BrainFacts

A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

COVER TO PAGE 35

A Companion Publication to *BrainFacts.org*

1121 14th Street, NW, Suite 1010
Washington, DC 20005 USA
sfn.org

Statistics for diseases and conditions were obtained from the Centers for Disease Control and Prevention, World Health Organization, National Institutes of Health, and voluntary organizations.

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.

Printed and bound in the United States of America

Eighth Edition

Brain Facts is printed on Burgo Chorus Art Silk, made with 30% post-consumer waste, and processed chlorine free.

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.

BrainFacts

A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

A companion to BrainFacts.org

A PUBLIC INFORMATION INITIATIVE OF:

Contributors

The Society for Neuroscience (SfN) would like to thank the dedicated team of SfN members — neuroscientists that volunteered their time and expertise — that guided and reviewed the eighth revision of *Brain Facts*. It is commitments such as these that build communities invested in science education, public outreach, and the advancement of the ever-evolving field of neuroscience.

SfN also recognizes the significant contributions of Charles Yokoyama, PhD, Suzana Herculano-Houzel, PhD, Public Education and Communication Committee Chair Frances Jensen, MD, and *BrainFacts.org* Editor-in-Chief, John Morrison, PhD.

Scientific Review: Angela Jane Roskams, PhD; Charles Jennings, PhD; Charles Yokoyama, PhD; Ed Bilsky, PhD; Emanuel DiCicco-Bloom, PhD; Frances Jensen, MD; James Giordano, PhD; John Morrison, PhD; Katalin Gothard, PhD; Kelley Remole, PhD; Lise Eliot, PhD; Martha Farah, PhD; Maya Sapiurka, PhD; Rebecca Shansky, PhD; Richard Wingate, PhD; Roberta Diaz Brinton, PhD; Robert Greene, PhD; Roberto Caminiti, MD; Rochelle Schwartz-Bloom, PhD; Sarah Dunlop, PhD; Stuart Firestein, PhD; Tracy Bale, PhD

Senior Director, Communications & Marketing: Kara Flynn

Executive Editor: Lisa Chiu

Production Editors: Alexis Wnuk, Emma Lindberg, Juliet M. Beverly, and Michael Richardson

Managing Editor: Jacquelyn Beals

Copy Editors: Kristina Reznikov and Randi Henderson

Writers: Alexis Wnuk, Alison Davis, Clinton Parks, Deborah Halber, Diane Kelly, Gail Zyla, Karen Hopkin, Karen Weintraub, Juliet M. Beverly, Knvul Safia Sheikh, Lindzi Wessel, Lisa Chiu, Marissa Fessenden, Melissa Galinato, Michael Richardson, Sandra Blumenrath, Susan Rojahn

Illustrators: Lydia V. Kibiuk, Baltimore, MD; Devon Stuart, Hershey, PA; Matt Wimsatt, Brooklyn, NY; Richard Lewis Media Group, Watertown MA

Consultant: Hilary Gerstein, PhD

Layout and Design: Dever Designs

Contents

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.

