal proteins in the brain contributes to age-related neurodegenerative diseases like **Alzheimer's** and **Parkinson's**. Buildup of proteins and other cell components can also contribute to cellular degeneration in the healthy brain. Cells normally

break down and recycle damaged proteins and molecules, using a process that is usually efficient but not perfect. Over time, damaged molecules can build up in cells and prevent them from functioning normally. Because neurons in the brain are not replaced as often as cells in other parts of the body (for example, bone marrow, intestinal lining, hair follicles), brain cells might be even more vulnerable to this buildup of damaged molecules. Also, the cellular machinery involved in breakdown and recycling processes degrades with age, reducing the efficiency of the "waste removal" systems.

Finally, remember that changes in the aging brain occur within the context of other changes throughout the body. Researchers speculate that worsening cardiovascular health, for

example, could contribute to, or even drive, many changes seen in the aging brain.

#### HEALTHY AGING



We have learned how the brain changes with age and why these changes can occur. Now let's turn our attention to a growing field in neuroscience that explores ways to slow these changes and preserve healthy brain function.

#### Diet and Exercise

Strong evidence now suggests that habits and choices that keep your body healthy also benefit your mind. Poor cardiovascular health puts a person at increased risk of age-related cognitive impairment. Diets rich in vegetables, fruits, and whole grains, and low in meat and dairy products, can reduce cardiovascular risk factors linked to cognitive impairment, such as high blood pressure and high levels of LDL cholesterol. Indeed, observational studies have found that people who follow plant-rich diets such as the Mediterranean diet or Dietary Approaches to Stop Hypertension (DASH) are less likely to develop cognitive decline and dementia.

Specific nutrients have been linked to improved cognitive performance and lower rates of dementia. Antioxidants, such as vitamins C and E, flavonoids, and omega-3 fatty acids have received considerable attention, with observational studies showing that high dietary intake of these compounds is beneficial. However, the results of lifestyle intervention studies using supplements have been more mixed. Finally, caloric restriction — substantially reducing the number of calories eaten without leading to malnutrition — has been linked to





istock.com/arymes3

Exercise has been shown to increase neurogenesis in the adult brain, and can slow the cognitive decline associated with aging.

improved cognitive health as well as a longer lifespan.

Growing evidence shows that aerobic exercise can improve cognitive function and offset some of the declines seen in aging. Numerous studies have found that people who engage in regular physical activity show improved learning, improved memory, and a reduced risk of developing dementia. Physical activity might even slow the progression of Alzheimer's disease and dementia, and higher levels of physical activity have been linked to improvements in some markers of structural brain health, such as reduced

cortical thinning and less shrinkage in the hippocampus.

Exercise exerts its neuroprotective effects in the brain by improving neuroplasticity — the brain's ability to form and reorganize connections between neurons in response to changes in behavior and environment. Scientists also believe that exercise increases neurogenesis (the formation of new nerve cells) which, in turn, enhances neuroplasticity. Evidence from rodent studies confirms that exercise increases neurogenesis: Older mice allowed to run on a wheel have higher rates of neurogenesis in the hippocampus than

sedentary mice, and they perform better on learning and memory tests. Exercise can also improve blood flow and increase production of neurotrophic factors that support new neurons and synapses. For humans, starting exercise later in life can be beneficial, but the studies suggest that adopting an exercise program earlier in life could yield even more neuroprotective benefits.

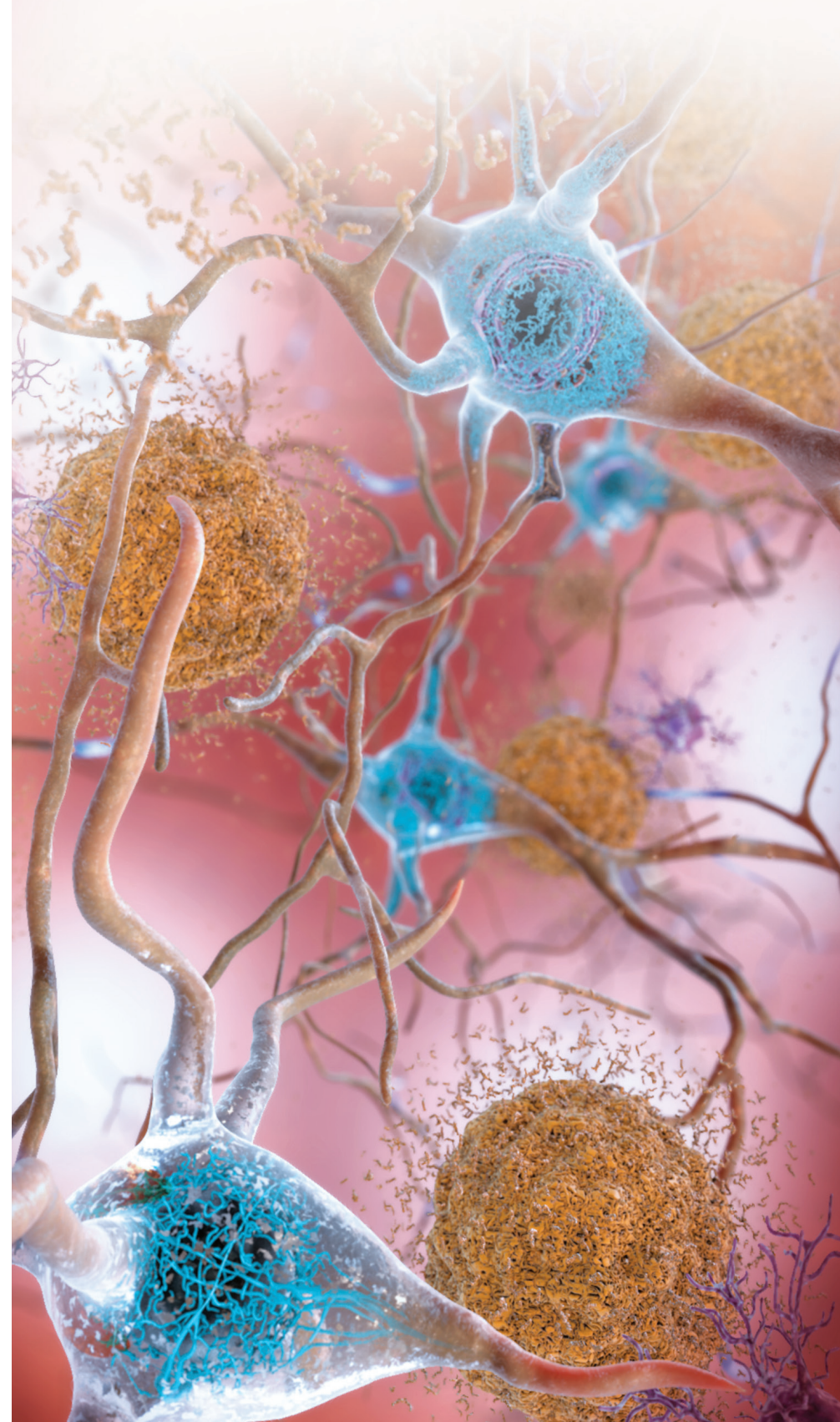
### Mental Stimulation and Social Networks

Mental stimulation and large social networks can also improve cognitive function in aging. In lab studies, mice housed in cognitively stimulating environments with many opportunities for social interaction perform better on learning and memory tests as they age compared to mice housed in standard cages. Much like physical exercise, cognitive stimulation appears to enhance neuroplasticity by increasing neurogenesis and boosting levels of important neurotrophic factors.

People who perform cognitively-demanding work or engage in stimulating activities such as reading, solving puzzles, or playing a musical instrument have lower rates of cognitive decline with aging. An active social life has also been shown to be beneficial for cognition as we age.

Neuroscientists have learned a lot about the aging brain — how it changes, why it changes, and how to maintain healthy cognitive functioning as we age. Even so, many questions remain. Answers to those questions could identify new strategies for protecting the brain, not only in our later years, but throughout our lives. ■

# Brain States



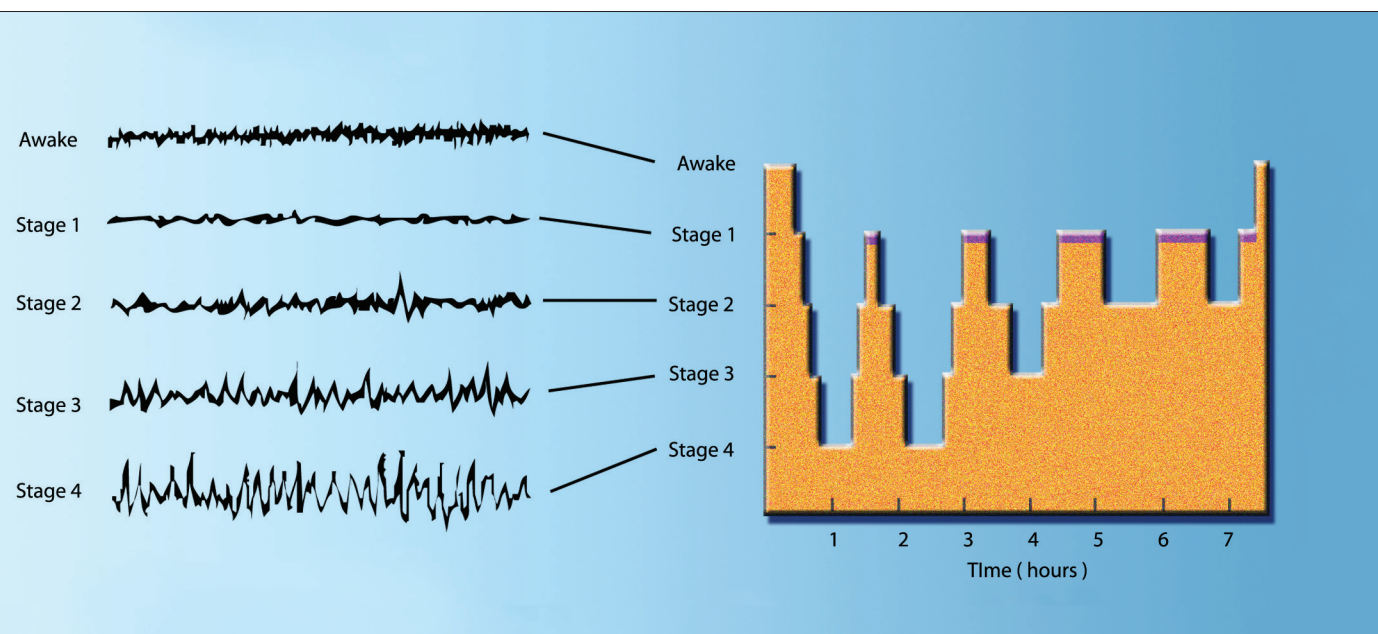
**H**ave you ever considered the ups and downs that occur during your day? Speaking literally, you are up and awake during the day and lying down sleeping at night. Speaking figuratively, ups and downs could mean that you experience periods of elevated alertness and arousal compared with your mood when you are tired or relaxed. Asleep, awake, aroused, and relaxed are different brain states, meaning that the brain's activity is different during each of these periods. Scientists have looked deep inside the brain to understand what sleep is and how rest differs from being alert. This research is especially important for people like doctors, pilots, and shift workers who sometimes must focus and make important decisions with very little sleep. Research on brain states can also help people who have disorders of sleep, attention, and learning.

### SLEEP

How many hours of sleep do you get every night? Most people spend one-third of their lives asleep. While that might appear to be a lot of time spent doing nothing, our brains are active while we rest each night. The activity in our brains during sleep is important for brain health and for solidifying memories.

Most people feel tired and unable to focus if they don't get enough sleep. In some cases, too little sleep can impair a person's driving as much as drinking alcohol. The long-term effects of lacking sleep also involve many health risks. Several studies in humans have revealed that sleep-deprived people are at increased risk for a wide range of health issues including diabetes, stress, obesity, high blood pressure, anxiety, cognitive impairment, and depression.





This chart shows the brain waves of an individual being recorded by an EEG machine during a night's sleep. As the person falls asleep, the brain waves slow down and become larger. Throughout the night, the individual cycles through sleep stages, including REM sleep, where brain activity is similar to wakefulness.

### Brain Activity During Sleep

Scientists can measure the brain's electrical activity using electroencephalography (EEG). Electrodes attached to the scalp detect and record the net electrical activity of hundreds of thousands of cortical nerve cells. When a neuron is active, ions move in and out of the cell, altering the electrical charge across the cell membrane. An EEG detects the net electrical charge produced when neurons increase and decrease their activity as a group, in synchrony. The results are "brain waves" — the cyclic rising and falling of brain activity that can be important indicators of brain function. In sleep studies, scientists now recognize two main states: slow wave sleep (SWS) and **rapid eye movement sleep (REM)**.

SWS gets its name from the high amplitude, low frequency, brain waves in EEG recordings. The high amplitude of slow waves indicates that many cortical neurons are switching their activity in a

synchronized way from a depolarized (more excitable) state to a hyperpolarized (less excitable) state and back again. These slow waves appear to be important to sleep function — the longer a person stays awake, the more slow waves they will experience during the SWS state. Slow waves become less frequent the longer the person is asleep. If awakened during SWS, most people recall only fragmented thoughts, not active dreams.

Have you ever seen a cat dreaming — twitching its whiskers or paws while it sleeps? Dreaming happens mainly during REM sleep, which takes its name from the periodic rapid eye movements people make in this state. Brain activity recorded during REM looks very similar to EEGs recorded while awake. EEG waves during REM sleep have much lower amplitudes than the SWS slow waves, because neuron activity is less synchronized — some nerve cells depolarize while others hyperpolarize, and the "sum" of

their electrical states is less positive (or negative) than if they acted in synchrony. Paradoxically, the fast, waking-like EEG activity during REM sleep is accompanied by atonia, a loss of muscle tone causing the body to become temporarily paralyzed. The only muscles remaining active are those that enable breathing and control eye movements. Oddly enough, the neurons of our motor cortex fire as rapidly during REM sleep as they do during waking movement — a fact that explains why movements like a kitten's twitching paws can coincide with dreams.

During the night, periods of SWS and REM sleep alternate in 90-minute cycles with 75–80 minutes of SWS followed by 10–15 minutes of REM sleep. This cycle repeats, typically with deeper and longer periods of REM sleep towards morning. To study sleep disorders, researchers often use mice that have sleep structures qualitatively very similar to humans; however, rodents have shorter

and more frequent sleep episodes lasting 3–30 minutes (sometimes longer). Rodents also sleep more during the day and are more active at night. Compare that to human adults, who are typically more active during the day and have one sleep episode at night lasting about 8 hours.

### Sleep Regulation



How does the brain keep us awake? Wakefulness is maintained by the brain's arousal systems, each regulating different aspects of the awake state. Many arousal systems are in the upper brainstem, where neurons connecting with the forebrain use the neurotransmitters **acetylcholine**, **norepinephrine**, serotonin, and

can be activated by insulin-induced low blood sugar. Thus, they are involved in energy metabolism. Given these functions, it comes as no surprise that orexin-producing neurons are important for preventing a sudden transition to sleep; their loss causes narcolepsy, as described below. Orexin neurons also connect to hypothalamic neurons containing the neurotransmitter **histamine**, which plays a role in staying awake.

The balance of neurotransmitters in the brain is critically important for maintaining certain brain states. For example, the balance of acetylcholine and norepinephrine can affect whether we are awake (high acetylcholine and norepinephrine) or in SWS (low

tone — hallmark signs of REM.

During SWS, the brain systems that keep us awake are actively suppressed. This active suppression of arousal systems is caused by the ventrolateral preoptic (VLPO) nucleus, a group of nerve cells in the hypothalamus. Cells in the VLPO release the inhibitory neurotransmitters galanin and gamma-aminobutyric acid (GABA), which can suppress the arousal systems. Damage to the VLPO nucleus causes irreversible **insomnia**.

### Sleep-Wake Cycle

Two main factors drive your body to crave sleep: the time of day or night (**circadian system**) and how long you have been awake (homeostatic system). The homeostatic and circadian systems are separate and act independently.

The circadian timing system is regulated by the **suprachiasmatic nucleus**, a small group of nerve cells in the hypothalamus that functions as a master clock. These cells express "clock proteins," which go through a biochemical cycle of about 24 hours, setting the pace for daily cycles of activity, sleep, hormone release, and other bodily functions. The master clock neurons also receive input directly from the retina of the eye. Thus, light can reset the master clock, adjusting it to the outside world's day/night cycle — this explains how your sleep cycles can shift when you change time zones during travel. In addition, the suprachiasmatic nucleus sends signals through different brain regions, eventually contacting the VLPO and the orexin neurons in the lateral hypothalamus, which directly regulate arousal.

What happens in the brain when we don't get enough sleep? The second system that regulates sleepiness is the

The balance of neurotransmitters in the brain is critically important for maintaining certain brain states.

glutamate to keep us awake. **Orexin**-producing neurons, located in the hypothalamus, send projections to the brainstem and spinal cord, the thalamus and basal ganglia, as well as to the forebrain, the amygdala, and dopamine-producing neurons. In studies of rats and monkeys, orexin appears to exert excitatory effects on other arousal systems. Orexins (there are two types, both small neuropeptides) increase metabolic rate, and their production

acetylcholine and norepinephrine). During REM, norepinephrine remains low while acetylcholine is high, activating the thalamus and neocortex enough for dreaming to occur; in this brain state, forebrain excitation without external sensory stimuli produces dreams. The forebrain becomes excited by signals from the REM sleep generator (special brainstem neurons), leading to rapid eye movements and suppression of muscle



homeostatic system, which makes you feel sleepy if you stay awake longer than usual. One important sleep factor is a chemical in the brain called **adenosine**. When you stay awake for a long time, adenosine levels in the brain increase. The increased adenosine binds to specific receptors on nerve cells in arousal centers to slow cellular activity and reduce arousal. Adenosine can increase the number of slow waves during SWS. As you get more sleep, adenosine levels fall and slow waves decrease in number. Caffeine acts as a stimulant by binding to adenosine receptors throughout the brain and preventing their interaction with adenosine. As a result, in the presence of caffeine, fewer receptors are available for the slowing influence of adenosine.

People often say they need to “catch up on sleep.” But can you really make up for lost sleep? Normally, the homeostatic and circadian systems act in a complementary fashion to produce a normal 24-hour cycle of sleep and wakefulness. Nonetheless, activating the brain’s arousal system can keep us awake even after a long period of wakefulness — for example, a late-night study session to prepare for an important exam. In normal circumstances, the homeostatic system will respond to the loss of sleep by increasing the duration of ensuing sleep and increasing the number of slow waves during the SWS episodes. As noted above, this rebound slow wave activity correlates with the previous time spent awake and is mediated by adenosine.

### Sleep Disorders

The most common sleep disorder, and the one most people are familiar with, is insomnia. Some people with insomnia have difficulty falling asleep



Electroencephalography measures brain activity through sensors placed on the head. It can record how the brain reacts to all kinds of stimuli and activities, including sleep.

initially; others fall asleep, then awaken part way through the night and can’t fall back asleep. Several common disorders, listed below, disrupt sleep and prevent people from getting an adequate amount of sleep.

Daytime sleepiness (not narcolepsy), characterized by excessive feelings of tiredness during the day, has many causes including sleep apnea (see below). Increased daytime sleepiness can increase the risk of daytime accidents, especially car accidents.

Sleep apnea occurs when the airway muscles of the throat relax during sleep, to the point of collapse, closing the airway. People with sleep apnea have difficulty breathing and wake up without entering the deeper stages of SWS. This condition can cause high blood pressure and may increase the risk of heart attack. Treatments for sleep apnea focus on reducing airway collapse during sleep; simple changes that may help include losing weight, avoiding alcohol or sedating drugs prior to sleep, and avoiding sleeping on one’s back. However, most people

with sleep apnea require breathing machines to keep their airway open. One such device, called a continuous positive airway pressure or “CPAP” machine, uses a small mask that fits over the nose to provide an airstream under pressure during sleep. In some cases, people need surgery to correct their airway anatomy.

REM sleep behavior disorder occurs when nerve pathways in the brain that prevent muscle movement during REM sleep do not work. Remember that dreaming happens during REM sleep, so imagine people literally acting out their dreams by getting up and moving around. This can be very disruptive to a normal night’s sleep. The cause of REM behavior disorder is unknown, but it is more common in people with degenerative neural disease such as Parkinson’s, stroke, and types of dementia. The disorder can be treated with drugs for Parkinson’s or with a benzodiazepine drug, clonazepam, which enhances the effects of the inhibitory neurotransmitter GABA.

### Narcolepsy: An Example of Sleep Disorder Research

Narcolepsy is a relatively uncommon sleep disorder — only 1 case per 2,000 people in the United States — in which the brain lacks the special neurons that help control the transition into sleep, so that the regular cycling is disrupted. People with **narcolepsy** have sleep attacks during the day, causing them to suddenly fall asleep, which is especially dangerous if they are driving. The problem is caused by the loss of orexin neurons in the lateral hypothalamus. People with narcolepsy tend to enter REM sleep very quickly and may even enter a dreaming state while still partially awake, a condition known as hypnagogic hallucination. Some people with narcolepsy also have attacks in which they lose muscle tone — similar to what happens in REM sleep, but while they’re awake. These attacks of paralysis, known as cataplexy, can be triggered by emotional experiences and even by hearing a funny joke.

Recent research into the mechanisms of narcolepsy has provided important insights into the processes that control the mysterious transitions between waking, slow wave sleep, and REM sleep states. Orexin (in the lateral hypothalamus) is critical for preventing abnormal transitions into REM sleep during the day. In one study, scientists inactivated the gene for orexin in mice and measured their sleep patterns. They found that mice lacking the orexin gene showed symptoms of narcolepsy. Similarly, humans with narcolepsy have abnormally low levels of orexin levels in their brain and spinal fluid.

Because orexin levels are disrupted in narcolepsy, scientists also began

studying neurons that were neighbors to orexin neurons to see what happened if the neighboring neurons were activated in narcoleptic mice. Those neurons contained melanin-concentrating hormone, and stimulating them (using a technique called optogenetics) induced sleep — opposite to the effect of stimulating orexin neurons. A balance between the activation of orexin neurons and their neighboring neurons could control the transition between waking and sleeping. These findings will be important in developing treatments for narcolepsy.

### AROUSAL

Think about what happens in your body and mind when you speak in front of a crowd — your brain state is very different from when you are asleep. Perhaps you notice changes in your breathing, heart rate, or stomach. Maybe your thoughts are racing or panicked. Or maybe you are energized and excited to perform for your audience. These are examples of the complex brain state called **arousal**.

Rather than merely being awake, arousal involves changes in the body and brain that provide motivations to do an action — teaching a class, speaking in public, or focusing your attention. People experience arousal daily when searching for food while hungry, or when talking with other people (social interaction). Arousal is also important for reproduction and for avoiding danger.

The level of arousal varies across a spectrum from low to high. When arousal falls below a certain threshold we can transition from wake to sleep, for example. But under heightened arousal, like intense **anxiety**, we cannot reach this threshold and we stay awake.

### Neurotransmitters

During arousal, the brain must devote resources to specific brain regions, much as an emergency call center redirects resources like ambulances and fire trucks during a fire. Specific types of neurons in the brain regions involved in arousal release multiple neurotransmitters, telling the rest of the brain and the body to be on alert. These neurotransmitters are dopamine (for movement), norepinephrine (for alertness), serotonin (for emotion), and acetylcholine and histamine, which help the brain communicate with the body to increase arousal.

### Sensory Input

While neurotransmitters provide the internal signals for arousal, external signals from the outside world — like the bright lights (visual input) and cheering crowds (auditory input) at a stage performance — can also stimulate arousal. Sensory input gets sorted in the brain region called the thalamus. Often called a “sensory clearing house,” the thalamus regulates arousal, receiving and processing sensory inputs from brain regions important in senses like vision and hearing and relaying these inputs to the cortex.

### Autonomic Nervous System

Once the brain is aroused, what does the body do? The reticular activating system, in the brainstem, coordinates signals coming from sensory inputs and neurotransmitters to make sense of events in the brain and pass that information to the rest of the body. The reticular activating system specifically controls the **autonomic nervous system**, which affects heart rate, blood flow, and breathing. By controlling these automatic body processes, the reticular activating system



sets up the physical state of arousal, bringing important resources like oxygen and nutrients to parts of the body where they are needed.

Together, the changes that happen in the brain and body during arousal enable us to be alert and focused, which helps us process information quickly. Using this information, we can choose the appropriate emotional response or physical action for a given situation.

### Sexual Arousal

Several complex brain systems and endocrine (hormone) systems contribute to sexual arousal and behaviors, but the brain regions, neurotransmitters, and body systems are similar to those involved in general arousal. The distinguishing factor is that sexual arousal also involves hormones such as **estrogen** and **testosterone**, which then activate neurons that release the same neurotransmitters that are released during general arousal. Many human and animal studies report interactions between sex hormones and neurotransmitters dopamine, serotonin, GABA, and glutamate. Researchers have also found that brain regions such as the hypothalamus, amygdala, and hippocampus contain many estrogen and progesterone receptors, and brain regions that mediate feelings of reward (nucleus accumbens) and emotions like pleasure (amygdala) motivate sexual behaviors. Overall, the primary involvement of sex hormones is a key in defining the brain state of sexual arousal.

### ATTENTION



If you are paying **attention** right now, there should be detectable changes in your heart rate, breathing, and blood flow. If that sounds familiar, it's

because those same physiological changes occur during arousal, which is necessary for being alert and paying attention. As mentioned previously, the state of arousal calls for reactions to the environment. To make decisions about what to do, you need to focus on what's happening in the environment, especially involving

## Scientists recognize two types of attention, which involve different brain processes: voluntary attention and involuntary attention.

anything relevant to your goals. For example, if your goal is to run away from an angry bear, you need to be alert and pay attention to where you're running so you don't trip and fall. Scientists have theorized that the state of arousal speeds processing and improves comprehension of environmental details. Otherwise, your brain would need an infinite amount of time and energy to process all of its sensory inputs (sounds, sights, smells, and other feelings), because the environment is always changing.

### Focus

Even with multitasking, it is impossible for the brain to process all its sensory inputs. Instead, people focus their attention on one thing at a time. Attention is a fascinating ability, because it enables you to have so much control and the ability to fine-

tune your focus to different locations, times, and topics. Consider the page you are reading right now. Although you can see the whole page, you focus on only one line at a time. Alternatively, you can turn your attention to the past — just minutes ago when you were reading about arousal. Or you can ignore the sentences alto-

gether and focus on the number of times the word “you” occurs on this page. Scientists recognize two types of attention, which involve different brain processes: voluntary (endogenous) attention and involuntary (exogenous) attention.

Voluntary attention happens when you choose what to focus on — like finding a loved one in a crowd. The frontal and parietal cortices of the brain are active when you control your attention or direct it towards a specific object or location. Involuntary attention occurs when something in the environment (like a sudden noise or movement) grabs your attention. Involuntary attention is a distraction from your chosen goals and, in fact, researchers often use distractor objects in attention experiments. Distractors can be emotional, like pictures of family, or non-emotional

images that stand out from other stimuli, like a red circle surrounded by gray squares. Brain regions in the right hemisphere, collectively known as the ventral frontoparietal network, form a system that processes new and interesting stimuli that distract you from the task at hand. Research on attention can help us understand visual tasks, learning, child development, and disorders of attention.

### Disorders of Attention



Paying attention for long periods of time, such as a 3-hour lecture, can be difficult for many people. For some people, even focusing for a short time can be hard. Several disorders that affect the ability to pay attention are attention deficit hyperactivity disorder (ADHD), schizophrenia, prosopagnosia, and hemineglect syndrome. It may seem strange to regard schizophrenia as an attention disturbance, but some psychiatric studies suggest that it involves a failure of selective attention. Prosopagnosia, or face blindness, is a cognitive disorder in which a person is unable to recognize faces — even their own family members. The severity of this condition varies, and genetic factors might be involved. Attention disorders have various causes, but we will focus on hemineglect syndrome, caused by damage to the right parietal cortex, a brain region important in involuntary attention.

Between 50–82 percent of patients who suffer stroke in the right hemisphere experience hemineglect syndrome, also known as spatial neglect and unilateral neglect. In these cases, patients with neglect ignore the left side of their visual field. Sometimes they ignore the left side of the body and the left side of individual

objects, as well. Diagnosis of hemineglect syndrome can be done with a pen and paper. For example, patients can be instructed to draw a copy of a picture like a butterfly or a castle, and those patients with hemineglect usually draw only the right half of the picture or leave out details of the left side. Research on patients with hemineglect syndrome contributes to our understanding of rehabilitation after stroke, as well as the role of the right parietal cortex in attention and perception.

### REST: DEFAULT MODE NETWORK



What is the difference between being alert and resting while awake? During times of rest and relaxation, you're usually avoiding heavy thinking or complicated tasks, and parts of the brain called the **default mode network** are more active. You may think of the default mode network as a personal lullaby or a playlist that turns on when you are ready to relax. Activity of the default mode network decreases (the lullaby gets quieter) when you start doing or thinking about a demanding task. Human studies using imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have identified which brain regions belong to the default mode network. These brain areas, which are involved in emotion, personality, introspection, and memory, include frontal brain regions (ventromedial prefrontal cortex, dorsomedial prefrontal cortex, and anterior cingulate cortex), as well as the posterior cingulate cortex, lateral parietal cortex, and precuneus.

Although the exact role of the default mode network is unclear,

the functions of its “participating” brain regions provide hints about its purpose. Studies on emotion have revealed that activity in the ventromedial PFC is directly related to how anxious a subject feels while performing a task — suggesting that the default mode network may play a role in regulating emotion and mood. Activity in the dorsomedial PFC (a region involved in self-referential or introspective thoughts) increases when a person is at rest and daydreaming. The dorsomedial PFC is also involved in stream-of-consciousness thoughts and thoughts about oneself in the past, present, or future (autobiographical self). The roles of these regions suggest that the default mode network may also function in self-reflection and our sense of self in time.

The posterior brain regions of the default mode network (posterior cingulate cortex, lateral parietal cortex, and precuneus) become more active when remembering concrete memories from past experiences. These brain regions are connected with the hippocampus, which is important for learning and forming memories. Both the hippocampus and the default mode network are more active when a person is at rest in the evening and less active when waking up early in the day. These patterns indicate that the default mode network helps to process and remember the events of the day.

Future studies using electrical recordings from inside the human brain can be paired with fMRI to tell us more about the brain activity patterns of the default mode network and how brain regions coordinate their activity during tasks that utilize the functions of this network. ■



# The Body in Balance

The cells of your body are immersed in a constantly changing environment. The nutrients that sustain them rise and fall with each meal. Gases, ions, and other solutes flow back and forth between your cells and blood. Chemicals bind to cells and trigger the building and release of proteins. Your cells digest food, get rid of wastes, build new tissues, and destroy old cells. Environmental changes, both internal and external, ripple through your body's physiological systems. One of your brain's less-visible jobs is to cope with all these changes, keep them within a normal range, and maintain the healthy functions of your body.

The tendency of your body's tissues and organ systems to maintain a condition of balance or equilibrium is called **homeostasis**. Homeostasis depends on active regulation, with dynamic adjustments that keep the environment of your cells and tissues relatively constant. The brain is part of many homeostatic systems, providing signals that coordinate your body's internal clocks and regulating hormone secretion by the endocrine system. These functions often involve a region of the forebrain called the hypothalamus.

## CIRCADIAN RHYTHMS

Almost every cell in your body has an internal clock that tells it when to become active, when to rest, and when to divide. These clocks broker changes in many of the body's physiological systems over a 24-hour, or circadian, period. For example, the clocks cause faster pulses of peristaltic waves in your gut during the day and make your blood pressure dip at night. But because these clocks are deep inside your body and cannot detect daylight, none of them can tell time

on its own. Instead, daily rhythms are coordinated by the suprachiasmatic nucleus (SCN), a tiny group of neurons in the hypothalamus.

Neurons in the SCN act like a metronome for the rest of the body, emitting a steady stream of action potentials during the day and becoming quiet at night. The shift between active and silent states is controlled by cyclic interactions between two sets of proteins encoded by your body's "clock" genes. Researchers first identified clock genes in the fruit fly *Drosophila melanogaster* and studied how they keep time; since then, a nearly identical set of genes has been found in mammals. The SCN also tracks what time it is based on signals it receives from photoreceptors in the retina, which keeps its activity in sync with the Earth's *actual* day/night cycle. That little nudge is very important because, on their own, clock proteins take slightly *more* than 24 hours to complete a full cycle. Studies of animals deprived of light have discovered that they go to sleep and wake up a bit later each day.