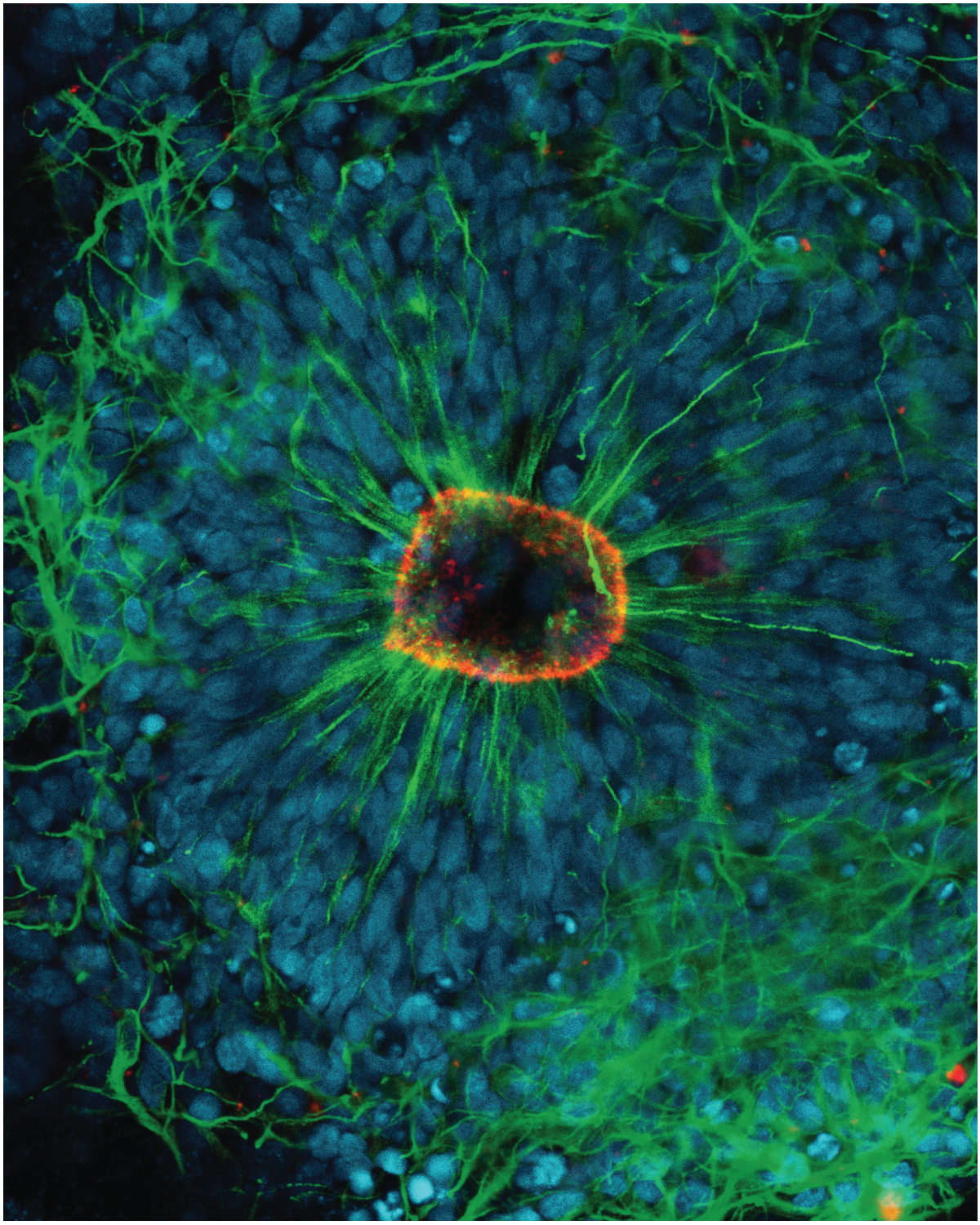
How Research Benefits Human Health

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 leach 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.



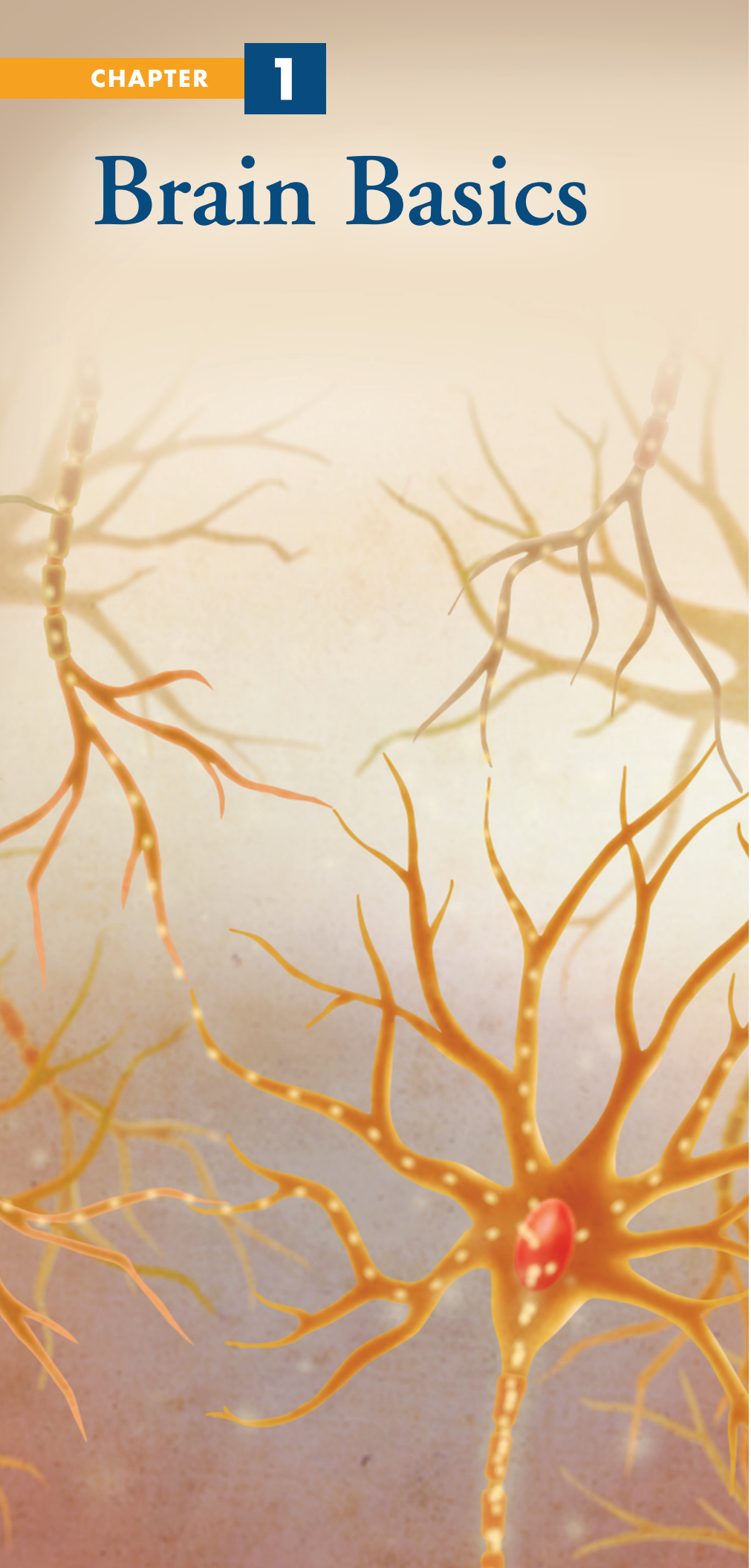
Coulthard, et al. Journal of Neuroscience, 2017.

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.

CHAPTER 1

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.

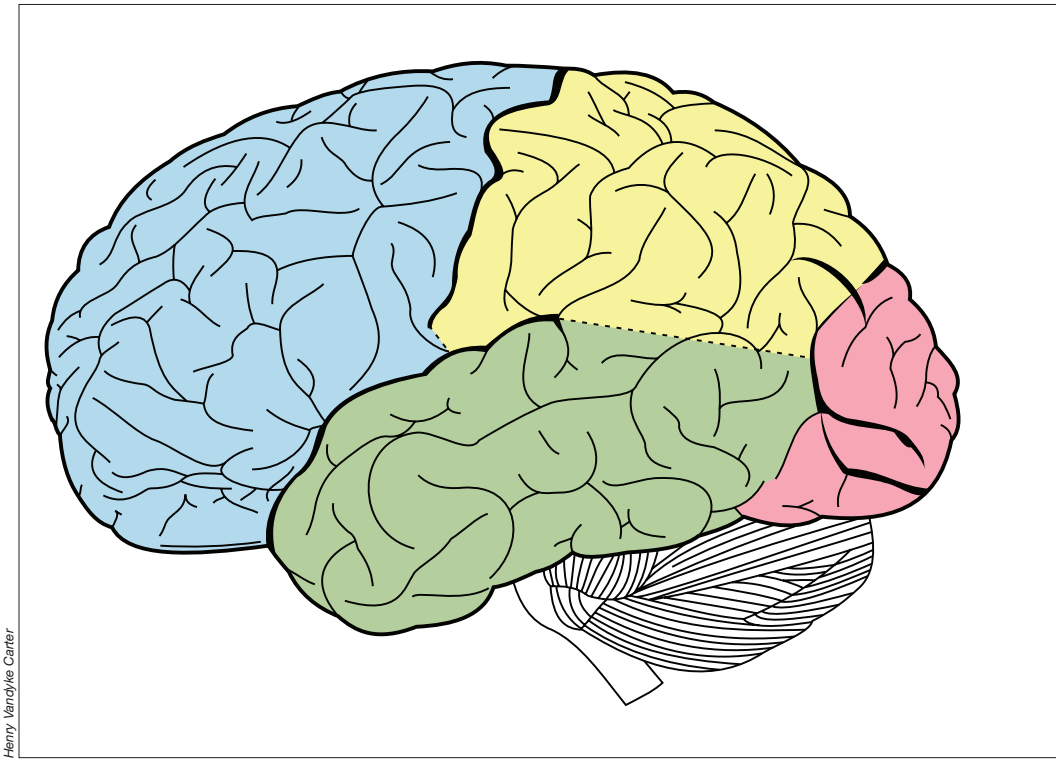
The parietal lobes are located at the top of the brain, immediately behind the frontal lobes. They integrate sensory signals from the skin, process taste, and process some types of visual information.