An autonomic neural pathway ties the daily rhythmic activity of the SCN directly to other clocks in the body. Neurons in the SCN stimulate an adjacent region of the brain called the paraventricular nucleus (PVN), which in turn sends signals down a chain of neurons through the spinal cord to the peripheral organs of the body. You've already learned how signals in part of this neural pathway stimulate orexin neurons to regulate the body's sleep/wake cycle. Related pathways also govern the secretion of **melatonin**, a hormone that influences sleep behaviors. Specifically, electrical activity originating in the SCN enters the PVN's neural network and sends signals up to the **pineal gland**, a small pinecone-shaped gland embedded between the cerebral hemispheres. The

pineal gland secretes melatonin into the bloodstream at night. Melatonin binds to cells in many tissues, and although it has no direct effect on clock gene expression in the SCN, its systemic effects seem to reduce alertness and increase sleepiness. Light exposure triggers signals that stop melatonin secretion, promoting wakeful behaviors.

are out of sync with day and night. Exposure to the local day/night cycle resets the brain and body, but it can take several days to get fully resynchronized. Circadian rhythms can also be disturbed by situations like late-shift jobs or blindness, which decouple normal daylight signals from wake/sleep cycles. Long-term circadian disruptions

Coordinated body clocks enable your body's physiological systems to work together at the right times.

Together, these signals keep all the body's clocks synchronized to the same 24-hour cycle. Coordinated body clocks enable your body's physiological systems to work together at the right times. When your body prepares to wake from sleep, 1) levels of the stress hormone **cortisol** peak in the blood, releasing sugars from storage and increasing appetite, and 2) core body temperature begins to drift upwards, raising your body's metabolic rate. These events, synchronized with others, prepare your body for a new day's activity.

Desynchronizing the body's physiological clocks can cause noticeable and sometimes serious health effects. You might have experienced a familiar example of **circadian rhythm** disturbance: jet lag. After crossing many time zones in a short time period, a person's patterns of wakefulness and hunger

are associated with health problems including weight gain, increased rates of insomnia, depression, and cancers.

## HORMONES, HOMEOSTASIS, AND BEHAVIOR

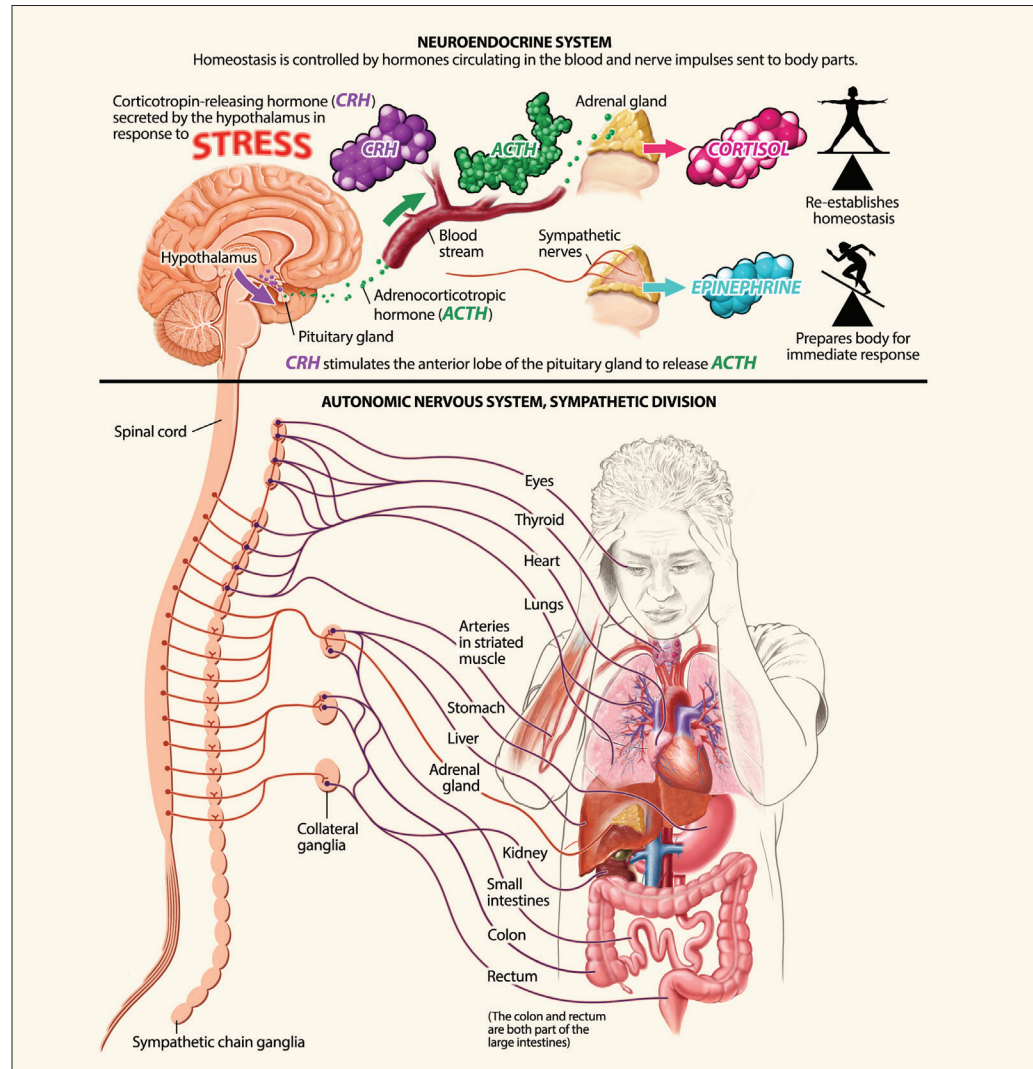
Neurons can quickly deliver the brain's messages to precise targets in the body. Hormones, on the other hand, deliver messages more slowly but can affect a larger set of tissues, producing large-scale changes in metabolism, growth, and behavior. The brain is one of the tissues that "listens" for hormonal signals — neurons throughout the brain are studded with hormone receptors — and the brain's responses play an important part in regulating hormone secretion and changing behaviors to keep the body systems in



equilibrium. The brain regions involved in hormone release are called the neuroendocrine system.

The hypothalamus oversees the production and release of many hormones through its close ties to the **pituitary gland**. The paraventricular and supraoptic nuclei of the hypothalamus send axons into the posterior part of the pituitary gland; activation of specific neurons releases either vasopressin or **oxytocin** into capillaries within the pituitary. Both of these molecules act as neurotransmitters inside the brain, but they are also hormones that affect distant tissues of the body. Vasopressin (also called antidiuretic hormone) increases water retention in the kidneys and constricts blood vessels (vasoconstriction). Oxytocin promotes uterine contractions during labor and milk release during nursing.

Other hypothalamic regions send axons to a capillary-rich area above the pituitary called the median eminence. When these neurons are activated, they release their hormones into the blood. These releasing (and inhibiting) hormones travel through local blood vessels to the anterior pituitary, where they trigger (or inhibit) secretion of a second specific hormone. Of the seven anterior pituitary hormones, five are trophic hormones — these travel in the bloodstream to stimulate activity in specific endocrine glands (thyroid, adrenal cortex, ovaries, etc.) throughout the body. The remaining two hormones act on non-endocrine tissues. Growth hormone stimulates the growth of bone and soft tissues, and prolactin stimulates milk production by the breasts. Hormones released from the anterior pituitary influence growth, cellular metabolism, emotion, and the physiology of reproduction, hunger, thirst, and stress.



The neuroendocrine system maintains homeostasis, the body's normal equilibrium, and controls the response to stress. The adrenal gland releases the stress hormones norepinephrine, epinephrine, and cortisol, which quicken heart rate and prepare muscles for action. Corticotrophin releasing hormone (CRH) is released from the hypothalamus and travels to the pituitary gland, where it triggers the release of adrenocorticotrophic hormone (ACTH). ACTH travels in the blood to the adrenal glands, where it stimulates the release of cortisol.

Many hormones produced by the pituitary and its target endocrine glands affect receptors inside the brain — thus, these hormones can alter neuronal function and gene transcription in the hypothalamus. The effect is to reduce the amount of hormone released by the hypothalamus when those circuits become active. These negative feedback loops enable precise doses of hormones to be delivered to body tissues, and ensure that the hor-

monone levels are narrowly regulated.

One of these three-hormone cascades regulates reproduction in mammals. Its underlying pattern is the same in both sexes: 1) gonadotropin-releasing hormone (GnRH) from the hypothalamus makes the anterior pituitary release 2) luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn make the gonads secrete 3) sex hormones and start the development of mature eggs or sperm.

Sex hormones, in turn, attach to receptors in the hypothalamus and anterior pituitary and modify the release of the hypothalamic and pituitary hormones. However, sex hormones regulate these feedback loops differently in males and females.

Male sex hormones induce simple negative feedback loops that reduce the secretion of gonadotropin-releasing hormone, luteinizing hormone, and follicle stimulating hormone. The interplay among these hormones creates a repetitive pulse of GnRH that peaks every 90 minutes. The waxing and waning of GnRH keeps testosterone levels relatively steady within body tissues, maintains male libido, and keeps the testes producing new sperm each day.

Female feedback patterns are more complex. Over the course of the month-long menstrual cycle, female sex hormones exert both positive and negative feedback on GnRH, FSH, and LH.

When circulating levels of the female sex hormones estrogen and progesterone are low, rising follicle stimulating hormone levels trigger egg maturation and estrogen production. Rising estrogen levels induce luteinizing hormone levels to rise. As the levels of female sex hormones rise, they exert negative feedback on FSH secretion, limiting the number of eggs that mature in a month, but positive feedback on LH, eventually producing the LH surge that triggers ovulation. After ovulation, high serum levels of sex hormones again exert negative feedback on GnRH, FSH, and LH which in turn reduces ovarian activity. Levels of female sex hormones therefore decrease, allowing the cycle to start over again.

Many other hormones are not regulated by the pituitary gland, but are released by specific tissues in response to physiological changes. The

brain contains receptors for many of these hormones but, unlike pituitary hormones, it does not directly regulate their secretion. Instead, when these hormones bind to receptors on neurons, they modify the output of neural circuits, producing behavioral changes that have homeostatic effects. One example of this is a pair of hormones called leptin and ghrelin.

Leptin and ghrelin change eating behavior by regulating food intake and energy balance. Both hormones affect hunger, and both are released in response to changes in an animal's internal energy stores. However, they have different effects on the circuits they regulate. Ghrelin keeps the body fed. Released by the wall of the gastrointestinal tract when the stomach is empty, ghrelin activates hunger circuits in the hypothalamus that drive a search for food. Once the stomach is full, ghrelin production stops, reducing the desire to eat. In contrast, leptin helps maintain body weight within a set range. Leptin is produced by fat cells and is released when fat stores are large. When it binds to neurons in the hypothalamus, leptin suppresses the activity of hunger circuits and reduces the desire to eat. As fat stores are used up, leptin levels decline, driving behavior that makes an animal eat more often and replenish its fat stores.

## STRESS

Your body reacts in stereotyped ways when you feel threatened. You breathe faster, your heartbeat speeds up, your muscles tense and prepare for action. These reactions may have helped our ancestors run from predators, but any stressful situation — arguing with your parents, a blind date, a looming deadline at work, abdominal cramps, discovering your apartment

was robbed, trying karaoke for the first time — has the potential to set them off. Scientists call this reaction the stress response, and your body turns it on to some degree in response to any external or internal threat to homeostasis.

## The Stress Response

The stress response weaves together three of the brain's parallel communication systems, coordinating the activity of voluntary and involuntary nervous systems, muscles, and metabolism to achieve one defensive goal.

Messages sent to muscles through the somatic (voluntary) nervous system prime the body to fight or run from danger (the fight-or-flight response). Messages sent through the autonomic (involuntary) nervous system redirect nutrients and oxygen to those muscles. The **sympathetic branch** tells the adrenal medulla to release the hormone **epinephrine** (also called adrenaline), which makes the heart pump faster and relaxes the arterial walls that supply muscles with blood so they can respond more quickly. At the same time, the autonomic system's **parasympathetic branch** restricts blood flow to other organs including the skin, gonads, digestive tract, and kidneys. Finally, a cascade of neuroendocrine hormones originating in the hypothalamus and anterior pituitary circulates in the bloodstream, affecting processes like metabolic rate and sexual function, and telling the adrenal cortex to release **glucocorticoid hormones** — like cortisol — into the blood.

Glucocorticoid hormones bind to many body tissues and produce widespread effects that prepare the body to respond to potential threat. These hormones stimulate the production and release of sugar from storage sites such as the liver, making energy available to



muscles. They also bind to brain areas that ramp up attention and learning. And they help inhibit nonessential functions like growth and immune responses until the crisis ends.

It's easy to imagine how (and why) these physiological changes make your body alert and ready for action. But when it comes to stress, your body can't tell the difference between the danger of facing down a bull elephant and the frustration of being stuck in traffic. When stress is chronic, whatever its cause, your **adrenal glands** keep pump-

(hardening of the arteries), increasing the risk of heart attacks. Because the hormones inhibit immune system function, they also reduce resistance to infection and inflammation, sometimes pushing the immune system to attack the body's own tissues.

Chronic stress can also have specific negative effects on brain tissue and function. Persistently high levels of glucocorticoids inhibit neuron growth inside the hippocampus, impairing the normal processes of memory formation and recall. Stress hormones can

important roles in brain development. If a pregnant woman suffers from chronic stress, the elevated stress hormones can cross the placenta and shift the developmental trajectory of her fetus. Glucocorticoids are transcription factors, which can bind to DNA and modify which genes will be expressed as proteins. Studies with animal models have shown that mothers with high blood levels of glucocorticoids during pregnancy often have babies with lower birth weights, developmental delays, and more sensitive stress responses throughout their lives.

Because metabolic stressors such as starvation induce high glucocorticoid levels, it's been suggested that these hormones might help prepare the fetus for the environment it will be born into. Tough, stressful environments push fetuses to develop stress-sensitive "thrifty" metabolisms that store fat easily. Unfortunately, these stress-sensitive metabolisms increase a person's risk of developing chronic metabolic diseases like obesity or diabetes, especially if they subsequently grow up in lower-stress environments with plentiful food.

The effects of stress can even be passed to subsequent generations by epigenetic mechanisms. Chronic stress can change the markers on DNA molecules that indicate which of the genes in a cell are expressed and which are silenced. Some animal studies indicate that when changes in markers occur in cells that develop into eggs or sperm, these changes can be passed on and expressed in the animal's offspring. Further research might reveal whether chronic stress has similar effects in humans, and whether inheriting silenced or activated genes contributes to family histories of cancer, obesity, cardiovascular, psychiatric, or neurodevelopmental disease. ■

also suppress neural pathways that are normally active in decision-making and cognition, and speed the deterioration in brain function caused by aging. They may worsen the damage caused by a stroke. And they can lead to sleep disorders — cortisol is also an important wakeful signal in the brain, so the high cortisol levels due to chronic stress may delay sleep. Stress-induced insomnia can then start a vicious cycle, as the stress of sleep deprivation leads to the release of even more glucocorticoids.

The effects of chronic stress may even extend beyond a single individual, because glucocorticoids play

## Chronic stress can also have specific negative effects on brain tissue and function.

ing out epinephrine and glucocorticoids. Many animal and human studies have shown that long-term exposure to these hormones can be detrimental.

### Chronic Stress



Overexposure to glucocorticoids can damage a wide range of physiological systems. It can cause muscles to atrophy, push the body to store energy as fat, and keep blood sugar abnormally high — all of these can worsen the symptoms of diabetes. Overexposure to glucocorticoids also contributes to the development of hypertension (high blood pressure) and atherosclerosis

# Childhood Disorders

## AUTISM SPECTRUM DISORDERS



**Autism** is often considered a childhood condition, although many of its symptoms persist lifelong. Some people with autism also have mood and anxiety disorders, seizures, intellectual disability, **attention deficit hyperactivity disorder (ADHD)**, and obsessive-compulsive disorder (OCD). However, more than 40 percent of people with autism have normal or above-average intelligence. With symptoms that range from mildly to severely disabling, autism is considered a spectrum. Autism spectrum disorders (ASD) are diagnosed based on two main criteria: impaired social communication and interaction, and repetitive behaviors or narrow, obsessive interests. For example, some people on the autism spectrum are unable to speak, while others are socially awkward but highly articulate. Many adults with an autism diagnosis think of their autism as a strength — enabling or motivating them to develop deep expertise in an area or a different perspective on the world — rather than a disorder that needs to be cured.

Currently, 1 of every 68 American 8-year-olds is estimated to meet the diagnostic criteria for an autism spectrum disorder. The prevalence of ASD has risen dramatically since the 1970s, but it is unclear whether changes to diagnostic criteria and wider recognition of ASD have contributed to the increase in diagnoses.

Four to five times more boys than girls are diagnosed with autism, although it is not clear whether some of that pattern is because of underdiagnosis of girls. Environmental factors such as parents having children later in life, fever and infection during pregnancy, and premature birth have been



linked to an increased risk of autism in children. A huge number of studies have found no connection between childhood vaccination and the increase in autism diagnoses.

Autism is believed to be at least partially driven by genetics, but how do scientists know that for sure? One low-tech approach uses twin studies: If one of a pair of identical twins receives an autism diagnosis, the other twin has greater than a 50 percent chance of also being diagnosed with ASD. Children who have an older sibling on the spectrum also have a higher likelihood of being diagnosed with autism — nearly one in five also receives a diagnosis of ASD.

The genetics of autism is very complicated in most cases, involving dozens (or more) of genes, leading to a unique condition in nearly every person. Recently, however, high-throughput genomic analyses have broadened the pool of potential genes, revealed their roles in the body, and suggested possible new therapies.

It appears that many genes, each with a small effect, contribute to the inheritance of most ASDs. But such small effects make these genes hard to identify in genome-wide association studies. Scientists are now looking at the rare variants associated with ASD. These afflict fewer people with ASD, but their effects are larger and easier to detect. Some of these rare mutations are in single genes whose impairment is already known to cause intellectual disability and social dysfunction. These genes include FMR1 (codes for fragile X mental retardation protein, but its non-mutant form is needed for normal cognitive development); PTEN (codes for a tumor suppressor enzyme that regulates cell division, so cells don't divide or grow too fast);

and TSC1 or TSC2 (tuberous sclerosis complex 1 and 2), which also code for proteins that help control cell growth and size. Between 50 to 60 percent of people with **fragile X syndrome** and approximately 40 percent of people with tuberous sclerosis complex have ASD. Children with a variant of the gene NF-1 develop tumors in childhood (neurofibromatosis) and a 2011 study found that nearly 10 percent met the criteria for autism.

Intriguingly, these ASD-related genes influence a major signaling pathway for regulating cell metabolism, growth, and proliferation, the mTOR pathway. This suggests a very real potential for treating autism with drugs that target the mTOR pathway.

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**The genetics of autism is very complicated in most cases, involving dozens of genes, leading to a unique condition in nearly every person.**

For example, mouse models with mutations in PTEN show traits similar to humans with these gene variants: altered sociability, anxiety, and repetitive behaviors. These behaviors can be relieved or reversed by drugs that inhibit the mTOR pathway. Clinical trials of these drugs (rapamycin and lovastatin) are underway.

Despite this progress, autism genetics is so complicated that it can't be used to diagnose the condition.

And unlike diabetes, kidney disease, or thyroid disease, there are no biochemical or other biomarkers of autism. Currently, autism diagnosis is based on behavioral analysis, but efforts are underway to use more objective criteria such as tracking eye movements and functional neuroimaging, which can even be done in infants.

How early can autism be detected? Parents often notice developmental issues before their child's first birthday, and autism can be reliably diagnosed based on behavioral characteristics at age 2. Despite these possibilities for early detection, most American children aren't diagnosed until they're about 4½ years old. With evidence mounting that interventions

are more effective the earlier they begin, researchers are hoping that more objective measures will enable earlier diagnoses and interventions.

Although the molecular causes and characteristics of autism are unclear, it appears that the condition results from unusual cellular development within the cerebral cortex — a brain region that is crucial to memory, attention, perception, language, and other functions. Both white

and gray matter of the brain show consistent, but subtle, alterations in people with ASD. Long-term studies also have found that a minority of children on the autism spectrum have abnormally large brain volumes and faster brain growth. Other toddlers with autism have shown unusual development and network inefficiencies at the back of the cerebral cortex. There is evidence that some atypical activity occurs in the cortex of people with ASD from older childhood into adulthood, and information might not be integrated in the usual way across distributed brain networks.

At this point, no medications have been proven to reverse autism. Some people get symptomatic relief from drugs designed for other uses, such as anxiety conditions, and several studies have reported social benefits from treatment with oxytocin — a hormone known to improve social bonding — but the findings have been mixed. For this challenging disorder, behavioral therapies are still the only proven treatments for autism, and early interventions are the most effective.

### ATTENTION DEFICIT HYPERACTIVITY DISORDER

**Attention deficit hyperactivity disorder (ADHD)** is one of the most commonly diagnosed childhood conditions. In 2014, approximately 11 percent of American parents with a child between the ages of 4 and 17 reported that their son or daughter had received an ADHD diagnosis. In at least 30 percent of those diagnosed with ADHD, the disorder continues into adulthood.

ADHD is usually characterized by inattentiveness, as well as hyperactivity or impulsive behaviors. Although all young children can be hyperactive,

impulsive, and inattentive from time to time, these symptoms are more extreme and last longer in children with ADHD. They often struggle to form strong friendships, and their grades in school can reflect their behavior instead of their academic ability. Executive functions, such as finishing what they start, remembering to bring homework back to school, and following multistep directions, can be especially challenging for those with ADHD. Young people with ADHD also have lower rates of high school graduation and a higher risk of suicide.

No objective diagnostic test exists for ADHD, so diagnosis requires a comprehensive evaluation, including a clinical interview and parent and teacher ratings. Because problems with attention and hyperactivity can be caused by other conditions such as depression, sleep issues, and learning disorders, careful evaluation is always needed to determine whether ADHD is truly the cause of the symptoms. To warrant an ADHD diagnosis, attention and behavioral problems must be severe enough that they interfere with normal functioning. In addition, the behavioral issues must be present in more than one context — not only at home *or* at school, but in both settings.

Although ADHD tends to run in families, no well-defined set of genes is known to be responsible for the condition. Environmental risk factors, such as extreme early adversity, exposure to lead, and low birthweight, can also be involved. People with ADHD do not demonstrate any obvious brain alterations, but research has found that people with ADHD might have differences in the structure of brain cells and in the brain's ability to remodel itself. Some people with ADHD show unusual activity in brain cells that re-

lease dopamine, a chemical messenger involved in rewarding behavior.

ADHD has no cure, but treatments include drugs, behavioral interventions, or both. Interestingly, ADHD medications include stimulants such as methylphenidate, as well as newer, non-stimulant drugs. The drugs are available in long-acting formulations so children do not have to interrupt the school day to take their medication. Determining the right drug and the right dose might require a period of experimentation and support from a specialist, since dosage is adjusted to how fast a child metabolizes the drug, and to minimize the side effects. Nevertheless, most children with ADHD are diagnosed and treated by their pediatricians. Effective behavioral treatments include organizational support, exercise, and meditation.

### DOWN SYNDROME

**Down syndrome** is named for the English physician who first described it in 1866, but nearly 100 years passed before scientists determined what caused the condition: possessing an extra copy of all or part of the 21st chromosome. People with this syndrome have three copies of this genetic material, instead of two. In some cases, the extra copy, or trisomy, does not occur in every cell, producing what's known as mosaicism. Currently, about 250,000 people in the United States are living with Down syndrome.

There is no clear cause of the genetic glitch, although maternal age is a major risk factor for Down syndrome. Mothers older than 40 are 8.5 times more likely to have a child with Down syndrome than mothers aged 20 to 24. Advanced paternal age has also been linked to higher incidence of Down syndrome.



Since late 2011, fetuses can be screened for Down syndrome using the mother's blood. In the past, the risk of test procedures meant that only older mothers (whose likelihood of having a Down syndrome child was known to be higher) should be screened. Younger mothers didn't know until delivery whether their child would have Down syndrome. The new blood test, unlike amniocentesis and chorionic villus sampling, poses no risk to the baby, so it can also be used for younger mothers whose chance of having a child with Down syndrome is quite small.


Children born with Down syndrome have distinctive facial features, including a flattened face and bridge of the nose, eyes that slant upward, and small ears. They usually have small hands and feet, short stature, and poor muscle tone as well. The intellectual abilities of people with Down syndrome are typically low to moderate, although some graduate from high school and college, and many successfully hold jobs. Other symptoms of Down syndrome can include hearing loss and heart defects, and virtually everyone born with Down will develop early-onset Alzheimer's disease, often in their 40s or 50s. Chromosome 21 contains the gene that encodes amyloid precursor protein (APP), an Alzheimer's disease risk factor, and possessing an extra copy of this gene might cause the early onset of this fatal disease. Interestingly, people with mosaic Down syndrome seem to have milder symptoms and are more likely to live past 50.

There is no real treatment for Down syndrome, nor any clear explanation of what occurs in the brain. Poor connections among nerve cells in the hippocampus, the part of the brain involved in memory (and the first brain area affected by Alzheimer's disease),

are believed to be a key factor in brain or intellectual differences in Down syndrome. Dysfunction in the mitochondria, the cell's power plants, might also play a role in development of related disorders that involve energy metabolism, such as diabetes and Alzheimer's.

Scientists have grown stem cells from fetuses with Down syndrome and used them to test potential treatments and confirm which molecular pathways are involved in the condition. In one such laboratory study, researchers took a gene that normally inactivates the second X chromosome in female mammals and spliced it into a stem cell that had three copies of chromosome 21. In these cells, the inactivation gene muted the expression of genes on the extra chromosome 21, believed to contribute to Down syndrome. Although this is a long way from any clinical applications, the model is being used to test the changes and cellular problems that occur with the tripling of the 21<sup>st</sup> chromosome, in hopes of eventually finding a treatment.

### DYSLEXIA

 **Dyslexia** is the most common and best-studied of the learning disabilities, affecting as many as 15 to 20 percent of all Americans. People with dyslexia have a pronounced difficulty with reading despite having normal intelligence, education, and motivation.

Symptoms include trouble with pronunciation, lack of fluency, difficulty retrieving words, poor spelling, and hesitancy in speaking. People with dyslexia might need more time to respond orally to a question and might read much more slowly than their peers. Dyslexia is usually diagnosed in elementary school, when a child is slow to read or struggling with reading. Although

reading skills and fluency can improve, dyslexia persists lifelong.

Deciphering printed letters and words and recalling their sounds and meaning involves many areas of the brain. Brain imaging studies indicate these areas can be less well connected in people with dyslexia. One of these areas is a region on the left side of the brain called the "word-form area," which is involved in the recognition of printed letters and words. People with dyslexia also show less brain activity in the left occipitotemporal cortex, which is considered essential for skilled reading. Researchers believe that the brain differences are present *before* the reading and language difficulties become apparent — although it is possible that people with dyslexia read less and, therefore, their brains develop less in regions associated with reading. Those with dyslexia appear to compensate for reduced activity on the left side of the brain by relying more heavily on the right side.

Genetic analyses have revealed a handful of susceptibility genes, with animal models suggesting that these genes affect the migration of brain cells during development, leading to differences in brain circuitry. Dyslexia runs in families, with roughly half of dyslexics sharing the condition with a close relative. When one twin is diagnosed with dyslexia, the second twin is found to have the condition 55-70 percent of the time. But the genetics of dyslexia is complex, and likely involves a wide range of genes and environmental factors.

Treatment for dyslexia involves behavioral and educational intervention, especially exercises like breaking words down into sounds and linking the sounds to specific letter patterns. Some researchers use a child's ability

to rapidly and automatically name things as an early indicator of dyslexia. This rapid automatic naming, and the ability to recognize and work with the sounds of language, are often impaired in people with dyslexia. Both skills can be used in preschoolers and kindergartners to predict their later reading skills. Research suggests that treatments targeting phonology, as well as multiple levels of language skills, show the greatest promise.

and become unaware of what is going on around them. The pattern of symptoms and after-seizure brain recordings using EEGs are used to distinguish between different types of epilepsy and determine whether the true cause of the seizures is epilepsy or a different medical condition.

Seizures are classified by where they occur in the brain. Generalized seizures affect both sides of the brain. They include absence or *petit*

spread to become generalized seizures. In some patients with severe epilepsy, multiple types of seizure can occur at the same time.

Epilepsy has many possible causes and thus is considered a spectrum rather than a single disorder. Causes include premature birth, brain trauma, and abnormal development due to genetic factors. Attributes of epilepsy patients such as head size, movement disorders, and family history suggest that genetics is involved.

Seizures can also accompany or cause intellectual or psychiatric problems. For example, some seizures may suppress the growth of dendrites, leaving the person emotionally unsettled or less able to learn.

Treatments for epilepsy are directed toward controlling seizures with medication or diet. For most patients, a single medication is enough to control seizures, although a significant minority cannot get adequate control from drugs. About half of epilepsy patients, particularly those with generalized epilepsy, can reduce their seizures by eating a ketogenic diet, which relies heavily on high-fat, low-carbohydrate foods, although it's unclear why this diet is effective. For severe cases that are not relieved by medication, doctors might recommend surgery to remove or inactivate the seizure-initiating part of the brain. In the most severe cases, if one side of the brain triggers seizures on the other side, surgeons may perform "split-brain surgery," cutting the corpus callosum, a thick band of white matter that connects the two sides of the brain. Once their seizures are controlled, people with epilepsy can resume their normal lives. ■

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**Epilepsy has many possible causes and thus is considered a spectrum rather than a single disorder.**

### EPILEPSY

If someone has two or more seizures that cannot be explained by a temporary underlying medical condition such as a high fever or low blood sugar, their medical diagnosis will be "epilepsy" — from the Greek words meaning to "seize," "attack," or "take hold of." About 1 percent of American children and 1.8 percent of adults have been diagnosed with this brain disorder. Seizures result from irregular activities in brain cells that can last five or more minutes at a time. Some seizures look like staring spells, while others cause people to collapse, shake,


*mal* seizures, which can cause rapid blinking or a few seconds of staring into space, and tonic-clonic or *grand mal* seizures, which can make someone fall, have muscle spasms, cry out, and/or lose consciousness. Focal or partial seizures are localized to one area of the brain. A simple focal seizure can cause twitching or a change in sensation, triggering strange smells or tastes. Complex focal seizures can leave a person confused and unable to answer questions or follow directions. A person can also have so-called secondary generalized seizures, which begin in one part of the brain but



# Psychiatric Disorders

Like many health conditions, psychiatric disorders can be caused by multiple factors. Genes often play a role, with many psychiatric disorders tending to run in families. Yet having a close relative with anxiety, schizophrenia, depression, or another psychiatric condition does not mean that you will develop the same problem. Many environmental effects, including life circumstances, medical conditions, and personal relationships, also have an influence. Environmental factors can be negative — like the death of a loved one, poverty, addiction, or being exposed directly to violence such as military combat — or they may be protective. These so-called resilience factors include a strong support system of family and friends, good coping skills, being physically active, and involvement in a range of activities.

## ANXIETY DISORDERS AND POST-TRAUMATIC STRESS DISORDER

 Everyone feels anxious at times, and worrying is a normal and healthy response to uncertainty or potential danger. But unhealthy, uncontrollable anxiety is the common thread in a variety of psychiatric disorders: post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and panic attacks. Collectively, anxiety disorders are the most common mental disorders experienced by Americans. They are more common in women, for reasons that are not clear but likely include both sex differences (biological) and gender differences (psychosocial).

Medications used to treat most anxiety disorders work by altering the levels of neurotransmitters that carry signals between brain regions.

Selective serotonin reuptake inhibitors (SSRIs) raise serotonin levels, which are known to be deficient in many psychiatric conditions. **Benzodiazepines** (such as diazepam, or Valium) were once the standard medication for anxiety because they boost levels of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). GABA acts like a “brake pedal” on neurons, helping to decrease their activity, especially in areas of the brain important in anxiety. However, because of the risk of dependence, benzodiazepines are no longer the first choice for treatment of anxiety.