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 movements 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.



Henry Vandyke Carter

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.

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 electrodes on your scalp, all these signals are in the microvolt range: 20–200 μV for alpha and delta waves, and 5-10 μV for beta and theta waves.

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

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 networks 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 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.

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.

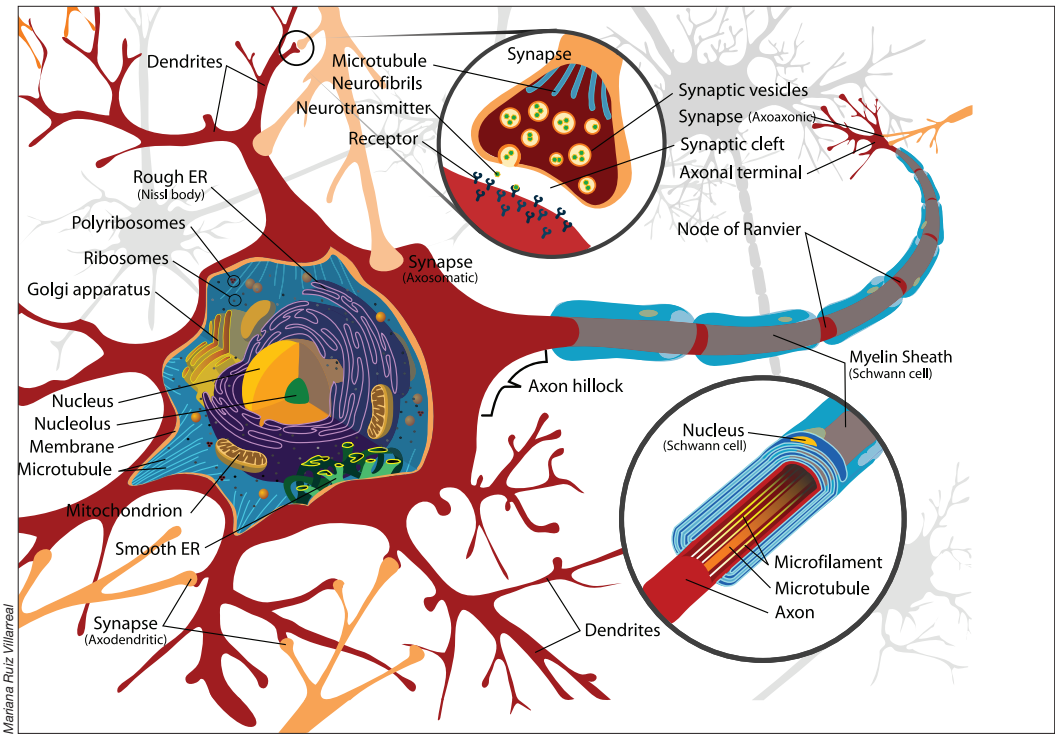
Neuroscientists think each column in the cortex is dedicated to one very specific processing task. But a column's final output can be influenced by the activity of nearby circuits. Every neuron in a circuit has other connections to neurons in neighboring columns. Since every neuron behaves like a microprocessor, 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.

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.

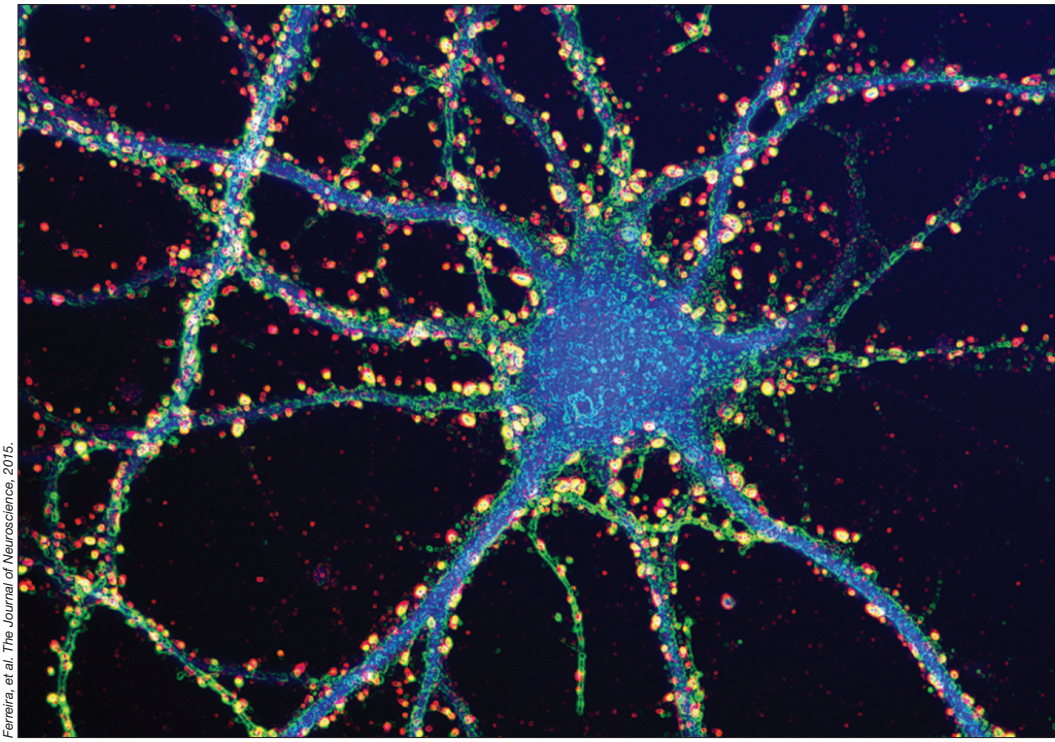
In mammals, the voltage difference across the membrane of a resting neuron is around -70 millivolts (mV), more negative inside the cell than on its outer surface. That membrane potential is affected by signals arriving from other neurons in its circuit, which can make the membrane potential less negative (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 nerotransmitters, including amino acids, gases, small organic chemicals, and short peptides. Neurons can synthesize



Ferreira, et al. The Journal of Neuroscience, 2015.

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 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 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 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 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.

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

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.

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.

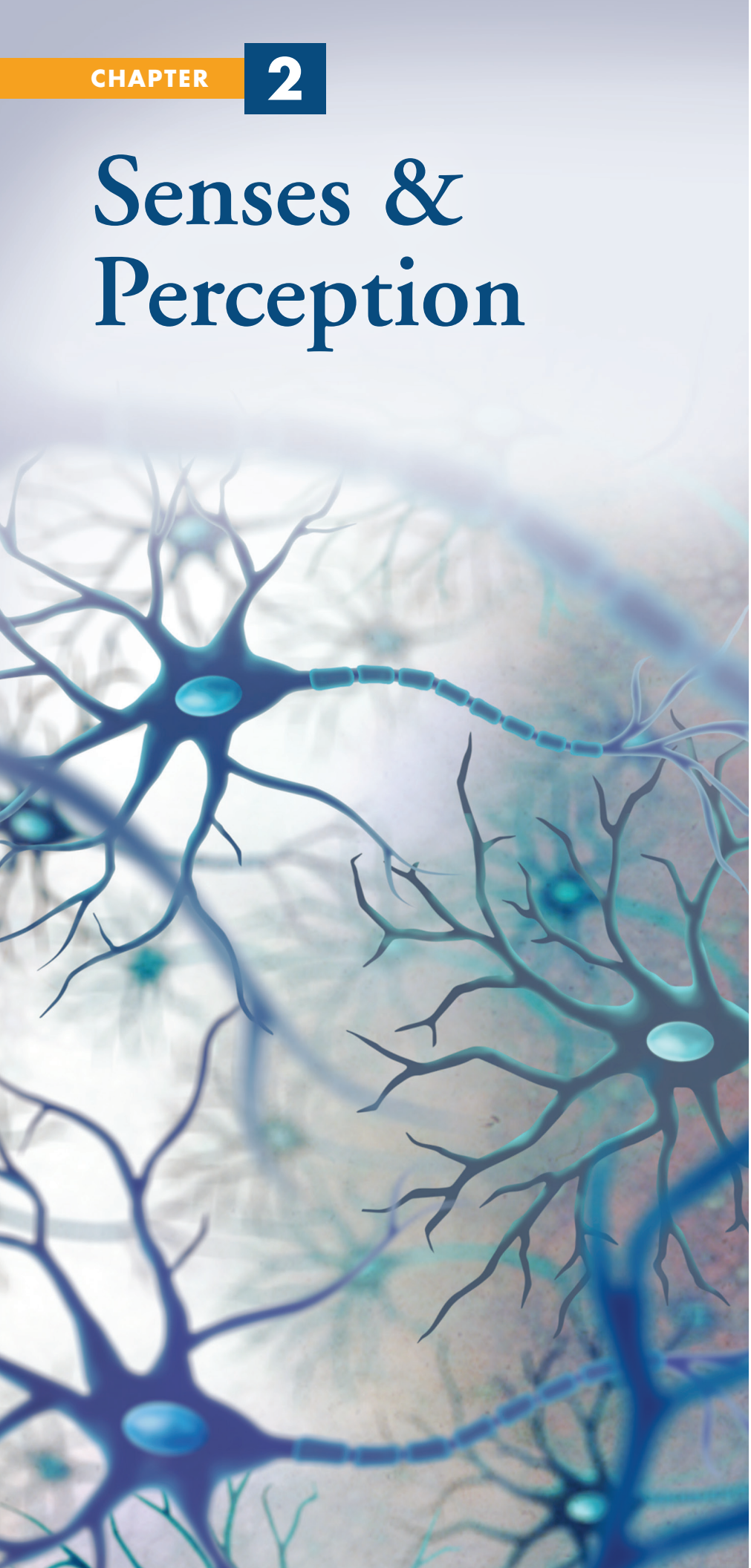
All cells in your body, including neurons, contain the same DNA housing the same genes. Differences among your neurons result from differences in which genes direct cellular activities, a process called gene expression. Each cell (or cell type) builds proteins from a slightly different subset of genes 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.