## Obsessive-Compulsive Disorder

OCD is a common, chronic condition aptly named for its symptoms: uncontrollable, recurring thoughts (obsessions) and repeated, ritualistic behaviors (compulsions) to banish, relieve, or compensate for the obsessions. OCD affects about 1 percent of U.S. adults, with an average age of 19 at diagnosis. Obsessions vary widely: A person may, for example, worry about getting sick from a contaminated object, or feel the need to be “perfect” all the time. Compulsions attempt to counteract those thoughts behaviorally — for example, by excessive hand washing, or constantly checking for mistakes or problems such as leaving appliances on. Another type of OCD is hoarding, provoked by the fear of losing or forgetting important information after discarding something. People with OCD are burdened by their obsessive thoughts and, although compulsive behaviors can provide relief, they do not bring pleasure.

Research studies that examine the brain with powerful imaging tools have enabled neuroscientists to define the brain regions involved in obsessions

and compulsions. One such region, the basal ganglia, connects with the cortex to help control our ability to move and think, but it also helps us conduct routine behaviors that we call habits. The basal ganglia are also involved in the brain’s reward system, our ability to feel good, and in learning and memory; these functions are mediated by the neurotransmitters dopamine, serotonin, and glutamate, respectively. Reward systems are often dysfunctional in people with psychiatric disorders, addiction, or both.

Researchers suspect that disrupted signaling between the basal ganglia and the cortex could set the stage for ritualistic behaviors. Studies of repetitive behaviors in mice have revealed electrical activity that starts and ends in nerves that connect these two brain regions. The ability to manipulate, or “override,” those circuits may point the way to breaking the obsession-compulsion cycle in people with OCD.


About 70 percent of people with OCD obtain limited relief with medication, primarily SSRIs, but at higher doses than are used for depression therapy. If SSRIs do not work to control OCD, other approaches include medications such as the tricyclic antidepressant clomipramine and neuroleptic (tranquilizing) drugs, both of which have significant side effects. **Cognitive behavioral therapy**, a form of counseling, can also be useful. Deep brain stimulation (DBS) is a therapeutic approach used for people with OCD who do not respond to standard drug or behavioral treatments. DBS was first used about 30 years ago to treat movement disorders like Parkinson’s disease, but is now being investigated for other uses. In DBS, electrodes implanted at specific brain locations emit high-frequency electrical

pulses intended to reset abnormal neuronal firing. Scientists are beginning to explore the use of DBS in the basal ganglia and several other brain regions to alleviate the symptoms of OCD.

## Panic Disorder

Panic disorder is a type of anxiety disorder characterized by sudden, unexpected bouts of intense, irrational fear and frightening physical symptoms such as difficulty breathing, a racing heart, sweating, and dizziness. It is more common than OCD, affecting 2.7 percent of U.S. adults and about the same proportion of teens. Panic attacks typically last several minutes or sometimes longer. Because the attacks occur unpredictably, people who experience them often live in fear of having an attack in public or while driving — further increasing their anxiety. About half of people with panic disorder also have mood disorders such as depression or bipolar disorder, as well as other psychiatric illnesses like OCD, phobias, and schizophrenia. Panic disorder is usually treated with psychotherapy, medications, or a combination of these. SSRIs are the primary drugs used for panic disorder, although benzodiazepines can be used in an emergency situation.

## Post-Traumatic Stress Disorder

 PTSD is somewhat unique among psychiatric disorders because it has a well-defined cause: a harrowing, traumatic event such as military combat, a natural disaster, a terrorist attack, a serious accident, or physical or sexual assault as a child or adult. PTSD can arise quickly after the distressing event, but sometimes it can take months to years for symptoms to



emerge. Symptoms are often severe enough to interfere with relationships or work. Some people have PTSD for many years, experiencing flashbacks and nightmares, intrusive memories of the traumatic event, and hyperarousal — feeling on edge and/or angry. To compensate, individuals with PTSD try to avoid trigger situations but nonetheless may experience memory loss, feelings of blame, and decreased interest in everyday activities. Currently, cognitive behavioral therapy is thought to be the most effective treatment for PTSD.

Neuroscientists have discovered physiological changes in people with PTSD. These changes include increased heart rate and heightened electrical sensitivity throughout the skin and on the face in response to audio or video triggers of traumatic scenes like gunfire or other violence. Simply recalling the initial traumatic event can also bring on these symptoms. Another hallmark of PTSD is shallow sleep with increased periods of rapid eye movement, which can lead to sleep deprivation over time. The body's general response to stress is maximal in PTSD, with altered levels of hormones such as cortisol and norepinephrine, the primary fuels in the fight-or-flight response to danger or fear. Not surprisingly, PTSD treatment includes drugs that block norepinephrine, such as the blood-pressure medication prazosin and beta-blocker drugs like propranolol. Scientists have also detected low levels of other neurotransmitters, such as serotonin, in people with PTSD, leading to the use of SSRIs for treatment. The neurotransmitter neuropeptide Y also appears to offer some protection against developing PTSD.


Neuroimaging studies have begun to reveal the neurobiological signatures

of PTSD, including changes in brain structure. Many people with PTSD have a smaller hippocampus (the brain region integral for learning and memory) and a smaller prefrontal cortex (the part of the brain that helps control thinking, emotions, and behavior). In contrast, the brain's emotional center, the amygdala, is apparently overactive

## Neuroimaging studies have begun to reveal the neurobiological signatures of PTSD, including changes in brain structure.

in responding to stimuli in people with PTSD. Genes are involved in PTSD susceptibility, but research results are not yet conclusive regarding the importance of their role or which genes are involved. What is clear, however, is that genes affecting PTSD risk also affect the risk for major depression, generalized anxiety disorder, and panic disorder — suggesting common biological components of these psychiatric conditions. Neuroimaging studies that pinpoint brain regions disrupted in PTSD support the development of new drugs targeting neural function in those regions. Among these drugs are cannabinoids, glutamate, and oxytocin — the latter, sometimes called the “love” or “happiness” hormone, is released by both men and women during orgasm and is secreted by mothers during childbirth and breastfeeding.

### MOOD DISORDERS

 Mood is a vague term describing a person's general state of mind. You can easily recognize someone in a good mood and, likewise, in a not-so-good mood. Your moods change frequently with your emotional state, and such changes are normal when they suit your context and

surroundings. Mood disorders, on the other hand, are mood changes that become longer lasting and independent of what is going on around you. The two main mood disorders are major depression and bipolar disorder. In recent years, neuroscientists have made major progress in linking genetic and other biological contributors to mood disorders and to disorders of cognition, like schizophrenia. Hopefully, their findings will lead to better treatments for people with more than one such condition.

#### Major Depression

Diagnosis of major depression is based on a set of criteria (at least four must be met) that have persisted for at least two weeks. These criteria include feeling empty or sad, loss of appetite, irritability, problems with sleep, and

changes in appetite or weight. Like anxiety, major depression is a common psychiatric disorder that contributes to considerable disability and death worldwide. Often, depression is accompanied by other diseases. Various medical and psychiatric conditions (for example, diabetes, cancer, heart disease, and addiction) are common in people who are depressed, and depression can make the other problems worse. Nearly 7 percent of American adults — about 16 million people — have experienced at least one major depressive episode in the past year, and 7 out of 10 of these are likely to be female. This striking sex imbalance is not thoroughly understood, but is an area of active research.

Several factors combine to cause depression: genes, biological risk factors, environmental triggers, and psychological influences. Many people develop depression in response to the stress of a difficult life experience or a disabling medical problem such as cancer or chronic pain. Inside the brain, depression appears to disrupt the hypothalamus. This region secretes a hormone that, via the pituitary gland, tells the adrenal cortex to produce more of the stress hormone cortisol. The monoamine neurotransmitter systems, which include dopamine and serotonin, are also disrupted. Some cases of depression — typically those evoked by a stressful incident, situation, or short-term illness — respond to treatment, and symptoms go away. In many cases, though, depression becomes a chronic condition and depressive symptoms persist without any outside influence.

As was also observed in people with PTSD, people with depression tend to have a smaller hippocampus and prefrontal cortex. These two brain

areas help manage stress, but can be damaged by excessive stress. When researchers showed negative pictures to depressed individuals and looked for brain activation, they noted activity in parts of the cortex linked to the limbic system. Even though the burst of activity soon died down, individuals who showed greater activation were more likely to have worse depression 18 months later. Such imaging techniques may help identify individuals at risk for relapse.

Identifying the underlying biological features of depression will help in the development of personalized therapy. Currently, approved antidepressant medications raise the levels of norepinephrine, serotonin, and dopamine in nerve cell synapses. Among the most widely used medications are SSRIs, which block serotonin reuptake and are also used to treat other psychiatric conditions. These molecules work by reshaping synapses, and usually require a few weeks to take effect. Cognitive behavioral therapy, often in combination with medications, is also effective in people with depression. This type of counseling works to change thought patterns and reroute negative, dysfunctional thinking. Treating people with depression can be challenging, as medications affect individuals differently. Sometimes, two or three tries are needed to find an effective treatment plan.

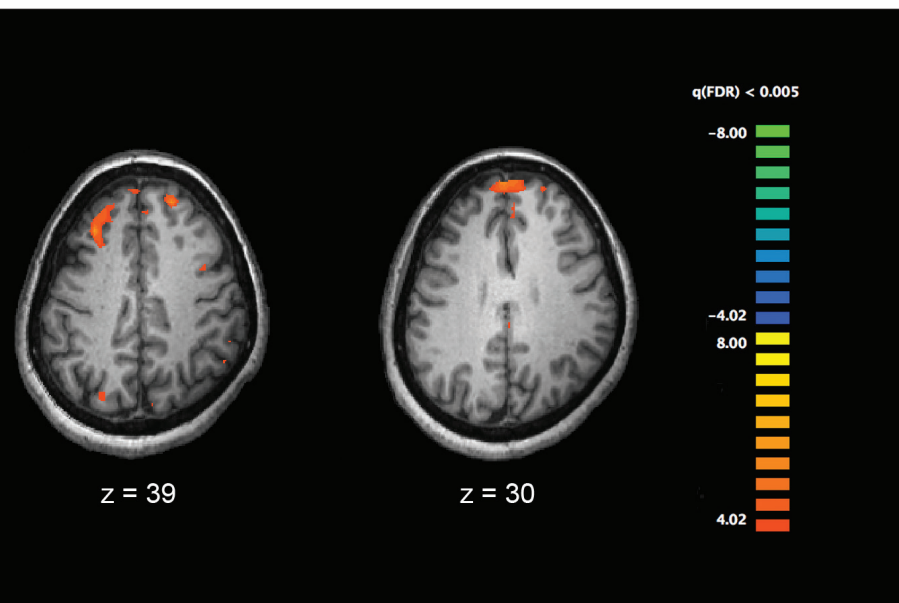
Unfortunately, for some people with depression, neither medication nor psychotherapy works. Researchers are actively investigating other approaches to treating depression, such as deep brain stimulation (DBS). Some promising studies have found that DBS can relieve intense depressive episodes that were resistant to other forms of treatment.

### Bipolar Disorder

Like most people, you probably have good days and bad days, days when everything goes well and days when the whole world seems against you. But people with bipolar disorder (formerly called manic-depressive illness) experience very intense mood changes. Their moods swing between extreme highs and severe lows, each lasting anywhere from a few hours to several months. High, or manic, episodes involve boundless energy, racing thoughts, and insomnia; they may also involve substance abuse and harmful behaviors like risky sex or other unsafe activities. During low, or depressive, episodes, people with bipolar disorder feel very sad and hopeless, worried, and sometimes suicidal. Some individuals with bipolar disorder are hypomanic; they are highly productive, feel great, and function better than normal. These changes may be outwardly subtle — only noticed by a friend or family member — but can be a clue to more intense developing mania.

Bipolar disorder is difficult to diagnose. No specific tests, other than a set of symptoms medical professionals use, differentiate it from other psychiatric disorders such as depression, psychosis, or schizophrenia. Researchers don't understand what causes bipolar disorder, although many individuals have a family history of a mood disorder or psychotic illness. Some people with depression may be at higher risk for bipolar disorder if a relative is bipolar or has another psychiatric illness like schizophrenia or autism. Studies analyzing the genomes of thousands of people with diseases like bipolar disorder have identified genetic changes that appear to be involved, but more research is





Kim, et al. PLoS One, 2010.

Brain imaging can reveal how the brains of individuals with schizophrenia function differently. In this image, the areas shown in orange were found to be less active in people with schizophrenia compared to healthy controls.

needed to understand how and why these DNA misspellings cause serious brain dysfunction.

Bipolar disorder is notoriously hard to treat. Psychiatrists typically prescribe separate drugs to lessen the highs and stabilize the lows. Medications such as anti-epilepsy drugs, lithium, or so-called atypical antipsychotics are used for manic periods, and antidepressants or cognitive behavioral therapy during depressed periods. Most treatments have significant side effects and, unfortunately, up to one-third of people with bipolar disorder do not respond to treatment at all, creating enormous hardship for the affected individuals as well as their family and friends.

#### DISORDERS OF COGNITION



##### Schizophrenia

Schizophrenia is a lifelong, severe psychiatric disorder that seriously disturbs thinking, emotion, and

behavior. People with schizophrenia appear to have lost touch with reality. They experience “positive” symptoms such as hallucinations, delusions, and confused thinking, and “negative” ones, including an inability to experience pleasure and a severe lack of motivation. Like many psychiatric disorders that first emerge when the human brain matures in the late teens and early 20s, schizophrenia usually appears between ages 15 and 25. This time period corresponds to development of the brain’s prefrontal cortex.

Although no cure exists for schizophrenia and many symptoms do not respond to treatment, some people can pursue personal and professional life goals with the help of medications, behavioral therapy, or a combination of these. Chlorpromazine, the first antipsychotic drug, was developed in the 1950s as an anesthetic for surgery but was soon employed to calm people with psychiatric disorders including

schizophrenia. Since then, more than 20 similar antipsychotic drugs have been developed. Most of these drugs work by damping the dopamine response, which is thought to drive schizophrenia’s “positive” symptoms. For that reason, these medications may cause tremors and other movement-related side effects resembling Parkinson’s disease, which involves low dopamine activity. The most recently developed drugs also suppress some serotonergic activity, which seems to help with the negative symptoms of schizophrenia.

Scientists have known for many years, through studying twins and extended families in which schizophrenia is common, that this condition is highly influenced by heredity. Only recently, however, with the emergence of powerful tools that scan massive amounts of DNA information, have scientists identified more than 100 common genetic misspellings and at least 11 rare ones in the DNA of people with schizophrenia. Current research is focused on learning more about these genes, which affect nerve cell growth as well as development, learning, and memory. Genes having a proven relationship to schizophrenia are potential targets for new medications.

Recently, research has uncovered a new and unusual perspective for thinking about schizophrenia therapies. Previous studies had noted that nearly 90 percent of people with schizophrenia smoke cigarettes, possibly to provide relief for their symptoms. Researchers have learned that nicotine seems to relax rigid nerve-cell shape and function in areas of the brain affected by schizophrenia. Thus, drugs containing nicotine may prove to be useful as future treatments for schizophrenia. ■

# Addiction

Drug abuse has been much in the news recently, with particular focus on the over-prescription and subsequent abuse of opioids. All too often, this abuse results in overdose and even death. In a 6-day period in late August 2017, one city (Cincinnati, Ohio) reported that 174 overdose cases flooded their hospital emergency rooms. The city is suing the pharmaceutical industry, as are counties in West Virginia, California, and New York. Addiction afflicts people around the world, often with chilling consequences. The National Institute on Drug Abuse estimates that the United States spends \$700 billion each year on addiction-associated treatments, crimes, and lost productivity.

Addiction is a chronic brain disorder that affects the body through physical and psychological dependence. Intentional, regular use of substances like opioids, alcohol, tobacco, or other drugs becomes an addiction when a person can no longer control his or her use despite negative consequences such as loss of control and harm to themselves or others. One factor fueling addiction is tolerance — when a person’s body becomes “used to” a drug and requires more of it to experience the same effect. Another facet of addiction is withdrawal, when lack of a drug causes the body to react with unpleasant or life-threatening physical symptoms. These may range from moderate headaches or muscle pain to severe tremors or seizures.

A combination of positive factors (pleasurable feelings) and negative ones (avoiding withdrawal) helps to create an addiction. Cues or triggers, such as being in a place associated with drug or alcohol intake or being around other drug or alcohol users, also provoke



drug-taking behavior. It is important to realize, though, that drug use does not always lead to addiction. Addiction is complex, and many researchers are working to understand the various interacting influences.

Almost all abused drugs produce pleasure by activating a specific circuit of neurons, the brain's reward system, which is controlled mainly by the neurotransmitter dopamine. This brain region, called the limbic system, drives healthy behaviors such as eating and socializing, but it is also activated by drugs of abuse. The limbic system helps people experience emotion, which somewhat explains the mood-altering properties of many drugs. In addition, the brain's reward system generates habits and learned behaviors: When a reward (a delicious food or a high-inducing drug) generates feelings of pleasure, we learn to repeat the actions that led to that reward.

### Mimics and Imposters



Drugs of abuse act as imposters that invade our nervous system, mimicking the messages of naturally occurring neurotransmitters in our brain circuits. While some drugs copy the actions of neurotransmitters, others can block neurotransmitter action, and still others alter the way neurotransmitters are released or inactivated. Ultimately, in all cases of addiction, drug use changes the brain's reward system and other regions involved in judgment and decision-making, contributing to addictive symptoms and behaviors.

Who is susceptible to becoming addicted? A precise answer to this question is still elusive, but we now know a great deal about vulnerability. As with most health conditions, vulnerability to addiction involves

internal risk factors, such as certain genes, and external risk factors, such as stress and a person's social environment. Often, a person's social environment both contributes to addictive behavior and is shaped by

social environment has a significant influence on drug-taking behavior during childhood and adolescence, the influence of hereditary factors is stronger in later stages of addiction, which usually occur in adults.

## Much remains to be learned about addiction's causes, but researchers are intrigued to find common genetic links in many different types of addictions.

addictive behavior, creating a cycle that is difficult to break.

Studies that track twins, and other closely related individuals with and without addictions, conclude that about 50 percent of addiction can be traced to genetic factors. Much remains to be learned about addiction's causes, but researchers are intrigued to find common genetic links in many different types of addictions — those involving a host of illicit drugs, marijuana, and legal drugs such as alcohol, tobacco, and even caffeine. Generally, the genes linked to addiction fall into one of two categories. Some of these genes affect how brain circuits respond to drugs; others influence the way the body metabolizes drugs, which then affects how quickly drugs enter and leave the body. Other biological factors important in addiction are gender and age: Females and males differ in their risk of addiction as well as their response to treatment. Also, while

### OPIOIDS

Dating back to prehistoric times, humans have consumed **opioids** by extracting opium (also known as morphine) from the juice of poppy flowers. The drug heroin is an opioid that is made (illegally) by drying morphine, adding various chemicals, and then heating it until it evaporates and becomes a powder. When injected into a vein, heroin reaches the brain in 15 to 20 seconds. Once there, it is quickly converted back to morphine, which binds to opioid receptors, switching on the brain's reward system and flooding synapses with pleasure-inducing dopamine. The result is a brief rush of intense euphoria, followed by a few hours in a state of relaxed contentment.

Opioids' effects vary in strength, toxicity, safety, and how quickly they act. But why do our brains have opioid receptors? Our pituitary gland produces natural versions of opioids

called endorphins, which help control motivation, emotion, food intake, and our response to pain. Laboratories produce synthetic opioids, which include heroin as well as prescription pain medicines like codeine, oxycodone (oxycotin), and fentanyl. Much more powerful than other opioids, fentanyl is used by doctors to treat severe pain. However, illegally made and distributed versions are sold on the black market and can be extremely dangerous. Opioids have many medically important uses — suppressing a cough, stopping diarrhea, and relieving pain — but, in excess, they can cause breathing to stop, the usual cause of death in an overdose.

Over the past two decades, the number of overdose deaths involving opioids (both prescription opioids and heroin) has quadrupled. Nearly 100 Americans, from every walk of life, die from opioid overdoses each day. As mentioned above, this opioid-addiction epidemic appears to stem directly from increased use of legally prescribed opioid medications that began in the mid-1980s to treat chronic pain. In fact, about 80 percent of current heroin users say their opioid use began with prescription pain medications; once hooked, they found heroin to be cheaper and easier to get than the prescription medications. Tragically, street heroin can be mixed with other dangerous substances, including high concentrations of fentanyl that can be immediately fatal. Another contributor to this epidemic was the 1995 introduction of a long-lasting version of oxycotin. Researchers now believe that, in medical as well as nonmedical users, addiction rather than abuse is the main driver of the opioid-overdose epidemic.

### Treatment



The most effective treatment for opioid overdose is an antidote-like approach using synthetic drugs that block opioid receptors. The "antidote," naloxone, binds to opioid receptors — without producing a biological effect — and prevents an opioid from binding. If given quickly enough, it can actually reverse a potential overdose caused by heroin or prescribed painkillers. Naloxone can also be used in prevention, to limit cravings in people highly motivated to quit. Doctors sometimes prescribe naloxone to a family member of someone at risk of opioid overdose so they can administer it, and many first responders across the country are taught how to administer naloxone in cases of overdose emergencies.

Drug-based treatment for overdoses can save lives, but other strategies are needed to treat opioid addiction itself and prevent future crises with these highly addictive substances. Two other drugs, methadone and buprenorphine, stimulate opioid receptors, but produce a limited high. They also reduce withdrawal symptoms from other opioids; both drugs have milder withdrawal symptoms of their own. Researchers have found that these therapies can help deter a person from seeking heroin or other abused opioids. Of the two, buprenorphine is safer because its effect is weaker than methadone, and it can be prescribed in an office setting. Psychosocial approaches, including cognitive behavioral therapy and behavioral change focused on positive reinforcement, can also be combined with drug treatments to treat opioid addiction.

### NICOTINE

Nicotine is the addictive substance in tobacco. Within 10 seconds of smoking a cigarette, nicotine arrives in the brain (as does any other drug that is smoked). There it attaches to proteins on nerve cells called nicotinic acetylcholine receptors, triggering release of many neurotransmitters. It also releases neurotransmitters outside the brain like adrenaline, a stimulant that raises a person's blood pressure and quickens their heart rate. In the brain, it creates a buzz of pleasure and energy — due to release of dopamine — followed by a calming sensation and a rapid boost in attention and memory. The latter finding has led to ongoing tests of non-addictive nicotine-like substances as possible treatments for cognitive disorders such as schizophrenia, attention-deficit hyperactivity disorder (ADHD), and Alzheimer's disease.

Tobacco is the leading cause of preventable deaths in the United States, accounting for approximately 90 percent of lung-cancer deaths, 60 percent of lung-disease deaths, and 30 percent of deaths from heart disease. Despite the well-known health risks of tobacco use, however, about 20 percent of Americans still smoke. Nicotine itself does not cause cancer, but of the thousands of chemicals in tobacco, about 70 are known to be carcinogenic. However, nicotine *is* responsible for other health risks of smoking, including heart disease and stroke. Like many other addictive substances, nicotine generates tolerance; over time, more and more nicotine is required to obtain the same effect. Also like other drugs of abuse, nicotine activates dopamine-producing reward pathways that induce feelings of pleasure and affect motivation, creating the urge to use more.



**Treatment**

Nicotine is so highly addictive that, even though most smokers want to quit, few succeed. For some smokers who are highly motivated to quit, some drug treatments (pharmacotherapy) can help. Nicotine packaged into gum, skin patches, lozenges, nasal sprays, or inhalers can sidestep the use of cigarettes or chewing tobacco. Nicotine replacement products provide users with lower overall nicotine levels than they get with tobacco use, totally eliminate exposure to smoke and its deadly contents, and relieve withdrawal symptoms. Buprenorphine, used to treat opioid addiction, can also help smokers quit by simulating nicotine's effect on dopamine.

One of the newest treatments for nicotine addiction is varenicline, approved by the U.S. Food and Drug Administration (FDA) in 2006 for tobacco-cessation treatments. Varenicline is a nicotine mimic that attaches to a special type of nicotinic acetylcholine receptor — one that is thought to be responsible for conveying nicotine's addictive properties. Doctors consider varenicline the best single-drug option for nicotine addiction, and it is even more effective when combined with counseling and behavioral therapy. For example, smokers are twice as likely to quit if the advice comes from their medical provider. Other useful resources are motivational tools such as cessation hotlines, websites, and social media that promote tobacco-free living.

**ALCOHOL**

Alcohol, although legal like tobacco, is also addictive. Together, alcohol abuse and alcohol addiction are a serious and costly national health issue. Aside from secondary behavioral

impacts such as drunken driving, sexual assault, and domestic violence, a primary chronic health problem is associated with alcohol addiction: cirrhosis, a late-stage of scarring of the liver. The annual U.S. cost of alcohol abuse and addiction is estimated at \$250 billion.

Ethanol, the addictive ingredient in alcoholic drinks, has tricky effects on our bodies. Ethanol is water-soluble so it easily enters the bloodstream and quickly travels to the brain. With just a drink or two, ethanol acts as a stimulant. At higher blood levels, however, it acts as a depressant, causing intoxication, sleepiness, and even “blackouts,” or short-term memory loss.

Ethanol targets gamma-aminobutyric acid (GABA) receptors, which drive the brain's inhibitory system. In this capacity, ethanol calms anxiety, weakens muscles, and delays reaction time. Ethanol also blocks the N-methyl-D-aspartate (NMDA) type of glutamate receptors, which alter mood and impair memory, both common features of intoxication.

Finally, ethanol can stimulate the brain's pain-relief circuits, fueled by natural opioid molecules. This accounts in part for ethanol's feel-good effects in many people. It is also a diuretic — a substance that pulls water from body tissues and can cause dehydration.

Binge drinking — excessive alcohol consumption in a short period of time — slows heart rate and causes breathing difficulties — usually the underlying cause of death in alcohol overdose.

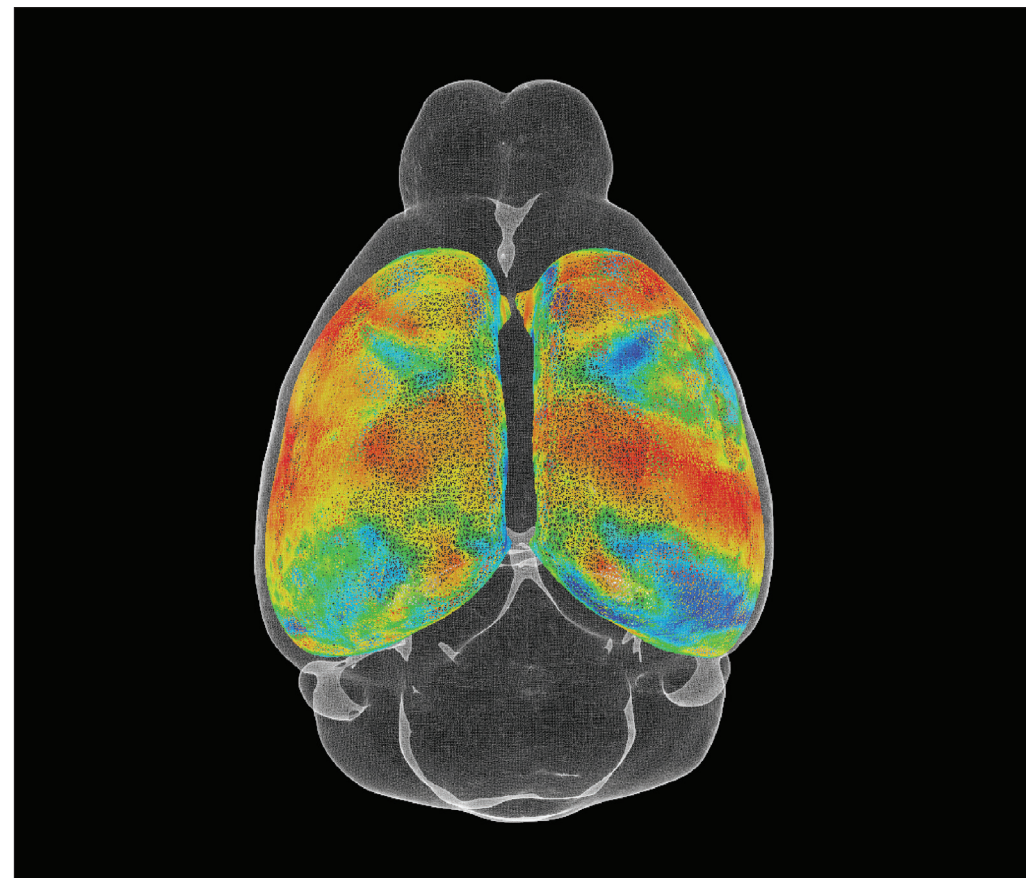
Chronic, heavy ethanol use can also change brain structure. People with alcohol use disorder (formerly called alcoholism) can have an unsteady gait, tremors, and slurred speech; these symptoms result from damage to the cerebellum, a brain

region important for movement and balance. They also suffer from memory loss due to the degeneration of neurons in the areas of the brain that govern learning and memory.

When does alcohol drinking become alcohol addiction? Federal surveys have found that nearly 9 in 10 Americans have drunk alcohol at some point in their lives, and an estimated 15 million have an alcohol use disorder, which might develop into addiction. As is true of addictions overall, about half the risk of alcohol addiction is thought to be linked to genetics. Yet, given that not all people who choose to drink become addicted to alcohol, it is clear that both genetic and environmental factors contribute to alcoholism. Currently, no single factor or combination of factors can predict the risk of developing an alcohol use disorder, although having a parent or grandparent with an alcohol use disorder is a good predictor. For this reason, neuroscientists often study genetic and environmental factors separately, designing some experiments to understand drinking behavior and others to investigate general issues related to motivation. Researchers often use animal models in these types of studies.

**Treatments**

Most people with a problem with alcohol use can benefit from some form of treatment before their use becomes a dangerous addiction. Treatments include behavioral therapy such as individual counseling, group therapy, and support groups. Some medications (disulfiram, naltrexone, and acamprosate) are used to treat alcohol addiction, and researchers can now use genetic testing to try to optimize therapy for individual drinkers.



Studies show that the brains of drug addicts look different than those of people who don't use drugs. This MRI scan reveals a mouse's thinning cortex, the part of the brain associated with higher-level functioning, following exposure to cocaine. Researchers found that changes in brain shape and volume were most pronounced when animals were exposed to cocaine in adolescence, suggesting the impact drug use has on brain development.

**MARIJUANA**

Also known as weed or pot, marijuana comes from the dried leaves, flowers, stems, and seeds of the *Cannabis* plant. The plant contains the mind-altering chemical tetrahydrocannabinol, or THC, which distorts perception and alters a person's sense of time, space, and self. Within minutes of smoking a marijuana “joint,” THC travels from the lungs to the blood and then into the brain. Eating foods containing THC can also create a high, usually within an hour of ingestion. Although the federal government deems marijuana illegal, in recent years several states have passed laws legalizing it. This has substantially

increased documented recreational use of marijuana in the United States.

Marijuana is not harmless. Neuroscientists have discovered that regular marijuana use is linked to abnormal neurobiology in brain regions related to reward, cravings, and thought control — all are key players in addiction. Marijuana use during the teen years can have long-lasting effects on thinking, memory, and learning. Although cannabis-use disorders have been less studied than other addictions, some known harms include higher stress levels due to craving and withdrawal, inability to think clearly, missing school or work, and risky behaviors while intoxicated. As with other addictions,

heavy marijuana use seems to increase vulnerability to drug use in susceptible people, through physical changes in the brain circuits of reward systems. In some users, long-term marijuana use has been linked to schizophrenia.

Our brains make a natural form of THC called anandamide, which acts through cannabinoid receptors in the body that help coordinate movement. This may explain why people's driving is impaired after smoking marijuana. The hippocampus, involved in memory and learning, also contains many THC receptors, possibly explaining the effects of marijuana on short-term memory. While relatively little research has been conducted on the role and usefulness of marijuana in treating medical conditions, some studies suggest that another active compound in marijuana called cannabidiol, or CBD, which does not produce a high, can control epileptic seizures, relieve pain and inflammation, and possibly even treat mental illness and addictions.

Many people with post-traumatic stress disorder (PTSD) self-medicate with marijuana to cope with anxiety, stress, and insomnia, and a few research studies appear to validate this strategy. These studies show that marijuana might reduce anxiety, improve sleep, and erase trauma-related memories in people with PTSD, but it is unknown whether this is due to CBD, THC, or some other ingredient. More research is needed to explore these findings. Similarly, marijuana has been widely regarded as a treatment for reducing nausea associated with chemotherapy. However, 2017 information from the National Cancer Institute (NCI) says there is currently too little evidence to recommend using cannabis to treat this side effect of cancer therapy.

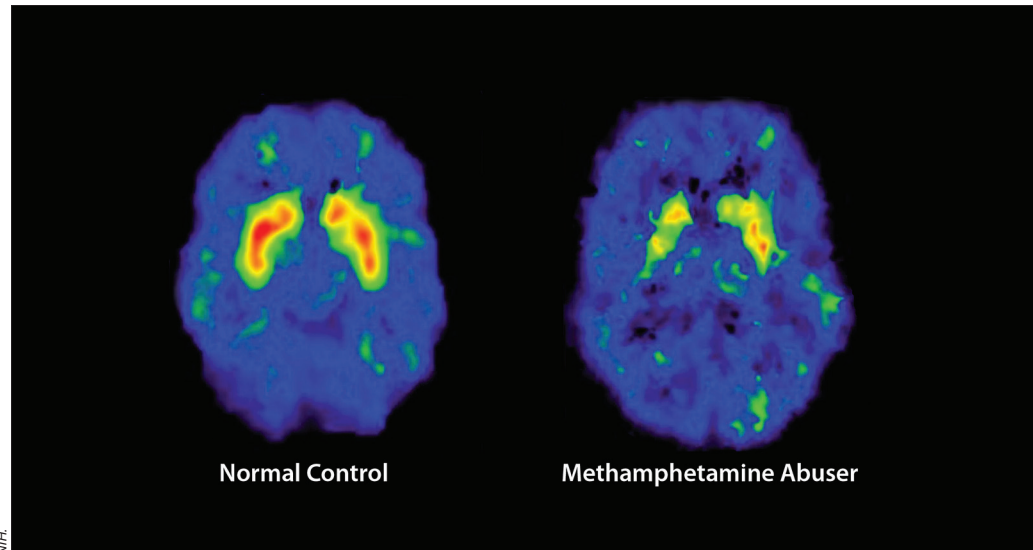


## PSYCHOSTIMULANTS

Psychostimulants are chemicals that excite the brain. They give a temporary boost to physical and/or mental function, earning some the nickname “speed.” One very common psychostimulant is caffeine, and another is nicotine. While both are legal and commercially available, nicotine is highly addictive and can create secondary problems as the main ingredient in cancer-causing cigarettes and chewing tobacco.

Other psychostimulants are in commonly prescribed medications that are sometimes abused recreationally. For example, doctors prescribe amphetamine (Adderall) and methylphenidate (Ritalin or Concerta) to treat ADHD and the sleeping disorder narcolepsy, but these drugs have migrated to the black market and are widely sold illegally. Amphetamines, including methylphenidate, are frequently abused by high school and college students. One study determined that, by their senior year, two-thirds of college students had been offered prescription stimulants and one-third had used them non-medically to increase focus and enhance concentration.

Illegal psychostimulants that are made in makeshift drug labs and sold on the street include cocaine and methamphetamine, or “meth.” Abusers sometimes smoke these — in particular, cocaine (crack) and crystal methamphetamine (crystal meth) — producing a rush of euphoria and feelings of power and self-confidence. Typically, the effects are short-lived, prompting repeated use and physical harm to various organs, including the heart. Meth, in particular, is quite destructive to the brain itself, as it generates harmful substances called free radicals that destroy dopamine neurons.



Methamphetamine abuse can reduce the number of dopamine receptors in the brain, disrupting mental functions.

In the brain, psychostimulants work by flooding the brain’s reward system with dopamine, the “usual suspect” in most addictions and many psychiatric disorders. Most psychostimulants act and wear off quickly, leading to a quick high and then an unpleasant “crash” that encourages more use and can be overwhelming, both physically and mentally. Meth is especially addictive, entering the brain very quickly and staying there longer than other psychostimulants. People who continue using psychostimulants develop a tolerance, needing more and more to get high. Over time, these drugs damage the body’s ability to release normal amounts of dopamine, causing a range of health problems, starting with a lack of drive to engage in activities that were once pleasurable.

Neuroscientists are working hard to figure out how to prevent and treat addiction to psychostimulants. In the course of their work, they have learned a great deal about the brain’s normal function in motivated behavior. For example, in addition to increasing dopamine in the reward system, psycho-

stimulants act in the prefrontal cortex to promote arousal and quicken our thinking. Studies show that low doses of psychostimulants (much less than taken in drug abuse) actually improve the brain’s executive function (as in some ADHD treatments), helping with impulse and emotional control, planning and organizing, and productivity. Such low doses do not lead to tolerance and addiction, but high doses can impair brain function.

## Treatments

Currently the best treatments for psychostimulant addiction are cognitive-behavioral therapy and motivational incentives, both of which help steer users away from situations that trigger drug use. So far, no effective drugs have been approved for cocaine or meth addiction. However, now that scientists better understand how psychostimulants work in the brain, they are pursuing treatment strategies that target many neurotransmitters separately to quell cravings and withdrawal symptoms. The neurotransmitter systems include serotonin,

glutamate, and GABA. Still-experimental meth treatments focus on entirely new targets, such as the brain’s immune cells (microglia) and oxytocin — the latter is sometimes called the “love” or “happiness” hormone because men and women release it during orgasm and mothers secrete it during childbirth and breastfeeding.

## DESIGNER DRUGS AND CLUB DRUGS

Designer drugs such as “bath salts” and “spice” (synthetic marijuana) are synthetic legal substances with psychoactive effects. They look like illicit drugs but can often be bought legally because the people who make them continually tweak their chemical structures to evade drug laws. We now know that these drugs can cause serious, permanent damage in many brain regions. Like designer drugs, club drugs are also synthetic psychoactive substances that look like legal drugs and are named for their use by youth at dance parties and all-night raves in crowded, high-energy

surroundings. Examples of club drugs include 3,4-methylenedioxy-methamphetamine (also known as MDMA, Ecstasy, or Molly), rohypnol (“roofies”), GHB (gamma hydroxy-butyrate), and ketamine. Designer and club drugs can be stimulants — such as Ecstasy — or depressants like rohypnol, GHB, and ketamine.

Ecstasy is a widely used recreational drug with similarities to both the stimulant amphetamine and the hallucinogen mescaline, which occurs naturally in the peyote cactus and has effects similar to lysergic acid diethylamide (LSD). When swallowed, Ecstasy works within 30 to 45 minutes, and its effects last for several hours. It initially boosts levels of neurotransmitters, especially serotonin, then temporarily depletes their levels in the synapses. Chronic Ecstasy use leads to long-term changes in areas of the brain critical for thought, memory, and pleasure. Researchers think this harm is a result of long-term damage to serotonin circuits.

Rohypnol and GHB are both de-

pressants, and mimic benzodiazepines like Valium. They are also known as “date-rape” drugs, as people have used them to facilitate sexual assault by slipping pills into drinks, sedating and incapacitating unsuspecting victims. Ketamine, called “Special K,” is also a depressant that is legally used as a veterinary anesthetic. When used recreationally, ketamine takes effect within about 10 minutes, putting users in a trance-like state. Its hallucinogenic effects last one or two hours. Recently, scientists have found a totally unexpected use for ketamine: treating depression. Ketamine alters signaling of the neurotransmitter glutamate, a non-traditional target for antidepressant medications. Perhaps most interesting are its very rapid effects, which occur within minutes to hours instead of the weeks required for other current antidepressant treatments. For this reason, neuroscientists consider ketamine a potential breakthrough, especially in people for whom no other treatments have been effective. ■



# Injury & Illness

Humankind has always sought ways to treat illness, injury, and pain. For example, the first known brain surgeries occurred about 6,000 years ago in Asia Minor. Also, archaeologists have found skulls of ancient Incas of Peru with small pieces of skull carefully removed (a process called trepanation) to treat head wounds, or possibly to cure epilepsy or infections. The earliest of these Incan skulls did not show any healing, indicating that the patients soon died. But by the 1400s, about 90 percent of the ancient skulls discovered showed bone regrowth.

How did those patients survive and how did they deal with the pain? It is likely that herbs like tobacco and coca leaves, and corn beer might have been consumed to provide some relief. As you learn about brain tumors, head trauma, pain management, and other problems caused by disease processes, remember that neuroscience seeks to understand the roots of these issues. Such insights will ultimately advance the medical field, enabling more effective treatments and therapies for the future.

## BRAIN TUMORS

Each year, more than 79,000 people in the United States are likely to be diagnosed with a tumor that originates in their brain — a primary brain tumor. An estimated 26,000 of these tumors will be malignant (cancerous), and 53,000 will be benign (noncancerous). In addition, more than 200,000 people will be diagnosed with brain tumors that develop when cancer cells from other parts of the body travel through the bloodstream to the brain. Called metastatic brain tumors, these cancers typically spread from tumors of the lung, breast, skin, colon, or kidney.

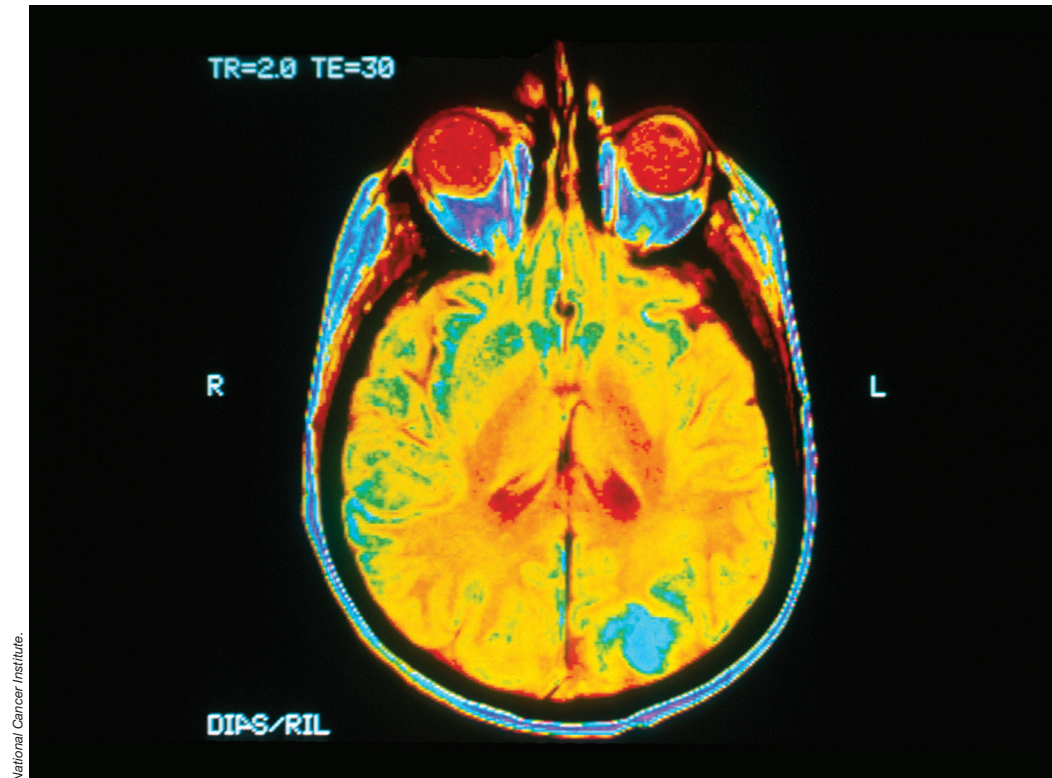
Regardless of its origin, a tumor, or any space-occupying lesion in the brain, can be lethal — thus surgical removal is required for survival.

Types of brain tumors are named according to the kind of cell from which they arise and the brain area where they develop. For example, many brain tumors are called gliomas — a general term for tumors that arise from the glial cells that support and protect neurons in the brain. The most common form of brain *cancer* is a glioblastoma — a proliferation of immature glial cells. The most common type of primary brain *tumor* is a meningioma: a benign tumor arising in the meninges, thin layers of tissue that cover the brain.

Symptoms of a brain tumor vary with its location and size and also differ among people. In some cases, a tumor causes general symptoms such as headache, due mainly to the pressure a tumor exerts on the brain. Or, a tumor located in a part of the brain controlling vision can cause difficulties with sight. In other cases, a tumor can damage healthy tissue as it grows. For example, as gliomas grow, they release toxic amounts of glutamate, which can destroy nerve cells near the tumor and cause seizures.

Several treatments — including surgery, radiation, targeted treatments, and chemotherapy — can be used alone or in combination to treat brain tumors. The goal of the treatments is to remove or shrink brain tumors to relieve pressure on the brain, as well as eliminating or reducing symptoms such as seizures and headaches.

If a tumor can be accessed without injuring nearby areas of the brain, surgery is usually the first step. Brain tumors can be removed with conventional techniques such as a craniotomy,



This brain scan shows a tumor in the brain's left occipital lobe, seen here in bright blue. Knowing exactly where a tumor is located can help doctors start the proper treatment.

in which the skull is opened and as much tumor as possible is removed. Another type of treatment for some tumors uses radiation. For this technique, called stereotactic radiosurgery, a high dose of radiation is aimed precisely at the tumor. A few radiation treatments can reduce or eliminate the tumor while sparing healthy tissue nearby. More recently, tumors are treated by multiple beams of ultrasound focused precisely to intersect exactly at the site of the tumor. These interventions can be carried out painlessly in awake patients inside imaging machines that visualize the tumor in the brain.

Following conventional surgery, doctors usually prescribe steroid medications to reduce swelling in the brain. Reduced swelling helps alleviate symptoms such as seizures, memory problems, or confusion that can occur after brain surgery. In patients with

cancerous brain tumors, radiation may be administered to surrounding brain areas to help eliminate any cancer cells that remain in the brain after surgery. People with cancerous brain tumors can also be given chemotherapy to prevent growth or regrowth of their tumors. In the past decade, researchers have developed new ways to administer chemotherapy that allow medication to be delivered directly to the brain (tumor), rather than traveling through the body before reaching the brain. For example, after surgical removal of a brain tumor, small wafers containing anticancer drugs can be implanted in the space previously occupied by the tumor. Over time, the wafers slowly dissolve and release the chemotherapy drugs to nearby areas.

Researchers have also been studying various promising treatments that target specific cell mechanisms thought



to be important to cancer cell growth. These targeted treatments zero in on genes and other cell mechanisms that fuel cancer cell growth, while sparing healthy tissues and causing less severe side effects than those that occur with conventional radiation or chemotherapy. For example, medications that help block formation of blood vessels are already being used to treat glioblastomas. Blocking tumor blood vessel formation is a key strategy in treating glioblastomas, because these tumors form strong networks of vessels that feed tumor growth.

Researchers are also testing ways to stimulate the ability of the body's own immune system to stop tumor growth — an approach called immunotherapy. For example, promising research is using substances called checkpoint inhibitors, which interfere with the signals some tumors send to inhibit the immune system's ability to block tumor growth.

Another promising area of research involves gene therapy. This technology identifies the genetic components that promote tumor growth and then interferes with their ability to work. Research is currently underway on a number of different gene therapies aimed at killing tumor cells and suppressing their growth-promoting genes.

Other approaches also under development focus on targeted delivery of antibodies, toxins, and growth-inhibiting molecules that can attach specifically to tumor cells and interfere with their growth. Researchers are also exploring the role of stem cells in both the development and treatment of brain tumors. Stem cells are undifferentiated, or unspecialized, cells with the potential to develop into any of a number of specialized cells, such as neurons. Normally, regulatory processes

prevent mature, specialized cells from dividing and spreading; *cancer* cells escape these regulations. Understanding the normal processes that allow stem cells to mature will allow researchers to understand what might be going awry in cancer cells.

### NEUROLOGICAL TRAUMA

Traumatic brain and spinal cord injuries can lead to significant disabilities and death. In the United States, an estimated 1.7 million people sustain traumatic brain injuries (TBI) each

(primarily gunshot wounds), and injuries due to participation in sports and recreational activities. Death rates among people with spinal cord injuries are significantly higher during the first year after the injury, especially people whose injuries cause severe neurological impairments.

Few effective remedies have been found to repair damage incurred by head and spinal cord injuries; however, new methods have come to light for preventing damage that develops after the initial injury. In addition, there are

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**U**nderstanding the normal processes that allow stem cells to mature will allow researchers to understand what might be going awry in cancer cells.

year. Of those, 275,000 are hospitalized, and about 52,000 will die as a result of TBI. Falls are the leading cause of all traumatic brain injury, and motor vehicle/traffic injury is the leading cause of TBI-related death. The direct medical costs and indirect costs of TBI, such as lost productivity, are estimated to be more than \$60 billion a year in the United States.

Each year, about 17,000 people suffer spinal cord injuries in the United States, and an estimated 282,000 people currently live with spinal cord injuries. Vehicle crashes are the leading cause of spinal cord injury, followed by falls, acts of violence

ongoing efforts to support better rehabilitation techniques as well as research into the regeneration and repair of injured tissue.

### Traumatic Brain Injury

Widespread use of computerized tomography (CT) and magnetic resonance imaging (MRI) techniques has afforded opportunities to observe the extent of tissue damage in TBI and determine its medical management. Traumatic brain injuries are caused by bumps, blows, or jolts to the head that cause multiple minuscule bleeds or by penetrating head injuries that directly destroy brain tissue. TBI can

be “mild,” such as concussion — a temporary disruption in brain activity — or “severe.” TBI can cause bruises in the brain, massive bleeding inside the brain, cuts in the brain tissue, direct nerve damage, and death of nerve cells. Brain injury can trigger swelling, fever, seizures, and other neurological impairments. Even mild TBI can cause damage to neurons, which release pro-inflammatory factors that initiate and sustain an inflammatory response.


People such as professional football players or boxers, who sustain repeated concussions and other brain trauma, might develop a progressive degenerative brain disease called chronic traumatic encephalopathy (CTE). CTE occurs when repeated head trauma triggers degeneration of brain tissue; this process includes a buildup of abnormal proteins, which can begin months, years, or even decades after the last brain trauma. Symptoms associated with CTE include memory loss, confusion, impaired judgment, impulse control problems, aggression, depression, and, eventually, progressive dementia.

Most people with mild brain injuries, such as concussions, recover fully in a short period of time. Yet a study of college ice hockey players who had concussions showed that their brain volume had decreased two weeks after the concussion, a change that lasted at least two months. Rest and avoidance of physically demanding activities give the brain time to heal and are key aspects of recovery. People who arrive in the emergency department with a severe head injury are carefully monitored for bleeding or swelling that puts pressure on the brain. Treatments for increased pressure inside the skull include removing an amount of water fluid from injured and inflamed brain tissue.

Severe TBIs can cause bruising on the surface or within the brain. The bruising might cause blood to leak from vessels and contact brain tissue directly, which can be toxic to brain cells. Pressure often increases in the injured area, compresses the blood vessels, and reduces critical blood flow to the injured tissues. If fluid removal and medications fail to decrease pressure on the brain, part of the skull can be drilled open or removed to relieve pressure on the brain. In extreme cases of TBI, bruising in the brain can contribute to development of a seizure disorder called post-traumatic epilepsy.

Once a person with a brain injury is stable, the long road to recovery begins. Physical and occupational therapy are used to help people regain lost functions such as speech and movement. A wide variety of medications can be used to treat other symptoms of TBI such as pain, seizures, muscle spasms, sleep disorders, depression, and anxiety.

### Spinal Cord Injury

 Like TBI, spinal cord injuries (SCI) can permanently damage nerve cells and cause a wide range of disabilities — including various degrees of paralysis. Methylprednisolone, a steroid drug, is the only treatment for SCI currently approved by the U.S. Food and Drug Administration (FDA). This medication appears to reduce damage to nerve cells and decrease inflammation near the site of the SCI. If administered within eight hours of injury, it can be effective in treating spinal cord injuries in some people.

There is no cure for spinal cord injuries, but scientists are investigating new ways to repair damaged spinal cords. These include protecting surviving nerve cells from further damage,

replacing damaged nerve cells, stimulating the regrowth of axons and targeting their connections, and retraining nerve circuits to restore bodily functions. In addition, scientists constantly search for new methods for rehabilitating patients with SCI and improving their quality of life. Rehabilitation focuses on physical therapy to strengthen muscles and improve mobility. Occupational therapy focuses on enhancing fine motor skills, such as the skills needed to write or type. Electrical stimulation is sometimes used to help restore function to muscles affected by the injury.

Scientists have also discovered that new nerve cells can be born in an adult brain. However, these new cells do not seem to help an injured brain repair itself, so studies are ongoing to determine how to jumpstart the pathway that stimulates the birth of new nerve cells. Stem cells, some even derived from a patient's own tissues, might be able to start a new population of cells that are able to produce many cell types, nerve cells among them. Researchers are also working to understand how certain neurochemical and cellular barriers that prevent regrowth and repair can be overcome and how the newly born cells can be induced to integrate into the injured circuit.

### NEUROLOGICAL ACQUIRED IMMUNE DEFICIENCY SYNDROME

In 2015, about 2.1 million people worldwide became infected with the human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS). Currently, an estimated 37 million people worldwide live with HIV. The vast majority live in eastern and southern Africa, and about 40 percent of people living with HIV are unaware



that they are infected with the virus. From 2008 to 2014, the estimated number of new HIV diagnoses in the U.S. fell by 18 percent, possibly due to targeted prevention efforts.

Globally, the number of people receiving treatment for HIV has increased dramatically in recent years, particularly in developing countries. In 2015, 17 million people living with HIV were receiving life-prolonging antiretroviral treatment. In 2010, only 7.5 million people were receiving this treatment.

Although HIV targets the immune system, the nervous system can also be affected. More than half of people with HIV develop HIV-associated neurocognitive disorders (HAND). HAND causes mental problems ranging from mild difficulty with concentration, memory, coordination, and complex decision-making to progressive dementia, called AIDS dementia. Even people who receive antiretroviral treatments can develop mild symptoms of HAND.

The mechanism behind the development of HAND is unclear. Most scientists speculate that certain proteins in the virus itself, or proteins released by cells infected with HIV, cause nerve damage leading to the disorder. Whatever the mechanism, HIV infection appears to be the key player in HAND, because antiretroviral treatment may prevent or reverse it in many people.

Mild forms of HAND have been reported in about one-third of people with HIV infection who have no other symptoms. In advanced disease, people can develop increasing problems with concentration and memory as well as an overall slowing of their mental processes. At the same time, they might experience leg weakness and loss of balance. MRI and CT scans show brain shrinkage in people with


HAND. Examination of the brains of people who die with AIDS sometimes reveal loss of nerve cells, white matter abnormalities, and damage to cellular structures involved in cell-to-cell communication. Inflammation and vessel disease can also be present.

Recently, research has indicated that “cocktails” of three or more antiretroviral (ARV) drugs active against HIV can reduce the incidence of AIDS dementia. These treatments can also reverse brain abnormalities caused by HIV.

Another neurological problem commonly developed by people with HIV is peripheral neuropathy. Peripheral neuropathy involves injury to the nerves of the extremities and causes discomfort ranging from tingling and burning to severe pain. HIV is believed to trigger the injury, and certain ARVs can cause the neuropathies or make them more frequent and serious. More than half of people with advanced AIDS have neuropathy.

Despite remarkable advances in new therapies, AIDS cannot be cured, and some of its neurological problems do not respond to treatment. In addition, people living with HIV are particularly vulnerable to certain infections and cancers because the virus weakens their immune system. Fortunately, combination ARVs have greatly reduced the incidence of most of these infections, as well as some of the neurological problems associated with AIDS.

### MULTIPLE SCLEROSIS

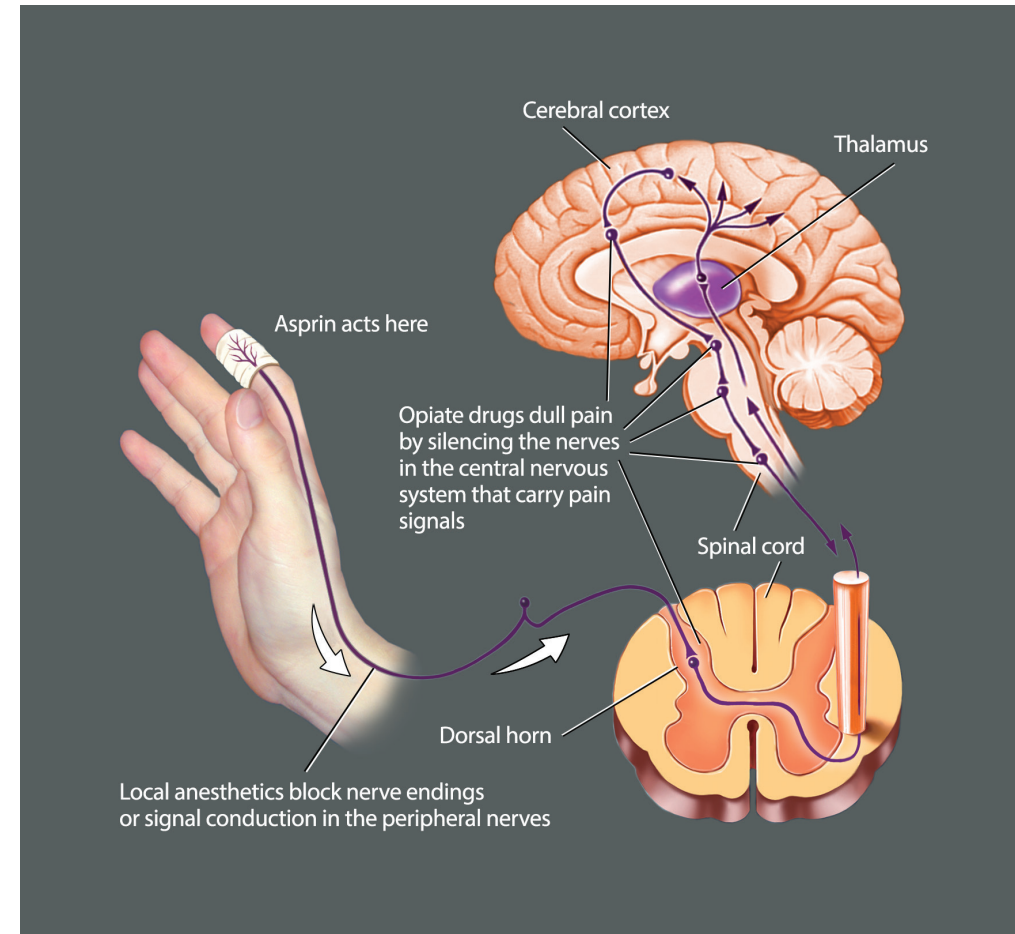
 Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, usually diagnosed in people between 20 and 40 years of age. For unknown reasons, the immune system of a person with MS launches an attack against its own

central nervous system, including the brain, spinal cord, and optic nerves. The target of this attack is the myelin sheath, a fatty substance that forms a protective coating around nerve fibers; the nerve fibers themselves can also be affected. As a result of the attack, the damaged myelin and the accompanying inflammatory cells form lesions, patches of scar tissue that look like sclerosis.

In MS, the patches of disease activity appear in multiple areas of the central nervous system, which is why the disease is called multiple sclerosis. Damage to the myelin sheaths and nerve fibers interferes with transmission of nerve impulses within the brain and spinal cord, as well as their communication with other body areas. The effects of MS are often compared to the loss of insulation around an electric wire and damage to the wire itself, interfering with signal transmission. Damage can occur in the white (myelin) and gray (nerve cell bodies, glia, etc.) matter of the brain.

The cause of MS is unknown, but there are some hints that a genetic factor is involved. Siblings of people with MS are 10 to 15 times more likely to develop MS than people with no family history of the disease. The risk is particularly high for an identical twin of someone with MS. Oddly, the disease is as much as five times more prevalent in temperate climates, such as the northern United States and northern Europe, than in the tropics. Although Caucasians run a higher risk than other races of developing MS, the prevalence of MS indicates that risk is shaped by both genetic and geographical factors.

Damage to the nervous system in people with MS can cause a wide array of symptoms. The spinal cord,



At the location of an injury, the body produces prostaglandins, which increase pain sensitivity. Aspirin blocks the production of prostaglandins, thus preventing pain. Opiate drugs act in the brain and spinal cord to block pain signals.

cerebellum, and optic nerve are commonly affected by MS, so problems often arise in functions controlled by those areas. Symptoms include numbness, clumsiness, and blurred vision. Other symptoms are slurred speech, weakness, pain, loss of coordination, uncontrollable tremors, loss of bladder control, memory loss, depression, and fatigue.

When a person is diagnosed with MS, treatment options depend on the type of disease that is present. Specialists classify MS as one of three categories: relapsing-remitting MS, characterized by flare-ups of new or worsening symptoms followed by complete or partial remission of symptoms; primary-progressive MS, defined

by progressive worsening of symptoms after disease onset; and secondary-progressive MS, in which relapsing-remitting disease has transitioned into a progressive form of disease that worsens over time.

Within each category, MS is further classified as “active” or “not active.” While the categories refer to the progression of symptoms, the classification refers to presence (“active”) or absence (“not active”) of new areas of inflammation, seen on MRI scans. In some cases, MS is defined as “stable,” meaning that symptoms are stable and no activity appears on routine MRI scans.

MS has no cure, but an increasing

number of medications are becoming available or are under investigation. Since 2010, six new or revised disease-modifying therapies have been approved for use in people with MS. In addition, several medications can now help control the inflammation and immune system attacks in relapsing-remitting MS. Steroid drugs, specifically glucocorticoids, reduce the inflammation and might also help shorten acute attacks. Medications and therapies are also available to control symptoms such as muscle stiffness, pain, fatigue, mood swings, and bladder, bowel, or sexual dysfunction.

### CHRONIC PAIN

Pain can be acute — a short-lived side effect of injury or disease — or a chronic condition that persists for weeks, months, or even years. For some people, pain is the disease itself. Pain affects more Americans than diabetes, heart disease, and cancer combined, afflicting the lives of approximately 100 million Americans. Back pain, severe headache or migraine pain, and facial ache are the most common culprits. In the US, the cost of healthcare, disability, and lost productivity due to pain ranges from \$560 billion to \$635 billion annually. Chronic pain can trigger a cascade of psychological processes that lead to changes in perception, attention, mood, motivation, learning, and memory. Increasing evidence indicates the value of a combination of treatments involving drugs, behavior, physical therapy, and other modalities to fully manage chronic pain.

### Treating Pain

Anesthesia is used to prevent pain during a wide variety of medical procedures and surgery. Local anesthetics

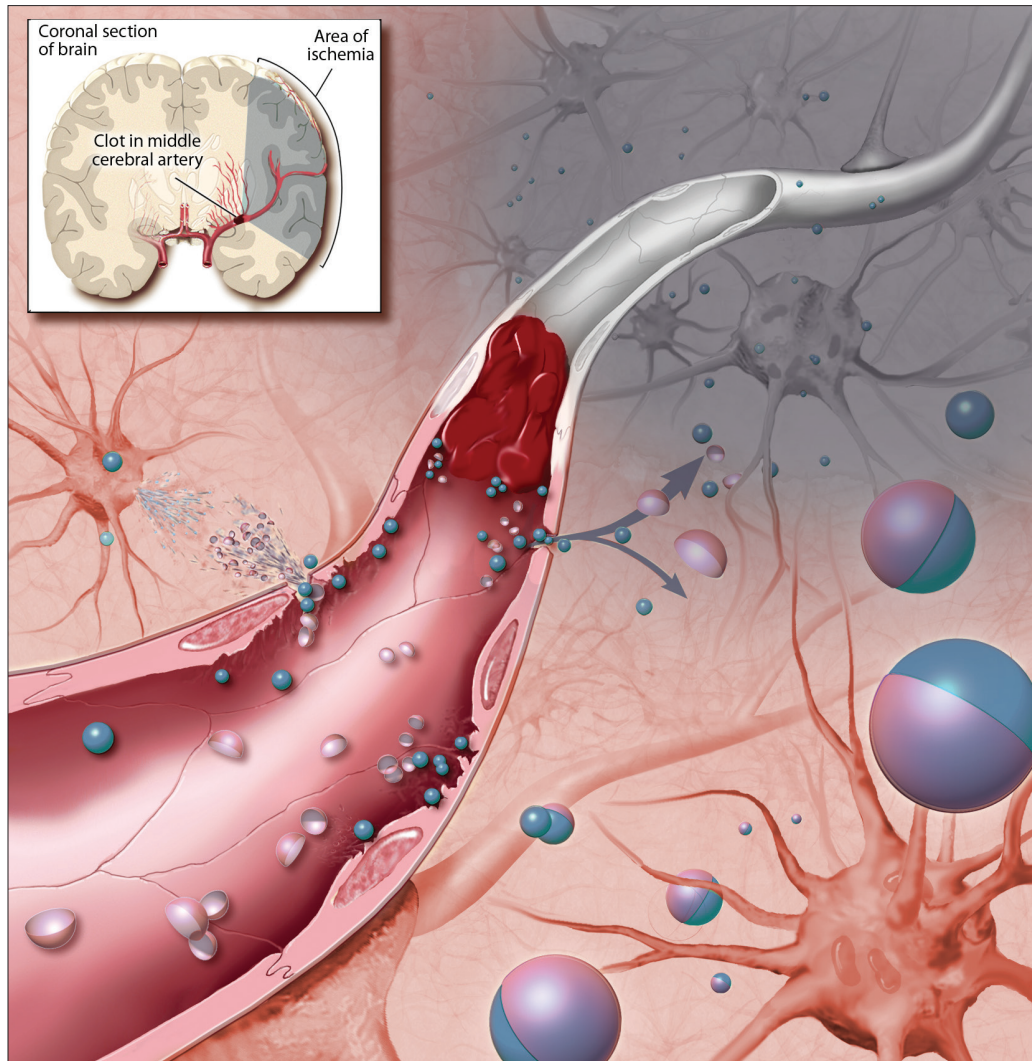


work by temporarily blocking pain receptors. Commonly used anesthetics include procaine (Novocain) and lidocaine.