CHAPTER 2

Senses & Perception



You 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.

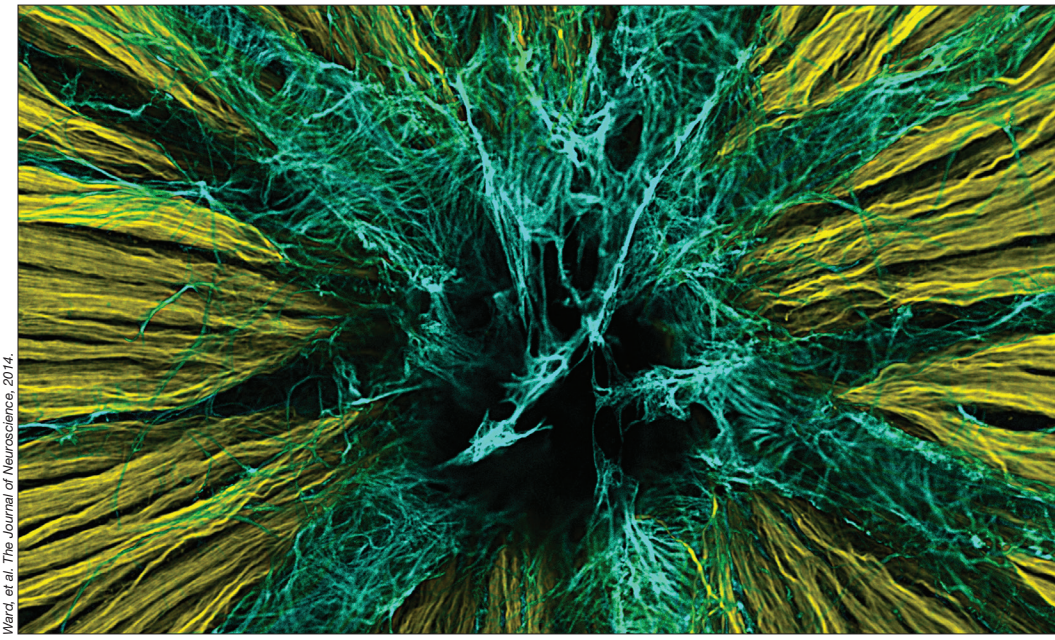
The Three-Layered Retina

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.



Ward, et al. The Journal of Neuroscience, 2014.