Once pain occurs, four main types of painkillers may be used to relieve it: aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen; opioids (powerful drugs that act directly on the nervous system) such as morphine and codeine; antiepileptic agents such as gabapentin; and antidepressants such as amitriptyline.

NSAIDs reduce inflammation and are effective for postoperative pain and for pain caused by inflammation such as arthritis. NSAIDs are also useful for treating the mild or moderate pain of headaches, sprains, or toothache. NSAIDs work by inhibiting substances that trigger the synthesis of pro-inflammatory and pain-producing chemicals (such as prostaglandins). Moderate pain is often treated by combining a mild opioid like codeine with aspirin or another NSAID.

Opioids, often used for severe pain, work directly in the central nervous system by attaching to receptors on nerve cells. These drugs not only reduce feelings of pain but also produce feelings of euphoria. While highly effective against pain, opioids do have many serious side effects, such as slowing a person's breathing. Most importantly, they are highly addictive. The current opioid epidemic in the United States is caused, in part, by the facility to obtain opioid prescriptions and poor pain management of chronic pain. The brain of a person suffering from chronic pain undergoes major changes, and the solution for this complex problem should include more than pharmaceuticals.



A stroke occurs when a blood vessel bringing oxygen and nutrients to the brain bursts or is clogged by a blood clot. Without blood, cells in the brain start to die within minutes. It can also cause dangerous molecules called free radicals to escape, which can further damage brain tissue. The effects of a stroke, such as movement or speech problems, depend on where in the brain the stroke occurs.

Psychological therapies such as cognitive behavioral therapy and biofeedback can also be used to stimulate relaxation and release muscle tension, thereby helping reduce the effects of chronic pain. Psychological treatments can also help people manage changes in mood, perception, memory, and other psychological factors often affected by chronic pain.

Antiepileptic and antidepressant drugs are generally used to treat nerve pain that results from injury to

the nervous system. Nerve damage and pain (neuropathy) can be due to chronic high blood sugar levels; viruses, such as shingles; phantom limb pain; or post-stroke pain.

### The Body's Pain Control System

Studies of the body's pain control system have shown that our bodies produce their own naturally occurring opioids, called endorphins. Scientists have also identified the receptors through which opioids work to

decrease pain. The finding that opioid receptors are concentrated in the spinal cord led to the use of injections of morphine and other opioids into the cerebrospinal fluid (CSF) surrounding the spinal cord. Remarkably, these injections enabled profound pain control without causing paralysis, numbness, or other severe side effects. This technique is commonly used to treat pain after surgery. In addition, some patients are given implanted opioid pumps to enable long-term treatment of severe chronic pain.

Scientists have identified many molecules that are involved in the body's pain response. Developing drugs that target these molecules could have great benefit for treating patients who experience acute or chronic pain.

Advances in brain imaging techniques have also broadened our understanding of how the brain perpetuates chronic pain after a painful stimulus has been removed and injuries have healed. As a result, pain researchers are moving toward a whole-brain approach for their studies, developing new technologies and techniques that could lead to better diagnosis and more effective treatment of chronic pain.

### STROKE

Each year, nearly 800,000 people in the United States suffer a **stroke** — an interruption in blood flow to the brain due to a ruptured blood vessel or a blood clot. Of these, about 600,000 are first strokes. Strokes are a leading cause of long-term disability in the United States, costing about \$33 billion each year, including the costs of health care services and medicines to treat stroke, and missed days of work. More than 130,000 Americans die of a stroke each year.

Risk factors for stroke include obesity, physical inactivity, and heart disease. Controlling these factors by maintaining a healthful weight, exercising, avoiding excessive alcohol intake, and taking medications for stroke-related physical problems such as high blood pressure, can reduce the risk of having a stroke. There is also a genetic component in stroke risk, especially evident if a parent has suffered a stroke by age 65. To date, several candidate genes have been suggested, but increased stroke risk is most likely due to multiple genetic factors.

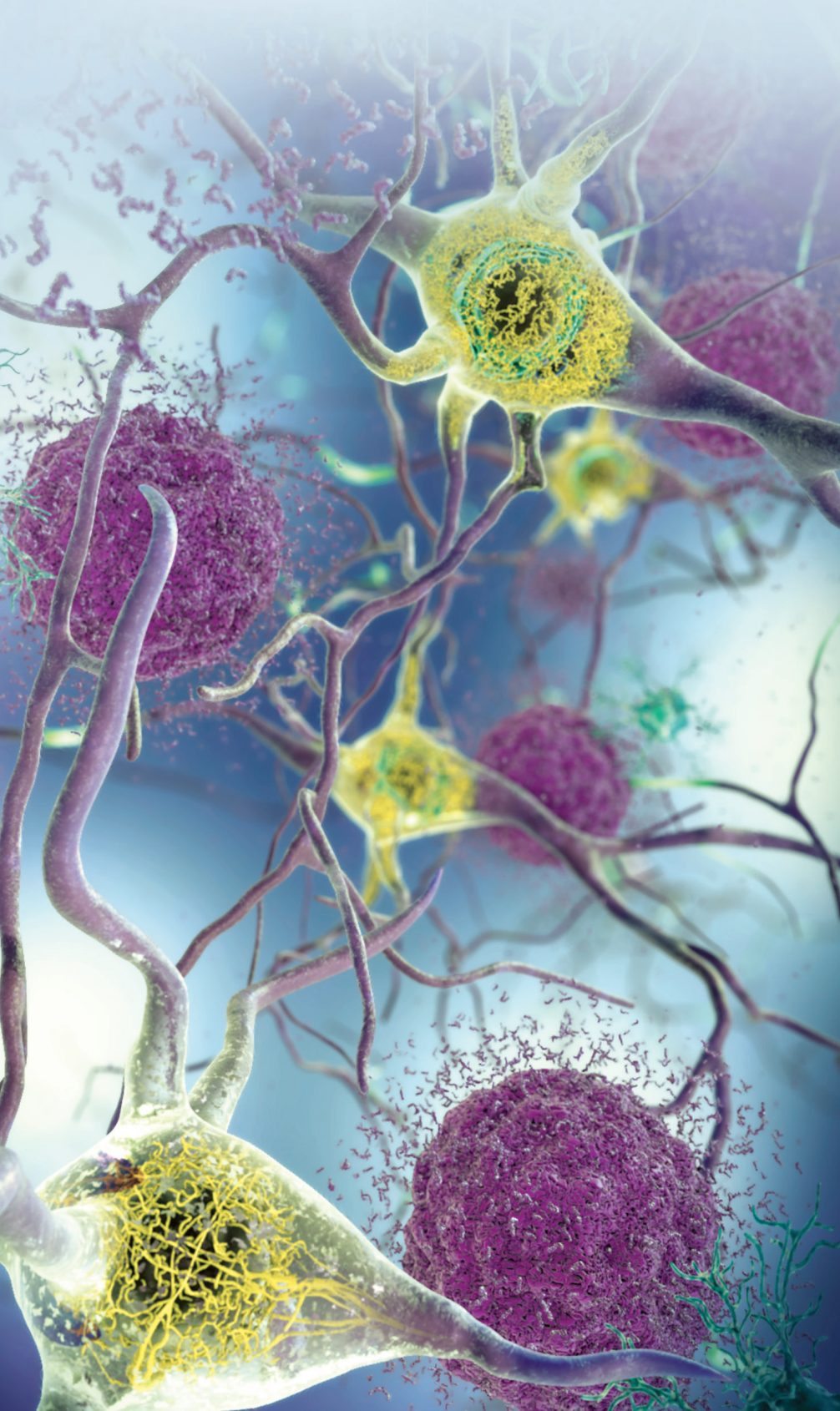
Until recently, treatments for a stroke did not go far beyond physical or speech therapy. Today, however,

clot-dissolving medications are a standard treatment. Tissue plasminogen activator (tPA), a clot-dissolving drug approved by the FDA in 1996, helps to break down blood clots and open blocked blood vessels. tPA can restore circulation before oxygen loss causes permanent brain damage; given within three hours of a stroke, its use often limits brain damage. In addition, surgery to clear clogged arteries and other treatments targeting heart disease can help prevent strokes. Anticoagulant drugs also help by reducing the likelihood of clots forming elsewhere in the body and traveling to the brain, causing a stroke.

Research is underway to find new methods for preventing and treating strokes. Some drugs have been shown to be effective at preventing damage to the nervous system, including nerve cell death following a stroke. Another promising research area is the use of neural stem cells to improve recovery after a stroke. Preliminary research suggests that injection of stem cells helps promote recovery, even when given several days after a stroke. Administering growth-stimulating substances along with the stem cells might enhance the benefits of the stem cell transplant. ■



# Neurodegenerative Diseases



**N**eurodegenerative diseases all involve a progressive destruction of nerve cells. They more often affect older people, and are likely to become more common as life expectancy rises due to improved medical care — not only in the U.S. but worldwide. From 2015 to 2060, the number of people 65 and older in the U.S. is expected to jump from 48 million (15 percent of the population) to 98 million (nearly 25 percent of the population). As scientists look ahead, the field of neurodegenerative disease promises to become increasingly important.

In the past two or three years, articles in *Nature*, *Scientific American*, and other major science publications have discussed the intriguing possibility that many, if not all, neurodegenerative diseases involve misfolded proteins called prions. You may have heard of prions in the context of “mad cow disease.” Scientists now wonder if prions also contribute to more familiar disorders such as Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis (ALS, known as Lou Gehrig’s disease). In the case of prions, a protein’s normal 3-D structure has somehow been altered, so that it no longer functions correctly. Worse still, the misfolding can cause proteins to collect in irregular clumps that can damage cells. Is this really the cause of neurodegenerative diseases? Many scientists are asking that question. As you read this chapter, remember that there’s still *a lot* to learn in this field — and each step toward understanding normal brain function aids the development of prevention or treatment for thousands of people in the future.

## ALZHEIMER’S DISEASE

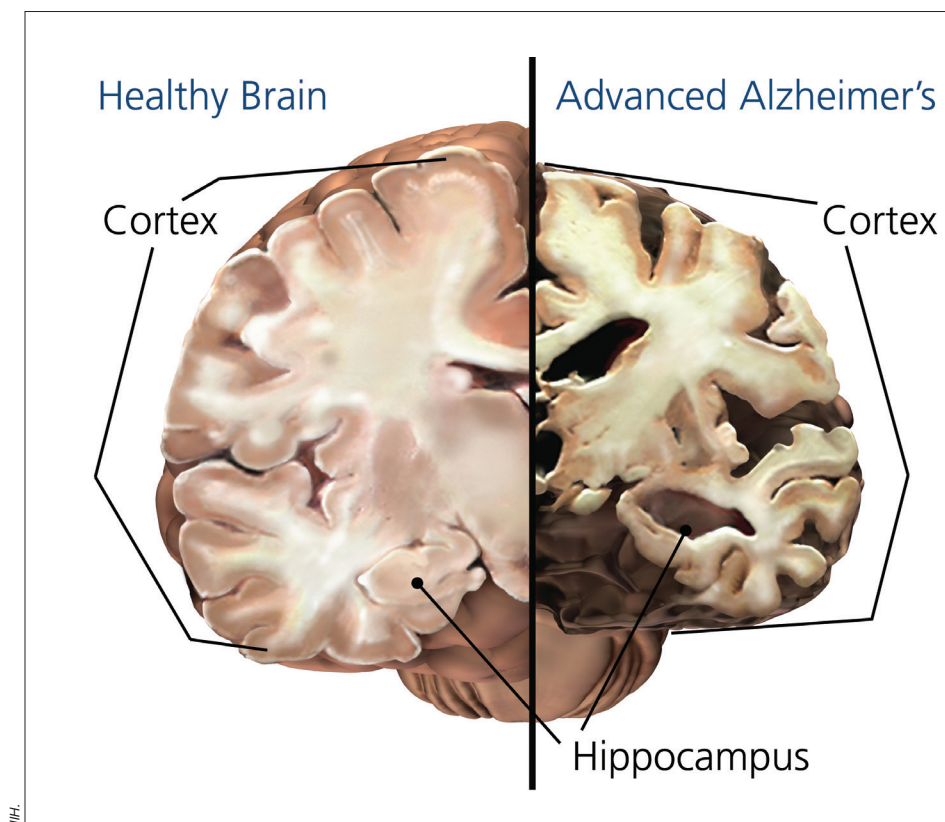
Alzheimer’s disease is a form of **dementia** that is eventually fatal.

Over time, a person’s brain undergoes irreversible, progressive degeneration that impairs his or her memory and reasoning. In the late-onset form of Alzheimer’s, patients display symptoms in their mid-60s or later, with symptoms becoming more severe with age. In early-onset forms of the disease, patients can start to experience symptoms in their 30s. Fortunately, early-onset Alzheimer’s occurs in less than 10 percent of cases of the disease.

## Prevalence and Impact

Alzheimer’s is the most common cause of dementia in older adults. Of the 47 million people with dementia worldwide, approximately 60 to 70 percent have Alzheimer’s. The disease affects 5 to 8 percent of all people over 65 years of age, 15 to 20 percent above 75, and 25 to 50 percent of those over 85. It’s estimated that more than 5 million people in the U.S. suffer from the disease; however, the actual number could be as high as 11 million, including many who are now asymptomatic. Conservative estimates are that Alzheimer’s will affect 13.8 million people in the U.S. by 2050.

In 2014, Alzheimer’s was the sixth leading cause of death in the U.S., accounting for 93,541 deaths. Deaths rose from 16.5 per 100,000 people in 1999 to 25.4 per 100,000 in 2014, but Alzheimer’s-related deaths are believed to be severely underreported. Some patients go undiagnosed, and others have dementia-related conditions (such as aspiration pneumonia) rather than Alzheimer’s listed as their primary cause of death. Some estimate that the number of Alzheimer’s-related deaths might be six to seven times higher than reported. If this is accurate, it would be the third leading cause of death among older Americans.



Alzheimer’s disease damages and destroys the connections between cells, causing widespread cell death. The damage causes problems with learning, memory, and thinking, and is eventually fatal.

## Symptoms of Alzheimer’s Disease

Alzheimer’s symptoms are classified by the disease’s progression. *Early stage* symptoms include memory problems (greater than expected in healthy people of a similar age), difficulty concentrating or finding appropriate words, problems judging and calculating, and disorientation in time or place. Most people are not diagnosed until the *mild stage* when symptoms include personality and behavior changes, wandering and getting lost, repeating questions, losing and placing objects in odd places, taking longer to complete daily tasks, and having trouble handling money and paying bills. In the *moderate stage*, some patients have trouble recognizing family and friends; inability to

learn new things; problems coping with new situations; difficulty getting dressed or performing other multistep tasks; hallucinations, delusions, and paranoia; and impulsive behavior. In the *severe stage*, patients are completely dependent on others for care, as their body begins shutting down. Their communication is reduced to groans, moans, and grunts; sleeping increases; and they become bedridden. Other severe stage symptoms include weight loss, seizures, difficulty swallowing, skin infections, and a lack of bowel and bladder control.

## Diagnosing Alzheimer’s

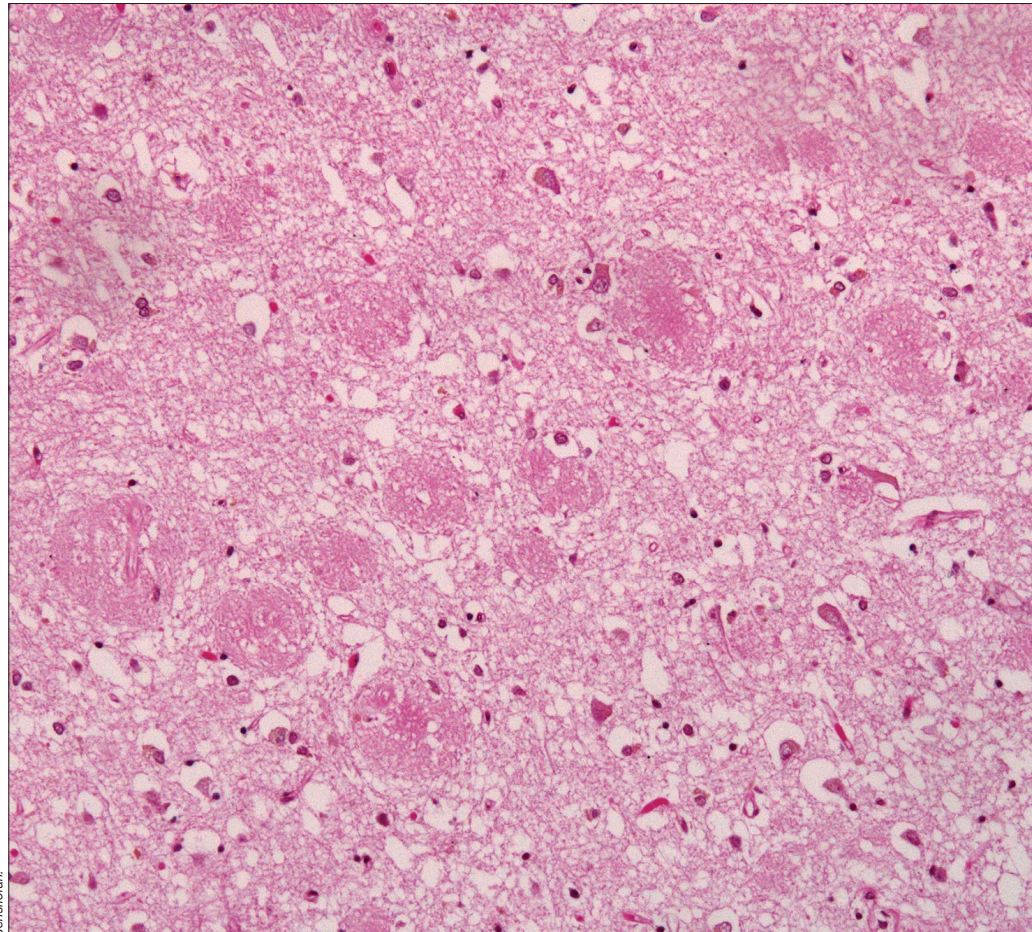
Alzheimer’s dementia is most commonly diagnosed by a physician asking the patient and a family member or friend about the patient’s



health, medical history, ability to perform daily activities, and changes in behavior and personality. Next, the physician conducts tests on memory, problem-solving, attention, counting, and language. Even if mental deficits are found, including dementia, the condition still might not be Alzheimer's. Similar deficits could be due to other conditions including Lewy body disease, frontotemporal dementia, Parkinson's disease, stroke, a tumor, sleep disturbances, side effects from medication, or infection.

Researchers are searching for a defining biomarker for Alzheimer's — a specific indicator that can physically identify a disease. Two candidate primary biomarkers are amyloid-beta (also called beta-amyloid) and tau. In Alzheimer's, amyloid-beta forms extracellular senile plaques, also known as neuritic plaques. These malformed clumps contain a fragment of the preliminary protein. In addition, tau, a type of protein that normally stabilizes the cellular skeleton, forms neurofibrillary tangles inside neurons. Both abnormalities are found in the brains of people with Alzheimer's but, at present, no definitive biomarker can diagnose the disease in its early stages. A diagnosis can only be confirmed by postmortem examination.

Some potential diagnostic methods for Alzheimer's include brain imaging, genetic risk profiling, and examining cerebrospinal fluid or blood. Neuroimaging, among the most promising areas of research focused on early detection, uses a mildly radioactive chemical marker that binds to amyloid plaques and shows their location in PET scans of living people. Starting in 2012, the FDA began approving the use of molecular imaging tracers to evaluate possible Alzheimer's



Amyloid plaques, seen here as dark spots against pink brain tissue, are a hallmark of Alzheimer's disease. Scientists are still investigating whether plaques cause the disease or are merely a symptom of it.

disease or other causes of dementia. To date, the FDA has approved the use of three tracers — florbetapir F-18, flutemetamol F18, and florbetaben F18 — to detect amyloid-beta in the brain. However, neuritic plaques are also present in the brains of people with no dementia or Alzheimer's, so these scans are not used for routine evaluation.

### Causes and Pathology

The causes and mechanisms underlying Alzheimer's disease are not fully understood. Most forms are likely caused by a combination of heredity, environment, and habits. Evidence has been building that head trauma is one contributing factor, based on

a condition known as chronic traumatic encephalopathy (CTE) seen in football players and other athletes who play contact sports. Those with CTE typically show a buildup of tau protein in brain cells; some also have amyloid-beta deposits, but this is less common.

It appears that patients experience the first cellular changes associated with Alzheimer's a decade or more before becoming symptomatic. The neuronal transport system shows damage early in Alzheimer's. Patients produce fewer neurotransmitters — chemical molecules that are released from an axon terminal, travel across gaps called synapses, and transmit signals to another neuron, organ, or other tissue

type. In Alzheimer's disease, axons and synapses are damaged and ultimately destroyed. Damage to neuronal transport impairs attention, memory, learning, and higher cognitive abilities. While the cause is unknown, neuritic plaques and neurofibrillary tangles are the two prime suspects. Plaques consist of amyloid-beta, which is formed from malformed clumps of a fragment of amyloid precursor protein (APP), a fibrous protein often found at neuronal synapses. In its soluble form, amyloid-beta can bind strongly to neural receptors, which initiates the erosion of synapses. Evidence indicates that this soluble form is highly synaptotoxic, while the insoluble form (which has low toxicity) tends to aggregate, and is found in much higher concentrations than the soluble form. Some research suggests that the highly toxic, soluble form would be a better target for effective therapies.

The amyloid hypothesis is currently the dominant theory of how beta amyloid and tau protein interact to cause Alzheimer's. This hypothesis asserts that amyloid-beta starts a sequence of events that ultimately lead to Alzheimer's disease. Amyloid-beta accumulations first appear in the neocortex. Its neurotoxicity might be due to the fact that it exacerbates oxidative stress and damages the mitochondria, the cell's primary energy supply unit, initiating a cascade of neuronal dysfunction and cell death. The formation of neuritic plaques induces tau proteins to become defective and tangle into neurotoxic neurofibrillary tangles (hyperphosphorylated tau protein) within neuron cell bodies. (In contrast, normal tau protein stabilizes microtubules, which are crucial to axonal transport). Neurofibrillary tangles are generally first seen in the entorhinal

cortex and the hippocampus, regions responsible for short-term memory and for transferring those memories to longer-term memory.

Although amyloid-beta and tau accumulations are found in people with Alzheimer's, there is no definite proof that they cause Alzheimer's. We *do* have evidence that tau and amyloid-beta might interact before clumping into their recognized disease forms. Even before it aggregates, malfunctioning tau can damage cellular transportation by blocking the microtubule tracks. Also, high tau levels can impair the function of amyloid-beta.

It's possible that inflammation and the presence of obesity can trigger these protein changes, increasing Alzheimer's incidence and severity. Plaques and tangles are known to negatively interact with microglia, non-neural brain cells that act as immune cells for the central nervous system, and astroglia, which offer physiological regulation and structural support in the brain.

### Genetics of Alzheimer's

Early-onset Alzheimer's is a rare, dominantly inherited form of the disease. Dominant mutations in three genes — APP, PSEN1, and PSEN2 — cause early-onset familial Alzheimer's disease that starts when people are in their 40s and 50s. In late-onset Alzheimer's, the ApoE4 variant of the Apolipoprotein E (APOE) gene is a major genetic risk factor but not a determining one. The normal protein, ApoE, is mainly produced by astroglia or damaged neurons and helps clear soluble amyloid-beta from the brain.

In most people, Alzheimer's results from a combination of genetic and environmental causes. Several genetic associations have been noted. A mutant

C9ORF72 gene has been found in people with both early- and late-onset forms of the disease. This gene codes for a protein that regulates transportation in the intracellular matrix. The mutation was already known to play a major role in ALS and frontotemporal dementia, but recent studies show that it also disrupts a key mechanism for DNA repair.

The TOMM40 gene, which codes for a protein responsible for moving proteins into mitochondria, has a complex relationship with Alzheimer's. People with a longer version of the gene were shown to be either predisposed or resistant to Alzheimer's — depending on whether a parent had the disease. Among those with an afflicted parent, people with the longer version of the gene were more apt to develop dementia than those with the shorter allele; but among those with *no* afflicted parent, people with a longer allele displayed better memory than those with a shorter gene allele.

With the TREM2 gene, loss-of-function mutations cause a sequence of physiological events associated with Alzheimer's disease. This suggests a possible genetic link between early- and adult-onset variants — the homozygous loss-of-function mutation is associated with early-onset and the heterozygous variant with adult-onset. Normally, TREM-2 protein helps regulate removal of cell debris, clearing amyloid proteins, and suppressing inflammation in microglia.

Two large programs are currently studying early-onset Alzheimer's. The Dominantly Inherited Alzheimer Network project is funded by the U.S. National Institute on Aging with 10 research centers in Australia, the United Kingdom, and the United States; and the Alzheimer's Prevention



Initiative is studying an extended family of 5,000 with the disorder in Antioquia, Colombia.

### Treatments for Alzheimer's

The FDA has now approved five prescription drugs for treating Alzheimer's. While they relieve some symptoms, they do not cure or halt the disease. Three of these drugs are cholinesterase inhibitors: donepezil, galantamine, and rivastigmine. Cholinesterase inhibitors stop the action of acetylcholinesterase, an enzyme that breaks down the neurotransmitter acetylcholine. This increases the available amount of acetylcholine (involved in learning and memory), which counteracts the damaging effect of the disease on production of this neurotransmitter.

The fourth drug, memantine, is an NMDA receptor antagonist. Normally, NMDA receptors bind the neurotransmitter glutamate, allowing calcium to enter the neuron. In Alzheimer's, the damaged cells become overwhelmed with calcium, further damaging the neurons — a condition called neuronal excitotoxicity. Memantine blocks the flow of calcium through NMDA-receptor channels.

The fifth approved medication combines donepezil and memantine. Donepezil can be used in all stages of the disease, galantamine for mild to moderate stages, memantine for moderate to severe stages, and rivastigmine in all stages. The donepezil/memantine cocktail is used to treat moderate to severe Alzheimer's.

Several clinical trials are now underway to find new and better treatments for Alzheimer's. The Alzheimer's Forum currently lists 14 treatments that are in the later stages of clinical trials. Overall, however, there is a high failure

rate for drugs on the road to approval. Between 2002 and 2012, just 0.4 percent (1 in 245) of Alzheimer's drugs were approved. Potential drugs have often proved ineffectual because they don't target Alzheimer's early pathology. Online registries may improve the situation by hastening participant recruitment for clinical trials and looking for people at ever-earlier stages of disease progression. Trials are also broadening their pool of participants to include people likely to develop Alzheimer's but currently asymptomatic, as well as other participants at the pre-dementia stage.

Another treatment strategy, based on the amyloid hypothesis, uses the body's immune response to attack and clear amyloid plaques. Trials for active immunization (which trains the immune system to build a person's antibodies) and passive immunization (which transfers already active defensive antibodies without bolstering the person's own immune system) have both been explored. So far, however, these types of therapies have been inadequate for people with moderate to severe symptoms.

### PARKINSON'S DISEASE

Parkinson's disease is the second most common neurodegenerative disorder in humans. Like Alzheimer's, its incidence increases with age, with the average onset around age 60. About 5 million people in the world's 10 most populous countries have Parkinson's, and its frequency is expected to double by 2030. With 50,000 to 60,000 cases diagnosed annually in the U.S., the actual figures may be much higher — especially since early symptoms can be mistaken for normal aging and thus are not reported.

From 2000 to 2013, the age-adjusted death rates for those with

Parkinson's disease increased in the U.S. from 8.8 to 11.0 per 100,000 for males and from 3.9 to 4.8 per 100,000 for females. For reasons not yet understood, the disease is more prevalent in men than in women. Five to 10 percent of cases are "early-onset," occurring before age 50. Rarer still, patients with "juvenile Parkinsonism" may develop symptoms before age 20.

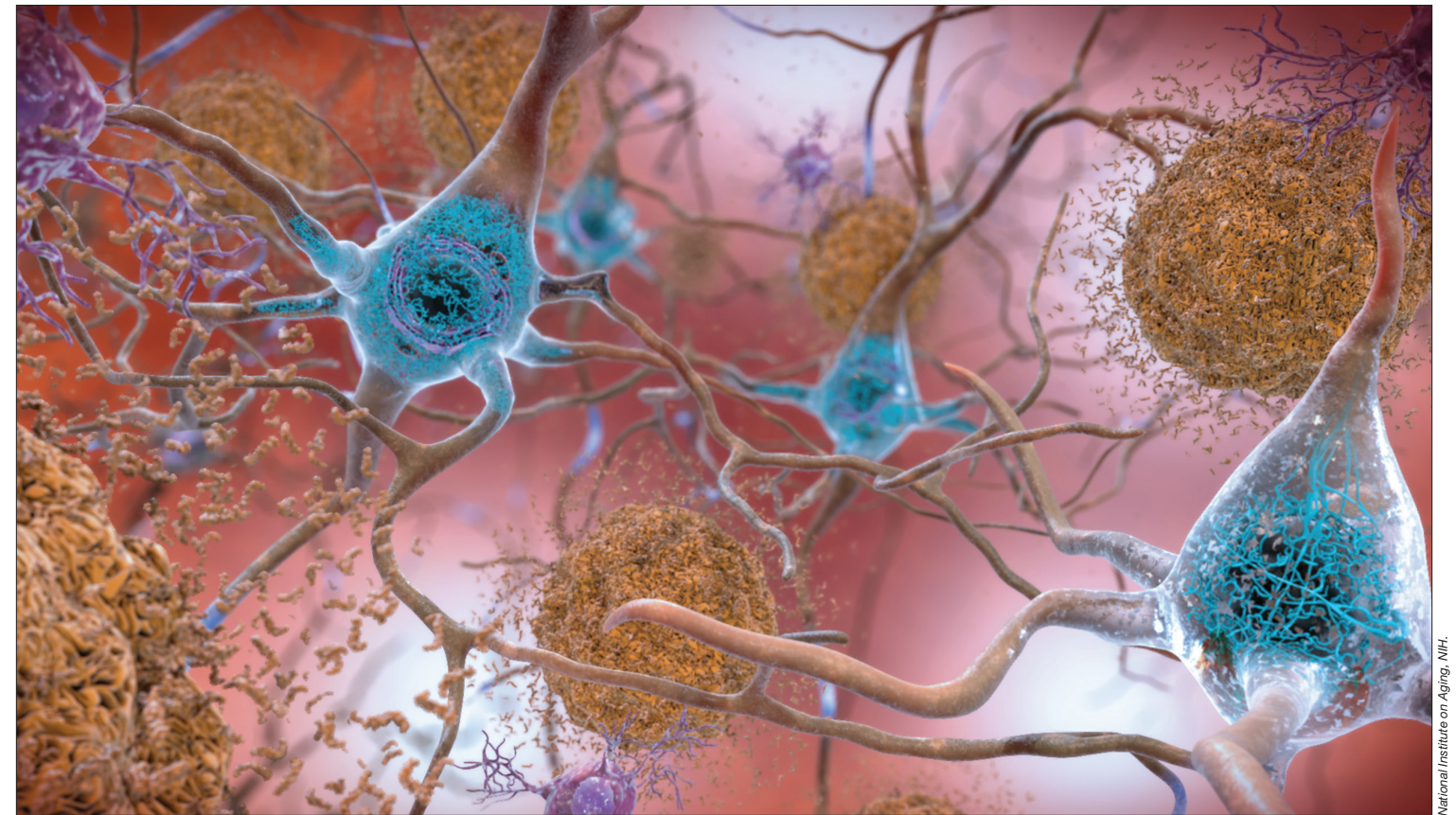
Estimates of the prevalence, or overall number, of Parkinson's patients vary widely, so incidence — the occurrence of new cases within a given time period (for example, per year) — is a better index for this disease. There is a higher incidence of Parkinson's in developed countries but the reason is unknown, although increased risk of the disease has also been reported in rural areas with increased pesticide use.

### Symptoms

At first, Parkinson's is characterized by motor problems: slow movement; muscular rigidity; poor coordination and instability; and shaking in hands, arms, legs, jaw, and face while at rest. As the disease progresses, the shaking, known as resting tremor, may worsen and interfere with walking, talking, and other simple tasks. Cognitive decline often occurs at later stages. Some people develop depression and other emotional changes, difficulty swallowing and chewing, skin problems, constipation or urinary problems, and sleeping problems. However, the rate and intensity of Parkinson's progression vary. Some people become severely disabled, while others have only minor motor disruptions.

### Pathology and Causes

Parkinson's is a motor system disorder caused by the loss of dopamine-producing cells neurons



Alzheimer's disease is associated with high levels of the beta-amyloid protein. This protein clumps together and forms plaques, which are pictured in brown. These plaques can build up between neurons and interrupt their activities. Tau proteins also accumulate and form tangles — seen in blue — within neurons, disrupting communications.

in the substantia nigra — a midbrain structure that is considered part of the basal ganglia. This brain region affects movement, reward, and addiction. At the cellular level, the death of neurons likely arises as a result of damage to mitochondrial respiration.

Some early-onset cases are linked to mutations in the PARK2 (or PRKN) gene, which codes for the protein "parkin." Most types of Parkinson's are caused by a combination of genetics and environment, but an estimated 15 to 25 percent of people with adult-onset Parkinson's have a known relative with the disease. Genes like alpha-synuclein (SNCA), repeat kinase 2 (LRRK-2), and glucocerebrosidase (GBA) also point to the importance of genetics as a causal factor. While

Parkinson's and Lewy body dementia are sometimes considered different disorders, Lewy bodies, accumulations of proteins in neuron bodies, have been implicated in both diseases. Lewy bodies are mainly composed of the protein alpha-synuclein entangled with other proteins, including neurofilament, ubiquitin, alpha B crystallin, and probably tau protein in neurofibrillary tangles. The Lewy body protein, alpha-synuclein, is involved in dopamine transport in the nervous system.

There is no definitive test for Parkinson's so, without accepted biomarkers, diagnosis is based on medical history and neurological tests that can include brain scans. Accurate diagnosis can be difficult, because some non-Parkinson's conditions display similar

symptoms. In the future, mitochondrial molecules could be a potential source of a Parkinson's biomarker.

### Research

Scientists can treat mice with the chemical MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) to create an animal model that can provide further insight into Parkinson's. In the body, MPTP metabolizes into the neurotoxin MPP<sup>+</sup> (1-methyl-4-phenylpyridinium), which causes a Parkinson's-like loss of cells in the substantia nigra and cognitive deficits. However, MPTP does *not* perfectly mimic the symptoms of human Parkinson's disease, including the motor deficits.

Research on using stem cells to replace damaged dopamine neurons



in Parkinson's patients has shown promise. There are two types of stem cells: the more flexible (and controversial) fetal tissue and induced pluripotent stem (iPS) cells, which are specialized adult (often blood or skin) cells that have been repurposed into a generalized embryonic state. There have been successful lab studies using iPS cells, and positive to mixed results in clinical studies with the fetal stem cells. A Kyoto University study, published in August 2017, transferred human iPS cells into the brains of monkeys treated with MPTP. Two years after this transplantation, the treated monkeys were shown to have healthy DA neuron integration, growth, and even functioning in the striatum.

#### Treatments



Treatment with levodopa (L-Dopa) temporarily relieves Parkinson's motor symptoms but does not slow disease progression. Ironically, the long-term use of L-Dopa can induce dyskinesia — abnormal and uncontrolled involuntary movements. Strategies for treating Parkinson's include gene therapy and targeting specific cellular molecules.

A surgical procedure called deep brain stimulation (DBS) is increasingly used to treat Parkinson's patients whose symptoms, including rigidity, tremor, slowed movement, and mobility problems, do not respond adequately to medication. The DBS technique implants a small neurostimulator device — like a pacemaker — that sends electrical impulses that interfere with and block brain signals that cause the motor symptoms of Parkinson's. Before implanting a neurostimulator into the brain, the neurosurgeon locates where the

patient's symptoms are originating, using MRI or CT scans. Most often, the problem areas in the brain are the thalamus, the subthalamic nucleus, and a portion of the globus pallidus (part of the basal ganglia). After the imaging, microelectrode recording — which involves a small wire that monitors the activity of nerve cells in the target area — is sometimes used to further localize problem areas in the brain. This approach has proven to be highly successful with a segment of patients.

**A**LS is also called Lou Gehrig's disease after the renowned New York Yankee first baseman, a famous patient with the disease.

One treatment still in the research stage is a strategy to break apart Lewy bodies. The idea is to use high hydrostatic pressure to break apart aggregated alpha-synuclein fibril plaques, like those found in Lewy bodies, and return the protein to its properly functioning form. Another novel approach to preventing Parkinson's was suggested by epidemiological studies that found that the disease is less common among coffee drinkers and cigarette smokers. If caffeine and nicotine offer protection, this could reflect some central action that benefits the brain's dopaminergic systems.

#### AMYOTROPHIC LATERAL SCLEROSIS

ALS is a group of progressive, ultimately fatal motor neuron diseases. ALS is also called Lou Gehrig's disease after the renowned New York Yankee first baseman, who was one of the most famous victims of the disease. ALS forced Gehrig to retire at age 36. Gehrig died two years later. ALS afflicts as many as 15,000 Americans, most between the ages of 50 and 70. Although men are slightly more likely than women to develop the disorder,

that difference lessens with increasing age. For unknown reasons, non-Hispanic whites are more likely than other ethnicities to develop ALS. Military veterans' likelihood of developing the disease is as much as 1.5 to 2 times higher than the rate in the general population — possibly due to exposure to environmental toxins like lead and pesticides.

#### Symptoms

Unlike the previously discussed neurodegenerative disorders, generally neither cognition nor personality is affected in individuals with ALS. Early ALS symptoms include muscle

weakness, twitching, and eventual paralysis in the hands and feet. These symptoms gradually spread as patients lose strength and the ability to move, speak, and eat. Most ALS patients die within three to five years after symptoms appear due to nerve damage affecting the respiratory muscles. However, 10 percent of ALS patients — like the physicist Stephen Hawking — survive 10 years or more.

#### Pathology and Causes

Motor neurons connect the brain to the spinal cord and to the voluntary muscles throughout the body. In ALS, the motor neurons degenerate and then die. Without this neural communication, a person's voluntary muscles weaken, begin twitching, and finally atrophy.

Only 5 to 10 percent of ALS cases are due solely due to genetic factors — a condition called “familial ALS”; the non-familial disease is called “sporadic ALS.” While several genes have been identified that increase susceptibility to ALS, there is no clear pattern of inheritance. Among cases with a genetic component, about 25 to 40 percent are caused by a harmful mutation in the C9ORF72 gene. Some individuals with this mutation show symptoms of both motor neuron and dementia disorders, a condition known as ALS-FTD (ALS-frontotemporal dementia). Another 12 to 20 percent of hereditary cases result from mutations that prevent the SOD1 gene from coding for superoxide dismutase — an enzyme that catalyzes the breakdown of cell-damaging superoxide radicals into more benign molecular oxygen or hydrogen peroxide. These and other hereditary forms of ALS, such as those involving UBQLN2 and VEGF genes, provide valuable insights into the mechanics of the disease.

#### Research and Treatments



There is no cure for ALS, nor has any medication been found that can stop or reverse its progression. But the FDA has approved edaravone and riluzole for treating ALS. Edaravone, an antioxidant that inhibits the production of cell-damaging free radicals, can ameliorate disease symptoms. Riluzole decreases glutamate levels, and has been shown clinically to extend the life of ALS patients by a few months.

A therapy called NurOwn, developed by BrainStorm Cell Therapeutics, is entering a phase 3 clinical trial (to confirm drug safety and efficacy over a longer testing time) after showing promise for halting or reversing ALS progression. NurOwn uses undifferentiated stem cells from the patient's own bone marrow, which are then modified to boost the production of neurotrophic factors that support and protect neurons destroyed by the disease.

For those with the SOD1 mutation, there is also hope for a gene silencing technique using an artificial RNA snippet. Lab tests in mouse models have preserved muscle strength and motor and respiratory functions, and delayed disease onset and death. This treatment has also safely silenced SOD1 in the lower motor neurons of nonhuman primate models.

Participation in a multidisciplinary ALS clinic, an ALS Association Certified Treatment Center of Excellence, or a Recognized Treatment Center can also improve ALS patients' quality of life.

#### HUNTINGTON'S DISEASE

Huntington's disease (HD) is a heritable disease that impairs voluntary movement and cognition. The disease afflicts 3 to 7 people of 100,000 people of European descent, but is less

common among Japanese, Chinese, or African populations. The HD variant of the HTT gene is dominant; if one parent has a single copy of the HD gene variant and the other parent has normal HTT genes, a child has a 50 percent chance of inheriting the HD variant and developing the disease. The most common form of HD begins earlier than most progressive brain diseases, becoming active when people are in their 30s and 40s. Death occurs 15 to 20 years after a patient becomes symptomatic. Juvenile HD begins in childhood or adolescence, and juvenile HD patients usually die 10 to 15 years after their symptoms appear.

#### Symptoms

Signs of HD begin with irritability, mood swings, depression, small involuntary movements (called chorea), poor coordination, and difficulty making decisions and learning new information. As the disease progresses, the chorea becomes more pronounced and patients have increasing trouble with voluntary movements like walking, speaking, and even swallowing. Their cognitive problems also worsen. While juvenile HD displays the same symptoms as the more common form, it also includes slow movements, clumsiness, frequent falling, rigidity, slurred speech, and drooling. School performance declines as thinking and reasoning abilities become impaired, and seizures occur in 30 to 50 percent of children with this condition.

#### Causes and Genetics

In 1993, Huntington's disease was found to be caused by mutations in the HTT gene, which codes for the huntingtin protein, located on chromosome 4. The protein likely interacts with other proteins involved in




signaling, transport, binding to proteins and other structures, and protecting the cell from self-destruction. The disease mutation involves an abnormal number of repeats of a three-part (trinucleotide or triplet) snippet of DNA in the HTT gene. This sequence of the nucleotides cytosine, adenine, and guanine (CAG) normally repeats 10 to 35 times, but occurs from 36 to 120 or more times in the mutation. The greater the number of CAG repeats, the earlier symptoms appear and the more severe they are.

The “expanded” huntingtin protein is susceptible to clumping. While aggregated huntingtin proteins don’t cause cell death directly, they disrupt the mitochondrial electron transport chain, initiating a cascade of neuronal dysfunction and death. Brain areas most often affected are the basal ganglia

(voluntary movement) and the cortex (cognition, perception, and memory).

#### Detection and Treatments

 In late 2015, Ionis Pharmaceuticals began the first human trials of a “gene silencing” or “huntingtin lowering” drug. IONIS-HTTRx is an antisense oligonucleotide — a single strand of a chemically modified DNA designed to interrupt and decrease the mutated form of the huntingtin protein produced in HD patients. The drug is now in phase 2 trials comparing it to a placebo in early-stage HD patients who are randomly assigned to treatment or control groups.


In spring 2017, the FDA approved the drug deutetrabenazine for treating chorea associated with Huntington’s disease. This is reportedly

only the second product approved for treating HD. Furthermore, there is now evidence for viable HD biomarkers. Tau (which turns up regularly in neurodegenerative diseases) and neurofilament light chain, a component of the neuronal cytoskeleton, are found at elevated levels in cerebrospinal fluid of HD patients. A recent study points to the neurofilament light chain, and to a lesser extent tau, as viable HD biomarkers. Interestingly, the neurofilament light chain is also being investigated as a biomarker for ALS and other neurodegenerative diseases. In mouse studies, the amount of neurofilament light chain found in the animals’ cerebral spinal fluid and blood increased before neurological signs appeared, likely coinciding with the development of brain lesions. ■

# Kinds of Research

**A**s you’ve seen in previous chapters, neuroscientific research has made astounding advances in the past 150 years. The development of new research tools and technologies has driven these discoveries, from the first images of individual neurons to revealing the genetic causes of neurological disorders. This chapter introduces you to some of the most important research methods used to understand the brain, including unusual types of microscopy, animal models, and cutting-edge molecular techniques.

#### TOOLS FOR ANATOMY

 Anatomy is the study of structure — most often, the structure of biological organisms. For the brain, anatomy starts with the structure of neurons, which are among the most complex and diverse cell types in our bodies. Scientists were first able to observe neurons in the late 19th century, thanks to histological techniques that start with a very thin slice of brain tissue to which scientists apply stains or other compounds that add contrast or color to specific structures. They then view the tissue with a light microscope, which passes visible light through the thin slice and lenses that make the structures look up to 1,000 times larger than they do with the naked eye.

Histology is the study of how cells form tissues. Histological techniques can reveal changes in the density of cell types or the presence of molecules that can suggest a particular disease. These techniques have helped illuminate the brain changes underlying some neurodegenerative disorders. For example, histological methods have shown that an enzyme that breaks down acetylcholine is associated with



the brain plaques and tangles of Alzheimer's disease. And in the brains of Parkinson's disease patients, histology has revealed the death of neurons that normally control movements through dopamine signaling.


Long after light microscopes gave scientists their first glimpses of neurons, a debate bubbled in the scientific community: Are neurons individual cells or a mesh of physically interconnected cell bodies? Neurons are so densely packed that the answer wasn't clear until the 1950s, after the development of a new technology called electron microscopy. Electron microscopes can produce useful detailed images of cellular structures magnified many 100,000s of times by directing a beam of electrons through very thin slices of tissue, then enlarging and focusing the image with electromagnetic lenses. With this technology, researchers were finally able to see that neurons are not physically continuous but, instead, are individual cells.

Although they are individual cells, neurons do act in networks, communicating across small gaps called synapses, where the axon terminal of one cell meets a dendrite or cell body of another cell. One method for mapping the signaling pathways within these networks involves injecting radioactive molecules or "tracers" into the cell body of a neuron. Researchers monitor the movement of radioactivity down the neuron's axon, showing where that neuronal path leads. A similar technique involves tracers that can actually travel across synapses, from one neuron to the next. Scientists have used such tracers to map the complex pathways by which information travels from the eyes to the visual cortex.

Another technique for examining brain anatomy is magnetic resonance

imaging, or MRI. Developed in the 1980s, MRI is widely used by researchers and doctors to view a detailed image of brain structure. MRI equipment uses radio waves and strong magnets to create images of the brain based on the distribution of water within its tissues. MRI is harmless and painless to the person being scanned, although it does require sitting or lying in a narrow tube, and the procedure can be quite noisy. With an MRI scan, researchers can tell the difference between the brain's gray matter and white matter. Gray matter consists of the cell bodies of neurons, as well as their dendrites and synapses. White matter mostly contains axons wrapped in the fatty myelin coating that gives these regions their white color. Based on the distribution of water in the tissues, MRI images clearly differentiate between cerebrospinal fluid, the water-rich cells of gray matter, and fatty white matter.

### TOOLS FOR PHYSIOLOGY

 Information is conveyed along the neuronal pathways that crisscross through our brains as electrical activity traveling down axons. To study this activity, researchers measure changes in the electrical charge of individual neurons using techniques of electrophysiology. A thin glass electrode is placed inside a neuron to measure the voltage across its cell membrane, which changes when the neuron is activated. This technique can measure neuron activity inside the brains of living lab animals such as rats or mice, enabling scientists to study how neurons transmit electrical information in their normal physical context. Alternatively, a slice of brain can be kept "alive" for a short time in a Petri dish, if the right environment (temperature, pH, ion

concentrations, etc.) is provided. In an isolated brain slice, researchers can better identify the exact cell they are recording from and can infuse drugs into the Petri dish to determine their effects on the brain.


Using these methods, scientists have made critical discoveries about synaptic plasticity — the capacity of a synapse to become stronger or weaker in response to sensory inputs or other activity. For example, repeatedly stimulating a neuron by training an animal in a particular task, or by direct electrical stimulation, increases the synaptic strength and the chance that the downstream neuron will react to the incoming signal.

A disadvantage of electrophysiology, as described above, is that the techniques are highly invasive. However, another method, called electroencephalography or EEG, is able to record human brain activity without invasive or harmful procedures. In EEG, about 20 thin metal discs are placed on the scalp. Each disk is connected by thin wires to a machine that records the activity of neurons near the brain surface. This approach has been especially useful for understanding epilepsy and the stages of sleep. However, it does not provide information at the level of individual neurons.

Researchers who need to look at individual neurons in a living brain can use a technique called two-photon microscopy. A lab animal such as a fly or mouse must be genetically modified so that some of its neurons produce a protein that glows when a laser beam shines on them. Two-photon microscopy has enabled scientists to understand changes in the brain during normal processes like learning, as well as changes that occur over the course of a disease — for example, watching how the branches on

neurons near Alzheimer's-like plaques break down over time.

### TOOLS FOR GENETICS

 The human genome is made up of 3 billion pairs of DNA letters or "bases." This multitude of adenine (A), cytosine (C), guanine (G), and thymine (T) bases comprises an estimated 20,000 genes that spell out instructions for making proteins, along with regulatory and other non-coding DNA regions whose functions are not fully known. Scientists study genetics in many ways, such as following diseases or other traits through family pedigrees or identifying the exact order of DNA bases (the DNA "sequence") that code for a given trait. More recent genetic tools enable scientists to manipulate genes and other genetic features to better understand how the brain works and how to treat it in cases of dysfunction or disease.

Scientists often don't know which gene or other DNA feature controls a trait. At the outset, a particular trait could be encoded on any of the 23 pairs of chromosomes in a typical human cell. But with genetic linkage studies, researchers have begun to map gene locations. First, researchers must identify another trait with a *known* chromosomal location that tends to be inherited with or "linked" to the trait of interest. This technique, which narrows down the likely location of the gene of interest, was the first step toward identifying the genetic basis of many neurological disorders.

When you think about mutations, you probably think of harmful changes in one or several DNA bases within a gene. But some disorders result from an overabundance of copies or repeats of a stretch of DNA. This is the case with Huntington's disease.

The normal HTT gene has about a dozen repeats of a small stretch of DNA within the gene, but Huntington's patients can have more than 100 of these repeats. Researchers now use DNA chips or microarrays to identify such variations in copy number. The "array" of a microarray refers to the thousands of spots arrayed in rows and columns on the surface of the chip; each spot contains a known DNA sequence or gene, which can grab onto corresponding bits of the genome being analyzed. Using this tool, scientists are able to compare DNA samples of two people, perhaps one healthy and one with a disorder, to see if certain pieces of DNA are repeated more in one person than in the other. Another type of microarray helps researchers determine if a patient has a chromosomal translocation — a chunk of a chromosome that has been misplaced onto another chromosome.

Recent years have seen great advances in DNA sequencing methods, allowing researchers to more efficiently and affordably explore the exact DNA sequence that might underlie brain disorders. In the early 2000s, the Human Genome Project made public the vast majority of the human genome sequence; in the years that followed, the science of genomics has enhanced scientists' understanding of brain function at the level of genes, cells, and circuits. Genomics can help identify genetic variations that cause conditions ranging from depression to schizophrenia to movement disorders.

Genetics research now goes far beyond reading the sequence of bases in the genome. In the last few years, scientists have harnessed a molecular tool that can edit the genome more precisely and efficiently than was

previously possible. This tool, called CRISPR (which stands for Clustered Regularly Interspaced Short Palindromic Repeats), evolved as a bacterial immune system that targets viral invaders. Scientists have harnessed CRISPR's components to home in on specific DNA sequences in lab animals and human cell cultures. By tethering DNA-cutting enzymes to this targeting system, scientists can recreate mutations found in patients with neurological disorders, or even insert new bits of DNA to test their effect. With CRISPR, scientists have been able to mimic Alzheimer's in rodents, in order to study the disease and its potential treatments. CRISPR is also used to study mutated human neurons in Petri dishes. Researchers can observe how mutations that cause autism, Parkinson's disease, or other conditions affect neuronal growth and function.

Optogenetics is another fascinating intersection of genetic tools with brain science. This ingenious technique allows researchers to control brain activity with flashes of light. Scientists genetically modify a lab animal like a mouse so that its neurons produce a light-responsive protein. Then, optical fibers are inserted into the brain to allow light to shine on those neurons — either activating or silencing them. Optogenetics has helped scientists better understand how neurons work together in circuits. This technique has also been used to control animal behaviors ranging from sleep to drug addiction.

Oddly enough, genetics is not always about genes. As mentioned above, much of the human genome contains DNA sequences that are not genes, whose job is to regulate gene activity. These regulatory sequences,



and the enzymes that make changes to them, help determine under what conditions (in what cells, at what age, etc.) a gene is expressed or repressed. These epigenetic changes occur in cells when chemical tags are placed on the regulatory regions of certain genes; the tags influence whether those genes will be turned on or off. In the past decade, epigenetics research has begun to clarify the role of gene regulation in brain development and learning. Epigenetics has also revealed how mutations in the regulatory regions of DNA can cause disease, just as mutations can in genes.

### Genetics in Neurological Diseases

The impact of mutations varies from person to person, and from disease to disease. A particular mutation might explain some cases of a disorder but not others, or it could be only one of several genetic changes affecting a patient. Lissencephaly is a brain malformation in which the surface of the brain is smooth, unlike normal brains whose surfaces have ridges and grooves. It affects development. Babies with lissencephaly start having spasms in the first months of life and develop drug-resistant epilepsy and severe intellectual and motor disabilities. Although about 70 percent of these patients have mutations in the LIS1 gene, at least two other mutations have been associated with the condition. Another complex genetic condition, Kabuki syndrome, is marked by intellectual disabilities, a distinctive facial appearance, slow growth in infancy, and other physical problems. Kabuki syndrome is hard to diagnose because some symptoms, such as intellectual disability, range from mild to severe. DNA sequencing has found that most patients, but not all,

have mutations in the KMT2D gene — and some patients carry the mutations in only some of their cells. In addition, people with Kabuki syndrome may have mutations in other genes that function like KMT2D.

It is also possible for a person to carry a mutation but exhibit no outward signs. Fragile X syndrome, the most common form of congenital intellectual disability in males, is caused by an excessive number of DNA sequence (CGG) repeats within the FMR1 gene. The protein product of the FMR1 gene, which is important for synapse function, is disrupted by these repeats. While some people with elevated numbers of the sequence repeats may not be affected, they are carriers with a risk of passing it on to their children.

### TOOLS FOR BEHAVIOR

To understand how brain function drives behaviors in humans, researchers often turn to animal models. An eight-inch long marine slug may not look like a very promising model of brain function but, over the years, the animal known as *Aplysia* has helped scientists uncover many principles of learning and memory. *Aplysia* has relatively few neurons (around 10,000, compared to approximately 86 billion in humans), but some of its neurons are large enough to be seen with the naked eye. *Aplysia* also exhibits simple behaviors that can be modified with training. For example, *Aplysia* will reflexively withdraw its gill after receiving an electric shock to its tail. It can be trained to withdraw its gill in response to an innocuous touch which, during training, was paired with an electric shock. Scientists have discovered how the timing of training sessions affects learning, and have identified proteins and other molecules

that strengthen synapses so the neuronal response is greater the next time *Aplysia* is stimulated. Many of the molecules and processes identified in *Aplysia*'s learning are also involved in human learning.

The fruit fly *Drosophila* is also commonly used to study behavior, especially how genes control behavior. For example, variations in a gene called 'foraging' determine whether flies tend to roam around as they eat or sit in one place. Flies with mutations in another gene called 'timeless' don't have normal circadian rhythms. Mutations have been identified that affect the full gamut of *Drosophila* behaviors — from aggression to courtship, as well as learning and memory. Many of the affected genes have correlates in humans.

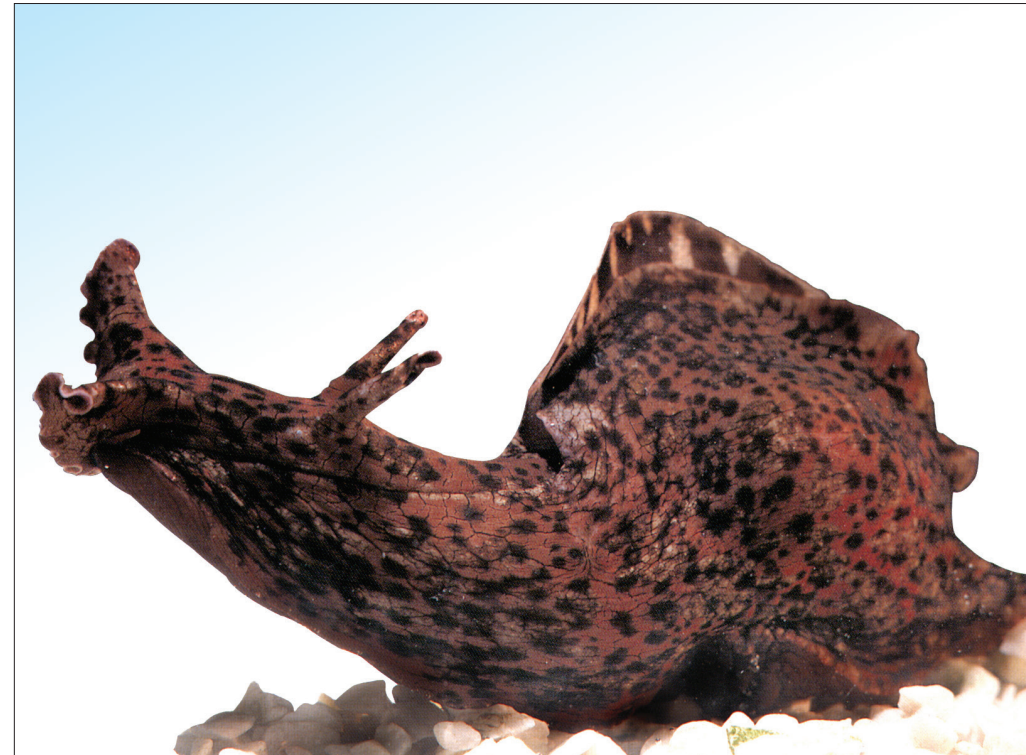
Addiction presents one of the most pressing challenges in studying human behavior — how to better understand it and how to treat it. Some lab animals like rats will consume alcohol and drugs even if accompanied by a bitter taste or foot shock. Scientists have uncovered changes in the brains of animals exhibiting such addiction-like behaviors that mirror changes seen in the brains of humans with addiction disorders. Interestingly, some breeds of rats are very likely to exhibit addiction and relapse behaviors while others are more resistant. By comparing the genetics of two breeds of rats with different predispositions to cocaine addiction, scientists identified genes that were differentially turned on or off in the two breeds; the study suggests that these genes, and their epigenetic regulation, play a role in susceptibility to addiction. This type of research helps scientists understand why some people are more prone to addiction or relapse, and could suggest ways to identify people at risk.

Behavior is also studied directly in humans. Early mapping of human behaviors to specific brain regions was done by observing personality changes in people who had lost small regions of their brain due to injuries or surgeries. For example, people who have lost their frontal lobe often become inconsiderate and impulsive. Modern imaging techniques, described in greater detail below, also help scientists to pair brain regions with certain behaviors. For example, imaging allows researchers to see certain brain areas "light up" when a person is shown human faces, but not when they see faces of other animals. These techniques are also useful to better understand brain disorders — such as identifying brain regions responsible for auditory hallucinations in schizophrenia.

### TOOLS FOR BIOCHEMISTRY

Although we talk a lot about the electrical signals transmitted along neurons, the brain also communicates with molecular and chemical signals. Neurotransmitters are chemical messengers that travel across a synapse, carrying signals from one neuron to the next. Using a method called microdialysis, researchers can monitor neurotransmitters in action. With thin tubes inserted into the brain, scientists are able to collect tiny volumes of liquid from just outside neurons and then analyze the compounds in that liquid. For example, a researcher could analyze liquid captured during learning to identify molecules that are important for that process.

Microdialysis can also be used to deliver compounds to the brain. Many drugs have powerful effects on the brain, so scientists can use these substances to tweak brain function in order to understand it better.



Because its nervous system is much simpler than that of a mammal, the sea slug *Aplysia* was an important animal model in early studies on the neurobiology learning and memory.



*Drosophila melanogaster*, pictured here, is widely used for studying many aspects of the brain and behavior.

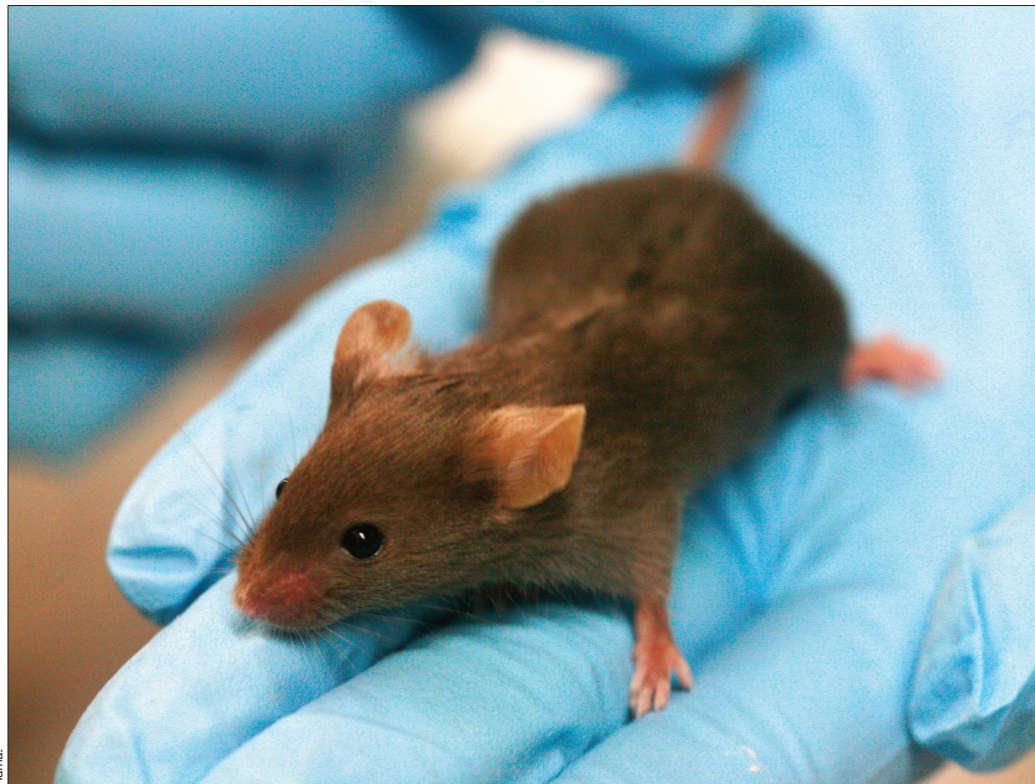


Pharmacology, the study of the effects of drugs, is also dedicated to identifying new drugs to treat conditions like pain or psychiatric illness, as well as understanding addiction and other negative consequences of drug use.

Another important method employed to study the molecules and chemicals at work in the brain is mass spectrometry. Once a sample has been collected — perhaps by using microdialysis — the compounds it contains are ionized (given an electric charge) and then sent through an electric or magnetic field. The behavior of each molecule in that field indicates its mass. That information alone provides valuable clues for identifying a molecule. Mass spectrometry has also been very useful in exploring neurodegenerative disorders. For example, one treatment for Parkinson's disease causes severe side effects, including involuntary movements. With mass spectrometry, researchers have identified the location within the brain where this side effect is caused; that information could point the way to interventions that can reduce or prevent those side effects.

### TOOLS USED FOR HUMAN RESEARCH

Many of the methods we have discussed are too invasive to use in humans. But several methods for imaging human brain function do *not* require holes in the skull or other lasting physical changes. Functional MRI (fMRI) can be used to follow changes in the brain activity of a person lying inside an MRI scanner. The machine is tuned so that it detects blood flow as well as differences in oxygen-rich and oxygen-poor blood, based on the idea that more active regions of the brain need more oxygen and nutrients, which



Mice are one of the most important animal models in neuroscience research.