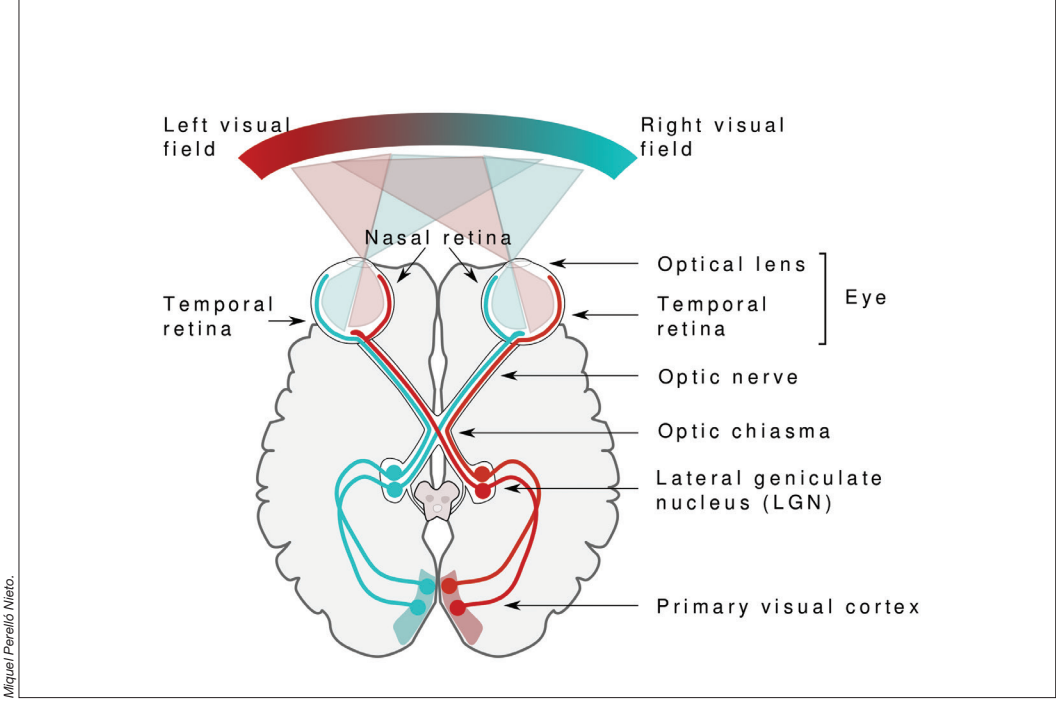
Here, in the back of the eye, is one of the first stops visual information makes on its way to the brain. In this image of a mouse retina, axons of nerve cells are labeled in yellow. They extend through a small opening in the back of the eye — labeled in black — through the optic nerve to higher vision 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 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.



Miquel Perelló 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.

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 detects, 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.

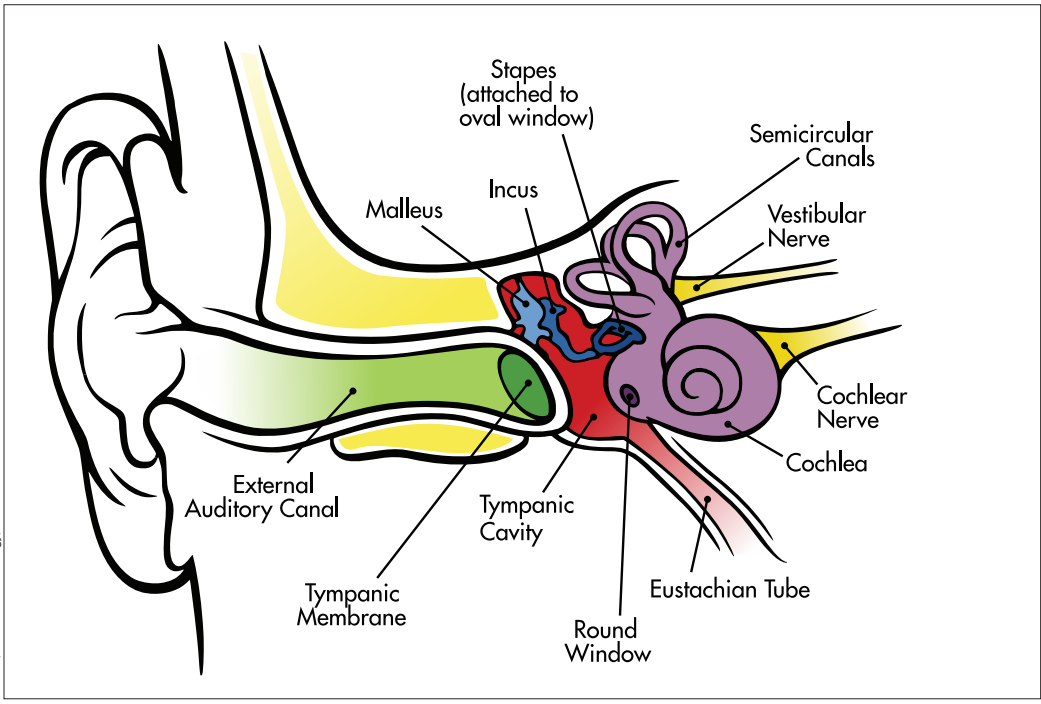
Although sound is processed on both sides of the brain, the left side is typically responsible for understanding and producing speech. Someone with damage to the left auditory cortex (particularly a region called Wernicke's area), as from a stroke, is able to hear a person speak but no longer understands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