Magnetic resonance imaging (MRI) scans are used to create detailed images of organs like the brain.

are supplied by fresh oxygenated blood. While this is an indirect indication of neuron activity, it can pinpoint brain activity to fairly small regions.

fMRI provides an indirect view of neuron activity, but magnetoencephalography (MEG) detects actual electrical currents coursing through groups of neurons. When neuron activities are synchronized, their combined electrical currents produce weak magnetic fields that MEG equipment can detect. A person undergoing the procedure sits or lies down, with his or her head surrounded by a helmet-shaped device that can sense magnetic fields. MEG has been useful in a variety of studies: from how the auditory cortex responds to sounds to identifying where epileptic seizures start in a patient's brain. MEG is useful for detecting rapid changes in brain activity (temporal resolution) but it does not provide the precise location of that activity (spatial resolution). For this reason, researchers can combine MEG data with fMRI data to obtain good anatomical detail from fMRI and high-speed readings of brain activity from MEG.

Near-infrared spectroscopy (NIRS) is similar to fMRI in that it monitors the flow of oxygenated blood as a way to estimate neuron activity. A major difference is that NIRS is only useful for measuring activity near the surface of the brain and does not provide as much detail; however, it is far less expensive and cumbersome than fMRI. NIRS is also more comfortable for the person undergoing the procedure, as the setup essentially involves wearing a cap with wiring hooked to it. Some of the wires transmit harmless laser beams (~1

megawatt of power or less) into the brain while others detect the light after it travels through the brain. NIRS can be used to determine the extent of brain injuries and to monitor oxygen levels in the brains of patients under anesthesia. Because of its portability, NIRS is very useful for studying brain activity during tasks — such as driving down the highway — that can't take place inside an fMRI scanner.

Positron emission tomography (PET) detects short-lived radioactive compounds that have been injected into the bloodstream. The radioactive compounds could be oxygen or glucose, or they might be a neurotransmitter. PET traces where these compounds go in the body. The location of labeled oxygen can indicate blood flow, while a labeled neurotransmitter can show which brain regions are using that signaling molecule. PET can also detect the amyloid plaques that are a hallmark of Alzheimer's disease; this technique could one day enable us to identify the disease in its early stages. Although PET has good temporal resolution like MEG, it lacks the detailed spatial resolution of MRI.

Some methods used in human research can change brain activity. In transcranial magnetic stimulation (TMS), a coil that generates a magnetic field is placed near a person's head. The magnetic field can penetrate the skull, temporarily activating or silencing a region of the cortex. TMS is used to treat psychiatric disorders such as anxiety, depression, and post-traumatic stress disorder and could be an effective option for patients with conditions that do not respond to medications.

Although neuroscience has progressed by leaps and bounds since neurons were first viewed under a microscope, many phenomena observed with these techniques are not fully understood. For example, mysteries still surround data obtained with EEG. EEG shows that several different brain regions have characteristic rhythms or oscillations — one pattern in the visual cortex, another in the sensory motor cortex, and so on. Even though this method of examining brain activity has been used since 1929, the generation of these patterns (sometimes called brain waves) at the level of neural circuits is not well understood.

One branch of neuroscience that can help bridge findings from the microscopic to the whole-brain level is **computational neuroscience**. Researchers in this field develop theories or models about how the brain processes information, then test these models against real-world data. For example, they can examine the data and images from EEG or fMRI, then develop mathematical models to explain the underlying neuron and circuit activity. Data from the many methods discussed in this chapter — electrophysiology, molecular studies, anatomy, and functional brain scans — can all contribute to these computational models.

This chapter provides an introduction to research methods that have driven, and continue to drive, discovery in neuroscience. As new techniques and technologies emerge, scientists will add them to their repertoire of techniques that can deepen our understanding of the brain and suggest new ways to help people whose lives are affected by brain disorders. ■



# Solving Human Problems

## BRAIN-MACHINE INTERFACE



If you know someone with severe neurological damage — perhaps cerebral palsy, trauma from a car or motorcycle accident, a military or sports injury, or a stroke — you’ve seen, firsthand, how communicating with the outside world and performing daily tasks can be a challenge. But during the past few decades, scientists have made impressive progress in developing technologies that can bypass such damage. Now brain-machine interfaces can read the activity of millions of neurons — through electroencephalographic (EEG) activity from the brain’s surface or from implanted electrodes — and predict the behavioral intentions of research participants. These advances give human and animal subjects neural control of parts of their surroundings: from computer cursors to video games to robotic limbs.

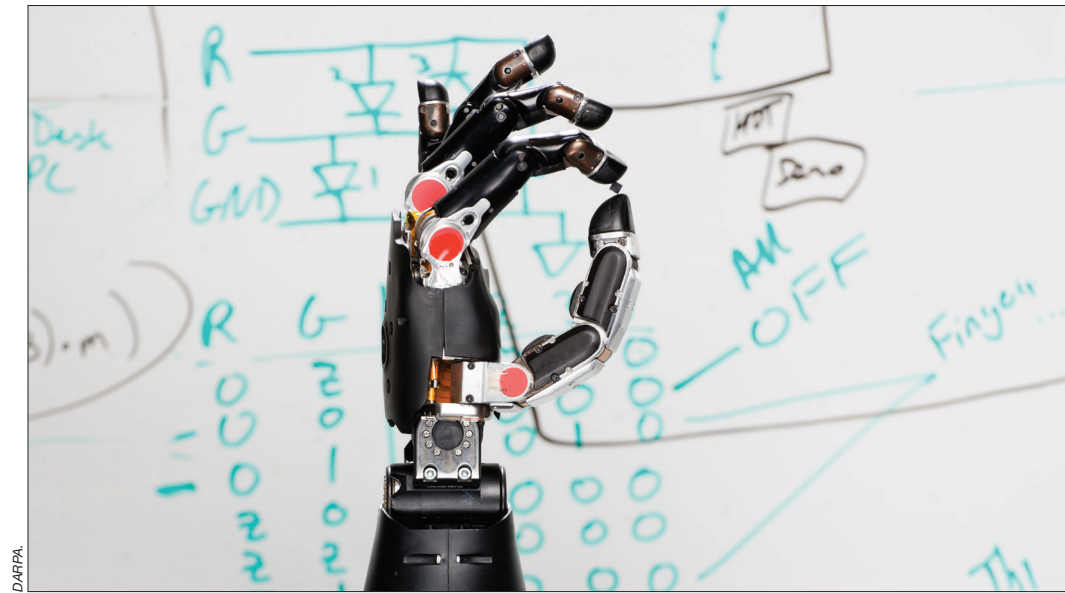
Despite the sci-fi sizzle, most of the work on electronic brain implants is derived from basic research on how animals and people plan and control various types of movement. Using hair-thin wires inserted into the brains of monkeys and rats, scientists first recorded the firing patterns of cells located in the premotor, primary motor, and posterior parietal cortical areas of the brain. As the animals performed repetitive tasks like pressing a lever to receive a reward, researchers found specific firing patterns associated with the motion. Eventually, these patterns were translated into computer algorithms that allowed animals to complete a task via a robotic arm or prosthetic device simply by thinking about it.

The clinical applications of brain-machine interfaces quickly became clear. Neuroscientists and surgeons implanted electrode arrays in the brains of patients with epilepsy, paralysis, stroke,

or Lou Gehrig’s disease (ALS), in hopes of enabling them to communicate and, someday, move independently. In early experiments, patients were only able to gain rudimentary control of a computer cursor. But a breakthrough occurred in 2011 when, after months of extensive training, quadriplegic patients learned to control movements of a third (robotic) arm — enabling them to grasp a drink of water or reach out to a loved one.

Honing this technology is allowing patients to control their own paralyzed limbs. Electrode chips implanted in their brains are connected to sleeves or gloves worn over the injured limbs. Sending tiny blasts of electricity into the patient’s nerves, located under the sleeve or glove, can reanimate paralyzed muscles. But brain-machine interfaces won’t become part of clinical medicine until they’re simplified, miniaturized, and made more reliable. Devices that wirelessly transmit commands from brain implants are a step in that direction.

A parallel line of research has explored applying this technology in the broader field of neuroprostheses. Neuroprosthetic devices not only receive output commands from a patient’s nervous system, but can also provide input — as occurs in retinal implants and prosthetic limbs. Prosthetic arms, for example, have remained frustratingly low-tech, but some brain-guided prostheses have integrated nerves and muscles at several different levels, allowing users to perform more precise and natural movements, and even enabling some to “feel” again. Still, even the most sophisticated neuroprostheses (such as brain implants) are limited by their number of electrodes and the lifespan of the implanted electrodes. Current arrays can only connect to 100 or so neurons, so a more complex and useful bionic future is still far away. Yet scientists and entrepreneurs



Advances in brain-machine interfaces are leading to incredible treatments, like this prosthetic arm that is controlled through thought.

are already thinking of new uses for the technology: restoring memory; enhancing cognition; and treating diseases such as depression, Alzheimer’s, and epilepsy.

## DEEP BRAIN STIMULATION

Insights into the pathophysiology of movement disorders have rekindled interest in the use of focused electrical stimulation as a form of treatment. The most advanced and precise method — deep brain stimulation (DBS) — was inspired by pacemakers engineered for the heart. Instead of electrodes implanted in the heart, the electrodes of the DBS device are surgically embedded in specific brain regions. Depending on where the electrodes are placed, DBS devices can help alleviate the symptoms of some brain disorders.

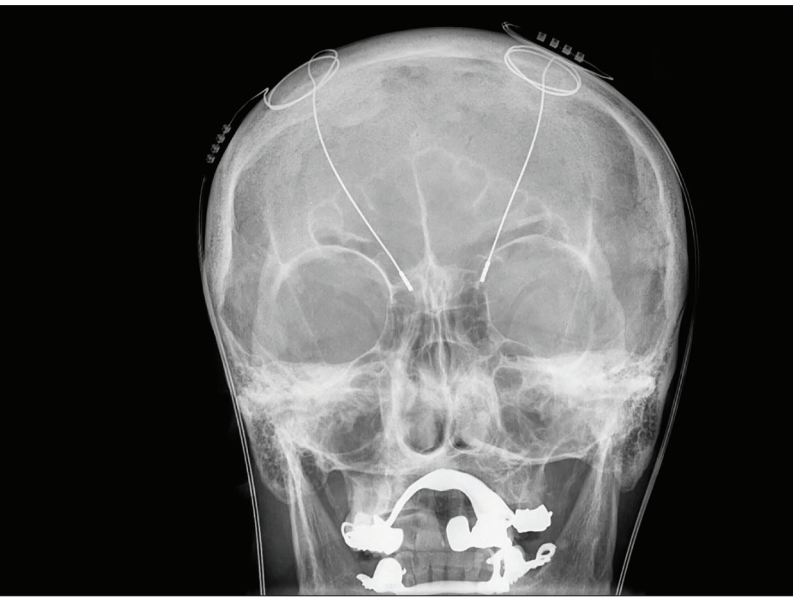
During most of these implantation surgeries, patients remain awake so that a neurologist can talk to them and ensure that the electrodes are stimulating the correct locations. While the patient’s head is held in place with a stereotactic frame, the surgeon drills a dime-sized hole (or smaller) in the skull. Then, a

thin insulated wire with electrodes at the tip or along the shaft is inserted deep into the brain; if both sides of the brain are to receive implants, a wire is inserted into each side. In a separate surgery, a battery-operated pulse generator is implanted in the upper chest and connected to the electrodes. When the device is turned on, it starts sending electrical currents that alter the activity of the targeted brain cells.

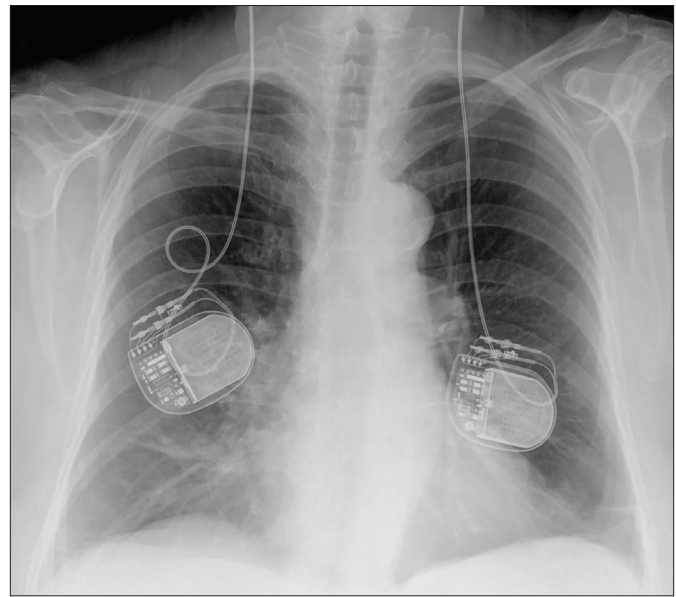
The implanted device relies on the fact that neuronal communication uses electrical signals. In many movement disorders, an abnormal signal or pulse can gain control of a circuit and can easily become magnified. Like someone shouting in a crowded room, this aberrant signal can drown out other activity. DBS interrupts the shouting, so that normal communication can continue.

To determine where brain activity needs to be silenced or induced, neurosurgeons must identify the locations of the problems. The brain areas first targeted for tremors and Parkinson’s disease were chosen after years of painstaking neuroimaging, neuroanatomy,





Deep brain stimulation uses electrodes implanted deep in the brain, which carry electric impulses to specific brain regions. The power packs that provide the electricity are implanted in the patient's back, as seen in this X-ray.



Hellerhoff.

and fundamental research, especially in nonhuman primate models. Since then, deep brain stimulation has been used to treat epilepsy, dystonia, Tourette's syndrome and, more recently, obsessive-compulsive disorder. Now researchers are investigating whether the DBS technique can potentially be extended to mood disorders such as treatment-resistant depression, as well as other complex mental disorders.

Yet DBS, like any surgical procedure, is not without some risks. It is highly invasive, and potential complications include infection, stroke, and bleeding in the brain. It also requires regular neurological follow-up and battery changes every 3 to 4 years.

## PSYCHOACTIVE THERAPIES

### Transcranial Stimulation

A few noninvasive treatments can stimulate cells near the surface of the brain: Transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS) all use magnetic fields or low

electrical currents to alter neural activity in a specific region of the human cortex and, indirectly, deeper brain structures to which it connects.

During TMS therapy, patients sit in a chair while a nurse or technician places a magnetic stimulator against their head. The device painlessly delivers brief magnetic pulses to the brain, similar in strength to those generated by magnetic resonance imaging (MRI) devices, but highly targeted. For patients with depression, pulses are focused over their left prefrontal cortex. Here, they generate electrical currents among neurons which, over time, help lift the patient's mood.

Similarly, tDCS uses one or two milliamperes of direct current to tune the brain. Although research into tDCS and its close cousin, tACS, is in its early stages, these techniques offer clear advantages over deep brain stimulation and even over TMS. Generally, patients report only a slight tingling or tapping feeling on their head as the therapy is administered. The devices used to administer these therapies are also cheaper, more portable, and lower

-tech compared to TMS and DBS.

A number of studies have suggested that tDCS and tACS might be used to improve working memory as well as to relieve chronic pain and the symptoms of depression, fibromyalgia, schizophrenia, and other disorders. However, despite the substantial literature, meta-analyses have failed to conclusively prove any effects of transcranial electrical stimulation. Currently, there is no consensus among scientists on how these treatments might work, or even on the best way to position the stimulation devices.

### New Types of Drugs

Most doctors still recommend medication as the first line of treatment for neurological and psychiatric disorders. The antidepressants, antipsychotics, and other mind-altering medications used today have been tested in extensive clinical trials and remain largely unchanged from their prototypes developed in the 1950s. Each of these classes of drugs is now filled with subsequent generations of closely



MRI scans can provide detailed images of brain tissue. Here, it displays tissue high in water and fat content in white.

Oxford Centre for Functional MRI of the Brain, Oxford University.

related drugs designed to interact more selectively with their targets, producing better therapeutic effects and fewer side effects, in some cases. Nevertheless, these are just slightly improved copies of one another. Truly novel drug candidates are rare, and hard to develop.

One of the biggest challenges in developing new drugs to treat neurological or psychiatric problems is finding molecules that can cross the protective **blood-brain barrier** — tightly packed endothelial cells lining blood vessels restrict the kinds of molecules that can enter the brain. While this barrier's fortress-like quality is good for normal function, it prevents most drugs delivered by typical means — including pills, patches, injections, or enemas — from having any useful therapeutic effects within the brain. Scientists have had to design extremely tiny molecules or adopt ingenious strategies such as nanoparticles that shuttle in drugs, enzymes that activate molecules after they've "snuck through" the barrier, and antibodies that were specifically engineered for the brain.

Preliminary trials of drugs that use the body's own immune system to confront and clear unwanted proteins from the brain have sparked a great deal of interest, particularly in the Alzheimer's disease community. When mice and monkeys receive a vaccine that contains a major component of amyloid plaques, their immune systems develop antibodies capable of traveling to the brain and "tagging" the amyloid-beta plaques that are the hallmark of Alzheimer's disease. This tagging seems to alert microglial cells in the brain, which head for the plaques and try to remove them. In some experiments, mice bred to develop an Alzheimer's-like disease remembered how to navigate through a Morris water maze, after being vaccinated — indicating that such vaccines might also relieve symptoms of the disease.

In the past, however, many Alzheimer's vaccines have failed in later-stage clinical trials. One reason for these failures was the development of harmful side effects. Several human participants experienced severe inflammation when

their brains reacted to the antibodies against its proteins. Since then, newer approaches have engineered antibodies or antibody fragments that bind to their specific targets without triggering an autoimmune response. Other researchers have engineered double-duty antibodies. These use one end to sneak into the brain by binding to a receptor on the blood-brain barrier. Once inside, the antibody's other end can cut off production of harmful amyloid-beta proteins even before plaques form.

By contrast, some therapies aim to boost helpful peptides and proteins called trophic factors, which are native to the brain. Neurotrophic factors support the growth and survival of specific groups of neurons. Scientists hope to modify these factors to reduce the amount of cell death in various neurodegenerative diseases.

The possible value of at least one trophic factor — nerve growth factor (NGF) — has already been demonstrated in several preclinical and early stage clinical trials. NGF slows the destruction of cholinergic neurons that plays a role in the cognitive decline of Alzheimer's disease. Injecting NGF into patients' brains stimulated the regeneration of these neurons and induced sprouting of new nerve fibers around the injection site. In some cases, evidence of this sprouting lasted up to 10 years after the initial therapy.

**Brain-derived neurotrophic factor (BDNF)** is showing potential for treating Alzheimer's disease, as well as Huntington's, Parkinson's, ALS, and Rett syndrome. Moreover, the effects of boosting BDNF could even be stronger than those of NGF. But, in an interesting twist, the *inhibition* of some neurotrophic factors such as the neurite outgrowth inhibitor might also benefit patients. Studies have



found that neurite outgrowth inhibitor is upregulated in the early stages of motor disease, and having too much of it around could prevent nerve regeneration. Scientists are now conducting clinical trials in which patients with ALS and spinal cord injuries receive custom-made antibodies to disable the neurite outgrowth inhibitor protein.

Ultimately, the ever-increasing global demand for therapies for neurological and mental diseases is a strong motivator for scientists and doctors in this field.

### PREDICTIVE NEUROIMAGING AND PERSONALIZED MEDICINE

As we gain understanding of the anatomical and functional changes underlying neurological illnesses, it becomes increasingly clear that these changes provide clues for earlier detection — even before symptoms appear. Many disorders, such as Alzheimer’s disease, are accompanied by specific brain activity and structural changes that can be tracked over time using MRI. By comparing this information with a baseline model of a healthy brain, researchers hope to predict which patients might one day develop neurological problems.

Although it is still too early for these “markers” to be used as clinical reference points, they could pave the way for objective diagnoses of brain disorders, much as electrocardiograms and laboratory tests are currently used to reveal heart problems. The first step in this process is to produce a generic brain template by averaging the images from hundreds of randomly selected MRI scans. Scientists can then use machine-learning software to characterize the sets of healthy brain scans and the sets of scans known to

show disease-associated changes.

Data from predictive neuroimaging can also be useful for guiding personalized treatment options and assessing a treatment’s clinical effectiveness. In studies of major depression, for example, patients whose brain scans showed an overactive amygdala (a brain region involved in emotional processing) were more likely to respond to psychotherapy. However, patients who exhibited higher activity in the anterior insula (another brain region involved in emotions) tended to improve with medication, but not with psychotherapy. In the future, psychiatrists could offer patients the best possible course of treatment based on their own biological characteristics, rather than relying only on symptoms or treatment preferences.

### CELLULAR MARKERS

In the past few years, a growing number of clinicians and scientists have rejected the boundaries of conventional DSM (Diagnostic and Statistical Manual of Mental Disorders)-defined diagnostic protocols that mental health professionals usually rely on. Rather than analyzing symptoms such as sadness, fatigue, or lack of sleep, the focus has shifted to finding biological markers that provide objective indices of those symptoms.

Much like neuroimaging, cellular markers could be used to predict a patient’s risk and diagnosis before disease symptoms become obvious, as well as indicate how a patient may respond to certain treatments. The markers may be proteins, lipids, hormones, nucleic acids, or other compounds that can be detected in samples of blood, urine, saliva, or cerebrospinal fluid.

Although neuropsychiatric research on biomarkers still lags behind other fields such as oncology, researchers are

investigating associations between genetic and cellular mechanisms and various mental disorders. A single biological cause for a mental disorder is hard to pin down — in fact, many skeptics say it is impossible to understand mental illness solely by understanding the brain. Causes of mental disorders are very complex and not easy to decipher. And yet, recent technological advances are enabling scientists to decipher more of the brain’s mysteries. Researchers can look deeper into the brain with imaging technology, map the circuits underlying specific mental states, and study how chemical levels change in individual neurons. Biomarkers reflect these physiological conditions, and studying them could lead to better targets for treatments. If chosen carefully, biomarkers might even provide useful ways to compare the effectiveness of treatments between patients, as well as in future clinical trials.

### CELL TRANSPLANT

To find new treatments for schizophrenia, stroke, Parkinson’s disease and other debilitating diseases, researchers around the world are turning to stem cells to study the biology of the diseases and disorders. These undifferentiated cells — from embryos or from certain adult tissues — have the remarkable potential to develop into any of the three major cell types of the brain: neurons; astrocytes, which nourish and protect neurons; and oligodendrocytes, which surround axons and enable them to conduct signals efficiently. Scientists hope that stem cells transplanted into the brain might be able to replace and repair neural cells that were lost due to disease or injury.

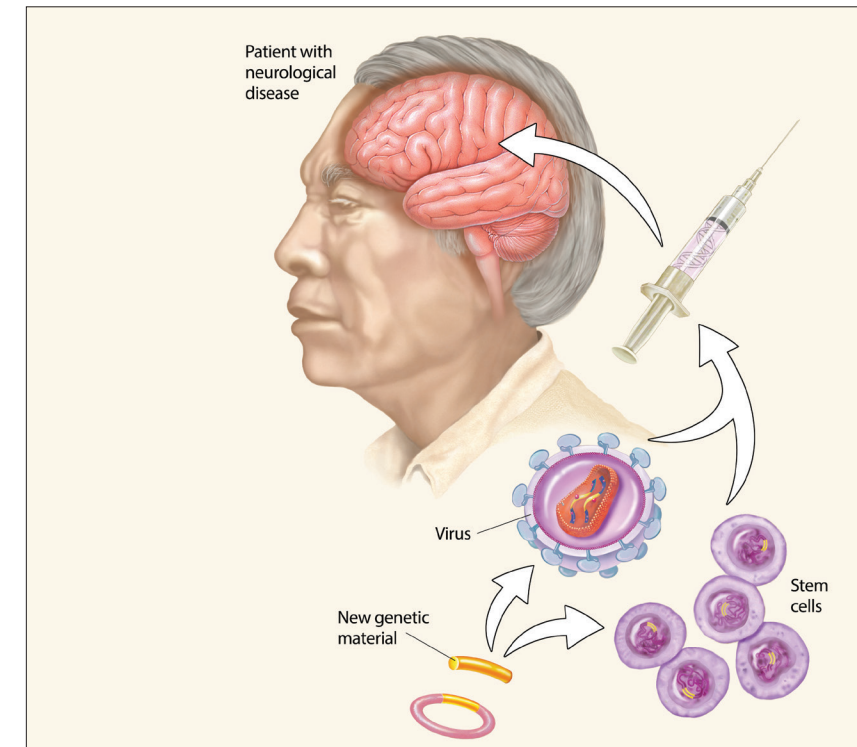
In mice, stem cell therapy has reversed the signs of serious spinal cord injury. Within weeks of treatment, researchers observed that previously

paralyzed mice could walk again. So far, only a few small trials of fetal and stem cell grafts have been conducted in humans. Some of the patients treated showed meaningful recovery from otherwise hard-to-treat disorders like stroke and Parkinson’s. Other trials were not successful, with replacement cells starting to produce excessive amounts of dopamine.

Thus, there are several challenges to overcome before successful use of neural stem cell transplant therapy. Embryonic cells and adult stem cells are difficult to harness and transplant into the brain. Controlling where and how stem cells differentiate into the necessary replacement cells is also tricky. Furthermore, stem cells carry a risk of being rejected by the recipient’s immune system. Scientists have recently discovered how to convert a patient’s own brain cells directly into dopamine neurons, which eliminates many risks, but the procedures are far from standard. None of them has yet been approved by the U.S. Food and Drug Administration.

### GENE REPLACEMENT

As researchers work to improve the safety and efficacy of genetic and cellular treatments, neuroscientists are finding new ways to deliver therapeutic genes into cells that need them. Designing therapies able to breach the blood-brain barrier is a challenge. Recent research has shown that small viruses with healthy genes tucked inside are able to cross the blood-brain barrier and replace faulty genes. Currently, adeno-associated virus and lentivirus seem to be the safest and most efficient vectors for gene therapy. These vectors are being used in clinical trials in patients with Parkinson’s and for some rare genetic diseases. Herpes simplex virus and



Stem cell and gene therapies hold huge potential for treating brain diseases. Therapeutic genetic material can be introduced in the brain through engineered viruses, while stem cells can be used to replace damaged or diseased cells in the brain.

adenovirus vectors have also been evaluated in early-stage human trials for treating brain tumors.

In recent years, a new gene-editing method, CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), has begun to rewrite “conventional” gene therapy. The new technique uses RNA-guided enzymes to snip out or add DNA segments to a cell, allowing researchers to make extremely precise changes in a cell’s genome. Neuroscientists have already used CRISPR to repair part of a gene that produces toxic protein aggregates in the brains of mouse models of Huntington’s disease. When scientists looked at the mouse brains a few weeks after the procedure, the aggregated proteins typical of Huntington’s were almost gone, and the animals’ motor abilities had amazingly improved.

Of course, the usefulness of

gene-editing technologies goes far beyond direct therapeutic applications. With CRISPR, dozens of mouse (and other animal) models can be made much more efficiently, facilitating studies of the brain and mental illness. But the technology is still relatively new, and it’s not perfect. The CRISPR system can make unintended cuts in the DNA if sequences are similar enough, so that unintended mutations could arise that affect the health of the animal being studied. In addition, this technology is not yet useful for treating complex conditions like schizophrenia and autism, which are thought to involve multiple genes. As with all new technologies, the ethical issues of using CRISPR as a gene therapy in humans are being hotly contested. Only time will tell whether CRISPR can be added to the expanding list of technologies that solve problems of the human brain. ■



# Neuroscience in Society

**B**y this time, you've learned a great deal about your brain and how complicated it is. The preceding chapters have mostly looked at the brain as a part of a thinking, behaving, and feeling individual.

But you rarely live your life as an isolated individual. In fact, you probably interact with a wide variety of people every day, from bus drivers to store clerks to your best friend. Those interactions, along with the interactions of people around you, form the basis of our society. It makes sense that what you've learned about the brains of individuals can help you understand groups of individuals — human societies — and how they function.

Neuroscientists constantly discover new things about the forces that drive the brain. If insights into questions like “How do I make decisions?” or “What causes addiction?” can change one person's life, they can have an even greater influence on groups of people, sometimes even inspiring them to transform the societies in which they live.

Many questions require critical thinking about how the human mind works: “Who decides what the law should be?” “What makes laws fair?” “How can we design the economy, and what groups of people does it leave behind?” Answering these questions requires a thoughtful understanding of the workings of the human mind. Neuroscience can provide evidence-based arguments for how to build a society, rooted in a solid understanding of brain science.

It might sound like science fiction, but the more we discover about the brain, the greater its potential to transform human society. Scientists need to grapple with the ethical dimensions of their work, engaging in conversations with sociologists, lawyers, politicians,

economists, and philosophers to determine the best ways to build on their groundbreaking revelations about the human brain.

## NEUROLAW



In earlier chapters, you learned all about decision-making, but many decisions have more drastic consequences than whether to buy a taco or stir fry for lunch. Behind every crime that makes the news is a decision — or a series of decisions — that may have individuals facing the legal consequences of breaking the law. As with so many things (including the brain), the more closely you look at this issue, the more complicated it gets.

Take addiction, for example. In the last few decades, the American prison population has grown by about 500 percent, largely because of drug-related arrests. In this book, you've learned how drug use affects the brain and is associated with significant changes to the prefrontal cortex (PFC), a part of the brain that oversees impulse control and suppressing cravings. Those changes in the PFC make resisting drug use much more difficult. Seen this way, ongoing drug use looks less like a bad decision and more like a symptom of a disease: addiction.

Now lawyers, judges, and scientists have to decide how drug users should be treated by the criminal justice system. Should they continue to be jailed, as a punishment for their decision to break the law? Or should they receive therapy or rehabilitation to treat, and help them recover from their altered brain states? Or should they receive some combination of both? What is the perfect balance?

Many examples muddy the waters of decision-making and punishment.

In one famous case, an individual who had brain surgery to remove a tumor suddenly developed a compulsion to view child pornography. During his trial, the man's doctor provided evidence that the surgery had damaged a part of the brain that typically suppresses such dark urges. Personality changes after brain surgeries are not uncommon — was it possible that his terrible fixation was a side effect of his life-saving surgery? If so, what should his punishment be? If the behavior wasn't his “fault,” what does a just society owe his victims?

than many types of forensic evidence. But recent research has shown that human memory is far from perfect, especially as time passes after a crime. As witnesses recall their memories, they introduce errors, which are then reconsolidated into new memories. This is true of even the most memorable events. In a study of New York City residents one year after the 9/11 terrorist attacks, their memories of the event differed in 40 percent of the details. This doesn't mean that eyewitness testimony is useless, but neuroscience has demonstrated that

**T**he more neuroscience reveals to us, the more we must accommodate our social structure to the ramifications of these new discoveries.

These are not easy questions to answer. They require us to temper our notions of fairness and justice with new scientific knowledge. The more neuroscience reveals to us about the mechanisms underlying memory, personal responsibility, and behavior, the more we must accommodate our social structure to the ramifications of these new discoveries.

For another example, consider eyewitness testimony, a common tool in the courtroom. Studies have found that the testimony of people who actually witnessed a crime is very convincing to juries — more convincing

it is far from infallible. Judges and lawyers must now come to terms with this change of perspective.

Nor is this the first time that neuroscience has helped to change the way the courts work. Polygraph tests, once a staple of television crime dramas, have been rejected in many courts (including the United States Supreme Court) as being unreliable. This decision was based on the work of many scientists, who showed that the physiological reactions measured by polygraph tests (sweating, increased heart rate, etc.) are *not* definitively linked to guilt or lying.



After all, dragging an innocent person to the police station to submit to a lie detector test might produce the same symptoms. Reliable lie detection technology might exist one day, but that day is too far in the future to affect current court decisions.

### NEUROECONOMICS



You are constantly making financial decisions for yourself. Should you stock up on all of your favorite snacks now that you are at the grocery store, or come back later for the items when there is a big sale? Are you saving enough for college? Do you like that new sports car enough to put up with its poor gas mileage? In recent years, economists and neuroscientists have begun collaborating to investigate the brain processes behind these decisions. This field, called “neuroeconomics,” has the potential to significantly alter the way people think about the economy.

A driving force behind modern capitalism is the belief that individuals make rational purchasing decisions — that everyone acting in their own self-interest creates a system in which resources will be distributed as fairly as possible. Yet that theory doesn’t explain why so many economic decisions are irrational, or based on gut instinct and rationalized later. Neuroeconomics is especially interested in those situations where choices are less clear-cut or rational and involve unknown (or unacknowledged) factors and risk.

To learn more about these decisions, scientists have measured brain activity as people complete economic tasks — for example, running brain scans as people play a simple double-or-nothing game. When a player decides to risk it all to double winnings,

activity increases in a part of the brain called the insular cortex. Scientists hypothesize that networks of the insular cortex interact with other brain areas, including parts of the limbic system that function in learning, memory and emotion, to let the player picture the negative consequences of taking such a risk. Suddenly risking a mortgage payment at the blackjack table might not look so appealing.

Scientists have also discovered that our hormones play a role in economic decisions. In one case, some participants in an investment game were

Another study of male stock traders looked at levels of the hormones testosterone and cortisol. Researchers took saliva samples from a small group of traders every day during a work week, before and after the bulk of their work was done. On days when the traders had higher testosterone levels than average, they took larger risks. However, higher-than-average levels of cortisol (a hormone associated with stress) correlated with risk-averse behavior. With millions of dollars on the line, hormones could be making the difference between a good day at

## Research into reward pathways and the way your brain promotes impulsive behavior can help prevent making purchases and decisions that you would regret.

given a dose of oxytocin, a hormone long associated with social bonding. Those who received the oxytocin boost were more trusting with their money and invested larger amounts with a broker. However, if they made investments through a computer program rather than a person, the oxytocin had no effect on their investment strategy. These results suggest that social and neurobiological factors interact to play a role in such decisions, and these kinds of effects are at the heart of many economic decisions. More research in this area could lead to more rational investment strategies.

the market and a very bad one.

Neuroscience can change our current thoughts about the economy in many other ways. Research on autism spectrum disorders is discovering promising treatments, but also revealing opportunities for workplaces to employ the unique abilities of neurodiverse people. Research into reward pathways and the way your brain promotes impulsive behavior can help prevent making purchases and decisions that you would regret. Scientists are also studying unconscious biases and discrimination, in an effort to help eliminate negative prejudices in hiring

and employment. These are only a few of the practical applications of neuroscience, and more are anticipated. Sometime in the near future, neuroscience could have all the tools needed to design a better, and more inclusive, economic system.

### ETHICS AND THE FUTURE OF NEUROSCIENCE



Modern science has the potential to change some of the most fundamental beliefs of our society. Brain science, in particular, has raised many ethical issues. Consider the history of brain research, where early attempts to understand the brain started or exacerbated practices such as phrenology, eugenics, forced sterilization, and unnecessary lobotomies. When the ethical frameworks of science fail, it can incur consequences that affect not only individuals, but society as a whole.

In the future, new technologies that are already on the horizon will raise serious ethical questions. Genetics is one area under intense scrutiny. As you’ve read in this book, you’ve seen that many brain diseases have their roots in your genetic code, and scientists are now able to screen for some of these diseases while children are in the womb. Emerging technologies might soon help us identify potential problems and alter a child’s genes to prevent it. But is it ethical to alter an unborn child’s genetics to cure autism? Other genetic diseases, like Huntington’s, will only manifest much later in life. Is it acceptable to “pre-treat” this disease with genetic alterations? What

about making children smarter or increasing their chance of getting a perfect math score on their SATs? Some people believe that all children have the right to be genetically enhanced, while others insist that they retain the right *not* to be enhanced.

And who would have access to these enhancements? Will they only be available to children of the rich and powerful, leaving most of us behind? Similar questions can be asked of other therapies, like drugs or devices like transcranial stimulation, which alter the brain in order to treat it.

In the past, these questions were often posed by authors of science fiction. But with the startling technological advances of recent decades, these real-world challenges might be closer than you think. In fact, many scientists and doctors already deal with serious ethical quandaries created by neuroscience. For example, scientists can detect specific biomarkers for disorders such as depression, psychosis, and certain types of chronic pain. Are medical professionals obligated to take steps to treat a disease or disorder that currently shows no symptoms and might never actually materialize? When is the right time to intervene?

There are even thornier questions to consider: When getting permission to treat the brain in some way, the organ that gives consent is the same as the organ being treated. How does that affect the idea of “informed consent” in cases like Alzheimer’s disease or a debilitating brain tumor? Should a doctor proceed with treatment when the patient (that is, his or her brain)

might not have had the ability to properly consent?

The questions raised in this chapter have no easy answers. Your responses could depend on your religion, your socioeconomic class — and, yes, on the activity of your hormones, your neurotransmitters, and the progressive maturation and aging of your nervous system. The brain is the most complicated structure in the known universe, and investigating its mysteries seems to produce as many questions as answers — and these questions are scientific, ethical, legal and social. But the progress of science has always stirred up “inconvenient” questions about ethical behavior, social conventions, and the proper use of our institutions. Asking those questions early will help researchers and the public work together to create strong ethical frameworks for our evolving society.

Science is an ongoing process. Neuroscience has made many beneficial advances, but facts are also evolving as discoveries emerge. We are only on the very cusp of understanding the billions of cells and trillions of connections that form the human brain. Stay curious about the neuroscience you read in the news, keeping in mind what you have learned in this book to give you context behind the headlines. You are part of science, too. Dialogues between scientists are as vital as dialogues between neuroscientists and society. Creating a forum for debate and discussion holds out the best hope of answering questions in ways that advance our society now and in the future. ■



# GLOSSARY

**Acetylcholine** A critical neurotransmitter that controls functions such as memory, attention, sleep, heart rate, and muscular activity.

**Action Potential** An electrical charge that travels along the axon to the neuron's terminal, where it triggers the release of a neurotransmitter. This occurs when a neuron is activated and temporarily reverses the electrical state of its interior membrane from negative to positive.

**Addiction** Loss of control over drug intake or compulsive seeking and taking of drugs, despite adverse consequences.

**Adenosine** A neurochemical that inhibits wakefulness, serving the purpose of slowing down cellular activity and diminishing arousal. Adenosine levels decrease during sleep.

**Adrenal Gland** An endocrine organ that secretes hormones. The outer layer (adrenal cortex) secretes the stress hormone cortisol. The inner portion (adrenal medulla) secretes epinephrine and norepinephrine in concert with the activation of the sympathetic nervous system in the “fight or flight” response.

**Alzheimer’s Disease (AD)** A major cause of dementia in the elderly, this neurodegenerative disorder is characterized by the death of neurons in the hippocampus, cerebral cortex, and other brain regions. The earliest symptoms of the disease include forgetfulness; disorientation as to time or place; and difficulty with concentration, calculation, language, and judgment. In the final stages, individuals are incapable of self-care and may be bedridden.

**Amnesia** A memory impairment usually caused by brain damage or disease, or by drugs such as some anesthetics. People with amnesia may be unable to recall events from the past, form new memories, or both.

**Amygdala** A structure in the forebrain that is an important component of the limbic system and plays a central role in emotional learning, particularly within the context of fear.

**Amyotrophic Lateral Sclerosis (ALS)** Commonly known as Lou Gehrig’s disease, ALS causes motor neurons in the brain and spinal cord to disintegrate, resulting in loss of control of voluntary muscle movements such as walking.

**Analgesic** A drug that relieves pain without causing a loss of consciousness.

**Anxiety** A state of heightened arousal characterized by intense worry.

**Aphasia** Disturbance in language comprehension or production, often as a result of a stroke.

**Apoptosis** Programmed cell death induced by specialized biochemical pathways, often serving a specific purpose in the development of an animal.

**Arousal** A physiological state involving changes in the body and brain that motivate behavior and enable response to stimuli.

**Astrocyte** A star-shaped glial cell in the central nervous system that nourishes neurons; regulates the formation, maintenance, and pruning of synapses; and contributes to the blood-brain barrier.

**Attention** A state of arousal in which the brain’s sensory processing is directed at a limited number of stimuli. Voluntary (endogenous) attention is a conscious decision to focus on a particular stimulus. Involuntary (exogenous) attention is an unplanned focus on a change in the environment, such as a loud noise or sudden movement.

**Attention Deficit Hyperactivity Disorder (ADHD)** A condition characterized by excessively inattentive, hyperactive, or impulsive behaviors.

**Auditory Nerve** A branch of the vestibulocochlear nerve that transmits auditory information from the cochlea of the ear to the brain.

**Autism Spectrum Disorder (ASD)** A set of conditions characterized, in part, by impaired social communication and interaction, and narrow, obsessive interests or repetitive behaviors.

**Autonomic Nervous System** A part of the peripheral nervous system responsible for regulating the activity of internal organs. It includes the sympathetic and parasympathetic nervous systems.

**Axon** The fiber-like extension of a neuron by which it sends information to target cells.

**Axon Terminal** The ends of axons where neurotransmitters are released to target cells.

**Basal Ganglia** A group of interconnected structures located deep in the brain that play an important role in voluntary movement, motor skill learning, and habits. These structures include the caudate nucleus, putamen, nucleus accumbens, globus pallidus, and substantia nigra.

**Benzodiazepines** A class of drugs that enhance activity of the brain’s primary inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), to produce sedative and anti-anxiety effects. Benzodiazepines are often prescribed to treat anxiety disorders and insomnia.

**Blood-Brain Barrier** A protective membrane composed of tightly packed endothelial cells lining the brain’s capillaries and highly specialized astrocytes, which controls the passage of certain molecules into and out of the brain.

**Brain Waves** Oscillating patterns of brain activity that can be detected and recorded using electroencephalography (EEG).

**Brain-Derived Neurotrophic Factor (BDNF)** A neurotrophic peptide that supports the growth and survival of neurons.

**Brainstem** The major route by which the forebrain sends information to and receives information from the spinal cord and peripheral nerves. The brainstem includes the midbrain, pons, and medulla, and it controls, among other things, respiration and the regulation of heart rhythms.

**Broca’s Area** A region of the frontal lobe — usually the left hemisphere — that governs speech production.

**Cell Body** Also called the soma, the part of a neuron that contains the nucleus (with DNA) and the organelles, but not the projections such as the axon or dendrites.

**Central Nervous System** The brain and spinal cord.

**Cerebellum** A large structure located at the roof of the hindbrain that helps to control the coordination of movement by making connections to the pons, medulla, spinal cord, and thalamus. It also may be involved in aspects of motor learning.

**Cerebral Cortex** The wrinkled, outermost layer of the cerebrum consisting primarily of neuron cell bodies.

**Cerebrum** The largest part of the human brain associated with higher order functioning, such as thinking, perceiving, planning, and understanding language, as well as the control of voluntary behavior.

**Circadian Rhythms** A cycle of behavior or physiological change lasting approximately 24 hours.

**Cochlea** A snail-shaped, fluid-filled organ of the inner ear responsible for converting sound into electrical potentials to produce an auditory sensation.

**Cognitive Behavioral Therapy** A form of counseling used to identify and change negative thought patterns that can contribute to anxiety and mood disorders.

**Computational Neuroscience** A field of neuroscience research that uses computer programs and algorithms to analyze information about the brain, and develops mathematical models to explain brain function.

**Cones** A primary receptor cell for vision located in the retina. It is sensitive to color and is used primarily for daytime vision.

**Corpus Callosum** The large bundle of nerve fibers linking the left and right cerebral hemispheres.

**Cortisol** A hormone manufactured by the adrenal cortex. In humans, cortisol is secreted in the greatest quantities before dawn, readying the body for the activities of the coming day.

**Cranial Nerves** Twelve pairs of nerves that can be seen on the bottom surface of the brain. Some of these nerves transmit sensory information; some control the movement of face, head, and neck muscles; others transmit information to internal organs to regulate functions such as blood pressure and heart rate.

**Critical Period** A period of heightened plasticity in brain development when certain experiences and sensory inputs are required for the formation of functional brain circuits.

**Declarative Memory** Also called explicit memory, a type of memory that can be consciously retrieved. It includes memory of facts (semantic memory) and memory of personal experiences (episodic memory).

**Default Mode Network** A collection of brain regions activated during quiet rest.

**Dementia** A decline in cognitive ability that interferes with day-to-day functioning.

**Dendrite** A treelike extension of the neuron cell body. The dendrite is the primary site for receiving and integrating information from other neurons.

**Depolarization** A change in a neuron’s membrane potential in which the cytoplasm becomes more positively charged. Neurons must depolarize beyond a certain threshold to generate an action potential.

**Depression** A psychiatric disorder characterized by sadness, hopelessness, pessimism, loss of interest in life, reduced emotional well-being, and abnormalities in sleep, appetite, and energy level.

**Dopamine** A catecholamine neurotransmitter present in three circuits of the brain: one that regulates movement; a second, thought to be important for cognition and emotion; and a third that regulates the endocrine system. Deficits of dopamine in the motor circuit are associated with Parkinson’s disease. Abnormalities in the second circuit have been implicated in schizophrenia.

**Down Syndrome** A condition that results from the presence of an extra copy of chromosome 21. This genetic anomaly is associated with physical and developmental characteristics, including mild to moderate intellectual disabilities; low muscle tone; and an increased risk of congenital heart defects, respiratory problems, and digestive tract obstruction.

**Dyslexia** A pronounced difficulty with reading despite normal intelligence, education, and motivation.

**Electroencephalography (EEG)** A technology used to record electrical activity of the human brain in response to a variety of stimuli and activities.

**Endorphins** Neurotransmitters produced in the brain that generate cellular and behavioral effects like those of morphine.

**Epilepsy** A disorder characterized by repeated seizures, which are caused by abnormal excitation of large groups of neurons in various brain regions. Epilepsy can be treated with many types of anticonvulsant medications.



**Epinephrine** A hormone released by the adrenal medulla and specialized sites in the brain. During times of stress, epinephrine, also known as adrenaline, is quickly released into the bloodstream. It then serves to put the body into a general state of arousal, which enables it to cope with the challenge.

**Episodic Memory** A type of declarative memory consisting primarily of memory of personal experiences.

**Estrogen** A female sex hormone produced primarily in the ovaries.

**Excitation** A change in the electrical state of a neuron that is associated with an enhanced probability of action potentials.

**Excitatory** A type of neuron (or neurotransmitter) that excites target neurons and increases the likelihood of their firing an action potential.

**Executive Function** Higher-level processing that takes place in the brain's prefrontal cortex. Executive function comprises impulse control, working memory, and mental flexibility.

**Forebrain** A region of the developing brain that goes on to become the cerebral hemispheres and major parts of the limbic system.

**Fovea** A small, pitted area in the center of the retina where visual acuity is highest, due to a high density of cones.

**Fragile X Syndrome** A genetic condition resulting from a mutation in the FMR1 gene that causes intellectual disability.

**Frontal Lobe** One of the four subdivisions of the cerebral cortex. The frontal lobe has a role in controlling movement and in the planning and coordinating of behavior.

**Functional Magnetic Resonance Imaging (fMRI)** A technology that uses magnetic fields to detect activity in the brain by monitoring blood flow.

**Gamma-Aminobutyric Acid (GABA)** An amino acid neurotransmitter in the brain whose primary function is to inhibit the firing of nerve cells.

**Glia** Specialized cells that nourish and support neurons.

**Glucocorticoid Hormones** Hormones that produce an array of effects in response to stress. Some of the actions of glucocorticoids help to mediate the stress response, while other, slower actions counteract the primary response to stress and help to re-establish homeostasis.

**Glutamate** An amino acid neurotransmitter that acts to excite neurons. Glutamate stimulates N-methyl-d-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA). AMPA receptors have been implicated in activities ranging from learning and memory to development and specification of nerve contacts in developing animals. Stimulation of NMDA receptors may promote beneficial changes, whereas overstimulation may be a cause of nerve cell damage or death in neurological trauma and stroke.

**Gray Matter** Portions of the brain that are gray in color because they are composed mainly of neural cell bodies, rather than myelinated nerve fibers, which are white. It includes the cerebral cortex as well as subcortical structures.

**Growth Cone** A distinctive structure at the growing end of most axons. It is the site where new material is added to the axon.

**Hair Cells** Sensory receptors in the cochlea that convert mechanical vibrations to electrical signals; they in turn excite the 30,000 fibers of the auditory nerve that carry the signals to the brainstem.

**Hindbrain** The most posterior part of the brain, comprising the pons, medulla, and cerebellum.

**Hippocampus** A seahorse-shaped structure located within the brain and considered an important part of the limbic system. One of the most studied areas of the brain, it is involved in learning, memory, and emotion.

**Histamine** A compound with multiple functions in the body. In the brain, histamine acts as a neurotransmitter to stimulate arousal. Local inflammatory responses in the body trigger the release of histamines from immune cells.

**Homeostasis** The normal equilibrium of body function.

**Hormones** Chemical messengers secreted by endocrine glands to regulate the activity of target cells. They play a role in sexual development, calcium and bone metabolism, growth, and many other activities.

**Huntington's Disease** A genetic disorder characterized by involuntary jerking movements of the limbs, torso, and facial muscles, often accompanied by mood swings, depression, irritability, slurred speech, and clumsiness.

**Hyperpolarization** A change in a neuron's membrane potential in which the cytoplasm becomes more negatively charged and therefore less likely to fire an action potential.

**Hypothalamus** A complex brain structure composed of many nuclei with various functions, including regulating the activities of internal organs, monitoring information from the autonomic nervous system, controlling the pituitary gland, and regulating sleep and appetite.

**Inhibition** A change in the electrical state of a neuron that is associated with a decreased probability of firing an action potential.

**Inhibitory** A type of neuron (or neurotransmitter) that prevents a target neuron from firing.

**Insomnia** A sleep disorder in which people have trouble falling and/or staying asleep.

**Interneuron** A neuron that exclusively signals another neuron.

**Involuntary Movement** A movement that occurs without conscious control, such as a reflex.

**Ion Channel** Proteins embedded in the cell membrane that allow ions or other small molecules to enter or leave the cell.

**Limbic System** A group of structures deep within the brain involved in motivation and emotion. The hippocampus, amygdala, thalamus, and hypothalamus are all a part of the limbic system.

**Long-Term Memory** The final phase of memory, in which information storage may last from hours to a lifetime.

**Long-Term Potentiation (LTP)** A long-lasting increase in synaptic strength resulting from an increased number of neurotransmitter receptors on the post-synaptic neuron.

**Magnetic Resonance Imaging (MRI)** A technique that uses magnetic fields to create a high-quality, three-dimensional image of organs and structures inside the body. This technology is noninvasive and does not expose the body to X-rays or other radiation.

**Magnetoencephalography (MEG)** A technique that can quantitatively measure the strength of activity in various regions of the brain at millisecond resolution.

**Medulla** Also called the medulla oblongata, a structure of the brainstem that controls basic functions like swallowing, breathing, and heart rate.

**Melatonin** A hormone produced in the pineal gland that regulates responses to light-dark cycles and induces sleep at night.

**Membrane Potential** The voltage difference between the inside and outside of a neuron. The typical membrane potential of a neuron at rest is -70mV.

**Mentalization** The ability to understand the mental states and thoughts of others and oneself.

**Microglia** Glial cells in the central nervous system that function as resident immune cells.

**Midbrain** The most anterior segment of the brainstem. With the pons and medulla, the midbrain is involved in many functions, including regulation of heart rate, respiration, pain perception, and movement.

**Migration** The process whereby new neurons find their proper position in the brain.

**Mitochondria** Small cylindrical organelles inside cells that provide energy for the cell by converting sugar and oxygen into special energy molecules, called adenosine triphosphate (ATP).

**Mood** A general state of mind and emotional disposition.

**Motor Cortex** A specialized region in the cortex involved in the planning and execution of movement.

**Motor Neuron** A neuron that carries information from the central nervous system to muscles.

**Motor Unit** A functional unit made up of an alpha motor neuron and all of the muscle fibers it contains and controls, ranging from a few to a hundred or more.

**Myelin** Compact fatty material that surrounds and insulates the axons of some neurons and accelerates the transmission of electrical signals.

**Narcolepsy** A sleep disorder resulting from the loss of orexin neurons in the hypothalamus that causes pronounced sleepiness during the day.

**Nerve Growth Factor (NGF)** A substance whose role is to guide neuronal growth during embryonic development, especially in the peripheral nervous system. Nerve growth factor also probably helps to sustain neurons in adults.

**Neurodegeneration** The progressive destruction and loss of neurons. Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS) are examples of neurodegenerative diseases.

**Neurogenesis** The production and growth of new nerve cells during development and, in select brain regions, throughout life.

**Neuromodulator** A chemical messenger that alters the strength of a synapse by modifying the production and/or response to neurotransmitters. Neurotransmitters, hormones, and immune molecules can all function as neuromodulators.

**Neuron** A nerve cell specialized for the transmission of information and characterized by long, fibrous projections called axons and shorter, branchlike projections called dendrites.

**Neurotransmitters** Chemical messengers released by neurons at a synapse for the purpose of relaying information to other cells.

**Neurotransmitter Receptors** Proteins embedded in the postsynaptic cell membrane that bind neurotransmitters to alter the cell's excitability.

**Nociceptors** Nerve endings that signal the sensation of pain.

**Nodes of Ranvier** Unmyelinated gaps in an axon's myelin sheath along which electrical impulses travel.

**Nondeclarative Memory** Also called implicit or procedural memory, a type of long-term memory that is stored and retrieved without conscious effort.

**Norepinephrine** A catecholamine neurotransmitter produced both in the brain and in the peripheral nervous system. Norepinephrine is involved in arousal and sleep regulation, mood, and blood pressure.

**Nucleus Accumbens** A region at the base of the forebrain that is a part of the basal ganglia and is important in motivation and reward.



**Obsessive-compulsive Disorder** An anxiety disorder characterized by uncontrollable, recurring thoughts (obsessions) and repetitive behaviors (compulsions) that attempt to mitigate the obsessions.

**Occipital Lobes** One of the four subdivisions of the cerebral cortex. The occipital lobe plays a role in processing visual information.

**Olfactory Bulbs** Round, knoblike structures of the brain responsible for processing the sense of smell. Specialized olfactory receptor cells are located in a small patch of mucous membrane lining the roof of the nose. Axons of these sensory cells pass through perforations in the overlying bone and enter two elongated olfactory bulbs lying on top of the bone.

**Oligodendrocyte** A type of glial cell in the central nervous system that forms myelin.

**Opioids** Substances that bind to opioid receptors in the brain to relieve pain. Endorphins are a type of endogenous opioid produced in the brain. Natural and synthetic opioids, such as morphine and codeine, can be prescribed to treat pain.

**Optic Chiasm** The place in the brain where the optic nerves meet and some axons cross over to the opposite (contralateral) hemisphere in animals with binocular vision.

**Optic Nerve** The bundle of neurons that transmit information from the retina to the brain.

**Orexin** A hormone produced in the hypothalamus that stimulates arousal.

**Oxytocin** A hormone produced in the hypothalamus and released by the pituitary gland that initiates the release of milk from mammary glands and stimulates uterine contractions. It is also involved in love and social bonding.

**Pain** An unpleasant sensory and emotional experience often signaling tissue damage, or the potential for damage.

**Paralysis** The loss of muscle function in all or part of the body, usually due to nerve damage.

**Parasympathetic Branch** A branch of the autonomic nervous system concerned with the conservation of the body's energy and resources during relaxed states.

**Parietal Lobes** One of the four subdivisions of the cerebral cortex. The parietal lobe plays a role in sensory processes, attention, and language.

**Parkinson's Disease (PD)** A movement disorder caused by the death of dopamine neurons in the substantia nigra, located in the midbrain. Symptoms include slowness of movement, muscular rigidity, and walking and balance impairment.

**Peripheral Nervous System** The nerves outside of the brain and spinal cord.

**Photoreceptors** A nerve ending, cell, or group of cells specialized to sense or receive light.

**Pineal Gland** A small endocrine gland in the brain that produces melatonin.

**Pituitary Gland** An endocrine organ closely linked with the hypothalamus. In humans, the pituitary gland is composed of two lobes and secretes several different hormones that regulate the activity of other endocrine organs throughout the body.

**Plasticity** The ability of the brain to modify its neural connections to adapt to challenges in the environment.

**Pons** A part of the hindbrain that, with other brain structures, controls respiration and regulates heart rhythms. The pons is a major route by which the forebrain sends information to and receives information from the spinal cord and peripheral nervous system.

**Positron Emission Tomography (PET)** A method of measuring brain function based on the detection of radioactivity emitted when positrons, positively charged particles, undergo radioactive decay in the brain. Computers then build three-dimensional images of changes in blood flow based on the amount of radiation emitted in different brain regions. The more brain activity, the more vivid the picture that is created.

**Postsynaptic Neuron** In a synapse, the neuron receiving chemical messages.

**Prefrontal Cortex (PFC)** A region at the front of the frontal lobe involved in the brain's higher-level functions such as planning, decision-making, working memory, and inhibitory control.

**Presynaptic Neuron** In a synapse, the neuron transmitting chemical messages to a target neuron.

**Prostaglandins** Small lipid molecules that enhance nociceptor sensitivity to increase pain and prevent further tissue damage.

**Rapid Eye Movement (REM) Sleep** The part of the sleep cycle when active dreaming takes place. It is characterized by neocortical EEG waves similar to those observed during waking. This state is accompanied by paralysis of the body's muscles; only the muscles that allow breathing and control eye movements remain active.

**Reflexes** Considered the simplest and most fundamental movements, they are relatively fixed, automatic muscle responses to particular stimuli, such as the slight extension of the leg when a physician taps the knee with a small rubber hammer.

**Retina** A multilayered sensory tissue that lines the back of the eye and contains the receptor cells to detect light.

**Reuptake** A process by which released neurotransmitters are absorbed for later reuse.

**Rods** A sensory neuron located in the periphery of the retina. The rod is sensitive to light of low intensity and is specialized for nighttime vision.

**Saltatory Conduction** The process by which action potentials "jump" along the unmyelinated nodes of Ranvier, speeding electrical transmission.

**Schizophrenia** A chronic disorder characterized by psychosis (e.g., hallucinations and delusions), flattened emotions, and impaired cognitive function.

**Schwann Cell** A type of glial cell in the peripheral nervous system that forms myelin.

**Selective Serotonin Reuptake Inhibitors (SSRIs)** Drugs that block the reuptake of serotonin, increasing its availability in the synapse. SSRIs are used to treat depression and other disorders.

**Semantic Memory** A type of declarative memory that involves memory of facts.

**Serotonin** A monoamine neurotransmitter believed to play many roles, including but not limited to temperature regulation, sensory perception, and the onset of sleep. Neurons using serotonin as a transmitter are found in the brain and gut. Several antidepressant drugs are targeted to brain serotonin systems.

**Short-Term Memory** A phase of memory in which a limited amount of information may be held for several seconds or minutes.

**Somatosensory Cortex** A region of the parietal lobe responsible for processing touch and pain signals from the body.

**Spinal Cord** A bundle of nerve fibers running through the vertebral column that primarily functions to facilitate communication between the brain and the rest of the body.

**Stem Cells** Unspecialized cells that renew themselves for long periods through cell division.

**Stress** Any external stimulus that threatens homeostasis. Many kinds of stress have a negative effect on the body, but some kinds can be helpful.

**Striatum** A cluster of neurons deep within the brain divided into ventral and dorsal regions. The ventral striatum consists of the nucleus accumbens and the olfactory tubercle, while the dorsal striatum consists of the caudate and putamen. The striatum is a part of the basal ganglia and is involved in reward processing.

**Stroke** A block in the brain's blood supply. A stroke can be caused by the rupture of a blood vessel, a clot, or pressure on a blood vessel (as may be caused by a tumor). Without oxygen, neurons in the affected area die, and the part of the body controlled by those cells cannot function. A stroke can result in loss of consciousness and death.

**Substantia Nigra** A region of the midbrain involved in movement and reward. Parkinson's disease destroys the dopamine-producing neurons in this region.

**Suprachiasmatic Nucleus (SCN)** A small group of nerve cells in the hypothalamus that express clock proteins, which go through a biochemical cycle of about 24 hours. This sets the pace for daily cycles of activity, sleep, hormone release, and other bodily functions.

**Sympathetic Branch** A branch of the autonomic nervous system responsible for mobilizing the body's energy and resources during times of stress and arousal.

**Synapse** A physical gap between two neurons that functions as the site of information transfer from one neuron to another.

**Synaptic Plasticity** The ability of synapses to alter their strength by changing their size, shape, number of receptors, and amount of neurotransmitter released.

**Synaptic Pruning** The elimination of weak or non-functioning synapses to fine-tune neural circuitry.

**Taste Buds** A sensory organ found on the tongue.

**Temporal Lobes** One of the four major subdivisions of each hemisphere of the cerebral cortex. The temporal lobe functions in auditory perception, speech, and complex visual perceptions.

**Testosterone** A sex hormone produced primarily in the testes but also in lower amounts in the adrenal cortex and ovaries.

**Thalamus** A structure consisting of two egg-shaped masses of nerve tissue, each about the size of a walnut, deep within the brain. The key relay station for sensory information flowing into the brain, the thalamus filters out information of particular importance from the mass of signals entering the brain.

**Trophic Factors** Small proteins in the nervous system that are necessary for the development, function, and survival of specific groups of neurons.

**Vagus Nerve** The tenth cranial nerve, it transmits signals from the brain to the heart, lungs, and digestive tract.

**Voluntary Movement** A motor action that is consciously planned and executed.

**Wernicke's Area** A region in the temporal lobe responsible for comprehension of language.

**White Matter** The part of the brain that contains myelinated nerve fibers. The white matter gets its color from myelin, the insulation covering nerve fibers.

**Working Memory** A temporary type of declarative memory, the ability to keep a piece of information "in mind." It is limited to a small amount of data and, unless transferred to long-term memory, decays within a few seconds.



# NEUROSCIENCE RESOURCES

The Society for Neuroscience  
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Canadian Association for Neuroscience  
can-acn.org

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cihr-irsc.gc.ca

Dana Alliance for Brain Initiatives  
dana.org

Faculty for Undergraduate Neuroscience  
funfaculty.org

Federation of European Neuroscience Societies  
fens.org

Foundation for Biomedical Research  
fbresearch.org

Gatsby Charitable Foundation  
gatsby.org.uk

International Brain Research Organization  
ibro.info

La Sociedad Mexicana de Ciencias Fisiológicas (Mexican Society of Physiological Sciences)  
smcf.org.mx

Lundbeck Foundation  
lundbeckfonden.com

The Kavli Foundation  
kavlifoundation.org

Stanley Center at Broad Institute  
broadinstitute.org/stanley

Wellcome Trust  
wellcome.ac.uk

U.S. National Institutes of Health (NIH)  
nih.gov

NIH Institutes and Centers  
National Eye Institute  
nei.nih.gov

National Heart, Lung and Blood Institute  
nhlbi.nih.gov

National Institute on Aging  
nia.nih.gov

National Institute on Alcohol Abuse and Alcoholism  
niaaa.nih.gov

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nibib.nih.gov

National Institute of Child Health and Human Development  
nichd.nih.gov

National Institute on Deafness and Other Communication Disorders  
nidcd.nih.gov

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nidcr.nih.gov

National Institute on Drug Abuse  
nida.nih.gov

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niehs.nih.gov

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nigms.nih.gov

National Institute of Mental Health  
nimh.nih.gov

National Institute of Neurological Disorders and Stroke  
ninds.nih.gov

National Institute of Nursing Research  
nintr.nih.gov

National Library of Medicine  
nlm.nih.gov

National Center for Advancing Translational Sciences  
ncats.nih.gov

National Center for Complementary and Integrative Health  
nccih.nih.gov

U.S. National Science Foundation  
nsf.gov

World Health Organization  
who.int

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The Kavli Foundation, established by Fred Kavli, is dedicated to advancing science for the benefit of humanity, promoting public understanding of scientific research, and supporting scientists and their work. The Foundation’s mission is implemented through an international program of research institutes in the fields of astrophysics and theoretical physics, nanoscience, and neuroscience, and

through the support of conferences, symposia, endowed professorships, journalism workshops, and other activities. The Foundation is also a founding partner of the Kavli Prizes, biennial \$1 million prizes that recognize scientists for their seminal advances in three research areas: astrophysics, nanoscience, and neuroscience.



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Gatsby is a trust set up by David Sainsbury to realize his charitable objectives in plant science research, neuroscience research, science and engineering education, economic development in Africa, public policy research and advice, and the arts.

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The Society for Neuroscience (SfN) is the world's largest organization of scientists and physicians devoted to understanding the brain and nervous system. The nonprofit organization, founded in 1969, now has nearly 37,000 members in more than 90 countries and over 130 chapters worldwide.

**SfN's mission is to:**

- Advance the understanding of the brain and the nervous system by bringing together scientists of diverse backgrounds, by facilitating the integration of research directed at all levels of biological organization, and by encouraging translational research and the application of new scientific knowledge to develop improved disease treatments and cures.
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