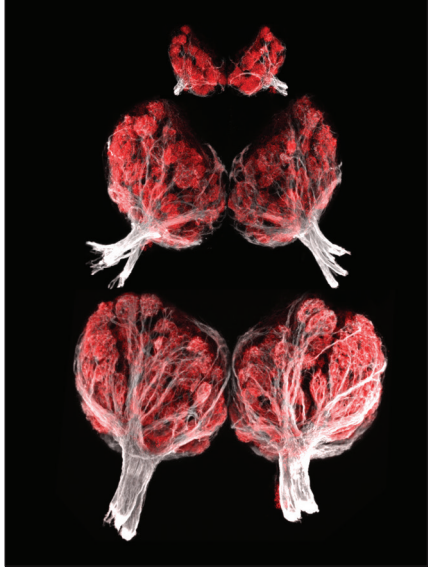


Chittka, et. al. PLoS Biology, 2005.

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.

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

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.



Braubach, et al. The Journal of Neuroscience, 2013.

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.

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, 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.

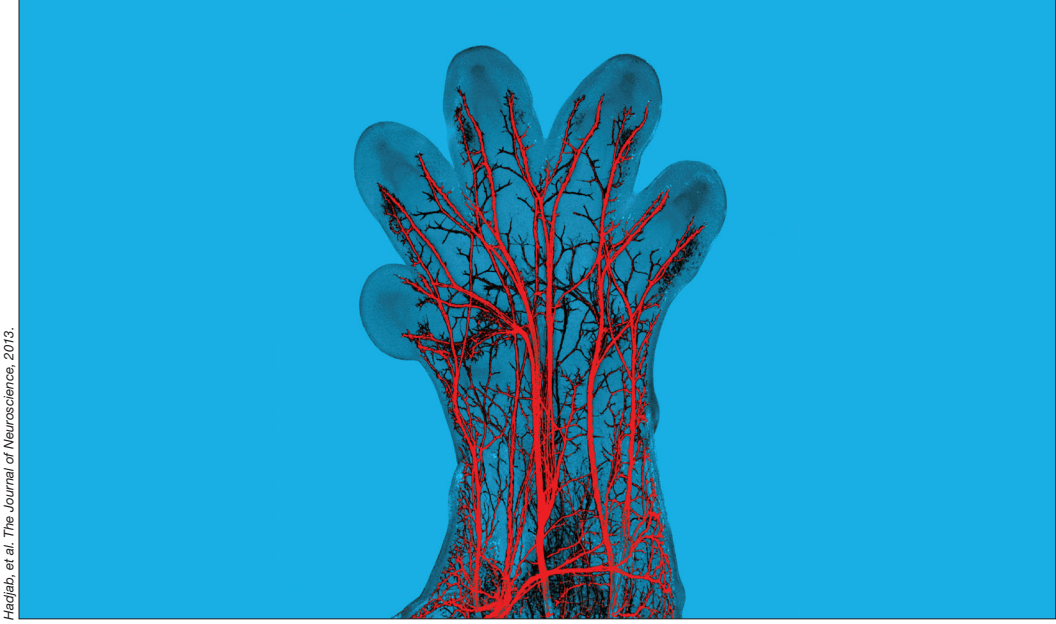
We have around 1,000 different types of olfactory cells, but can identify about 20 times as many smells. The tips of olfactory cells are equipped with several hair-like cilia that are receptive to a number of different odor molecules, and many cells respond to the same molecules. A specific smell will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



Hadjab, et al. The Journal of Neuroscience, 2013.

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.

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 headphones. 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 to opportunity to change how it responds to these messages.

Pain Management

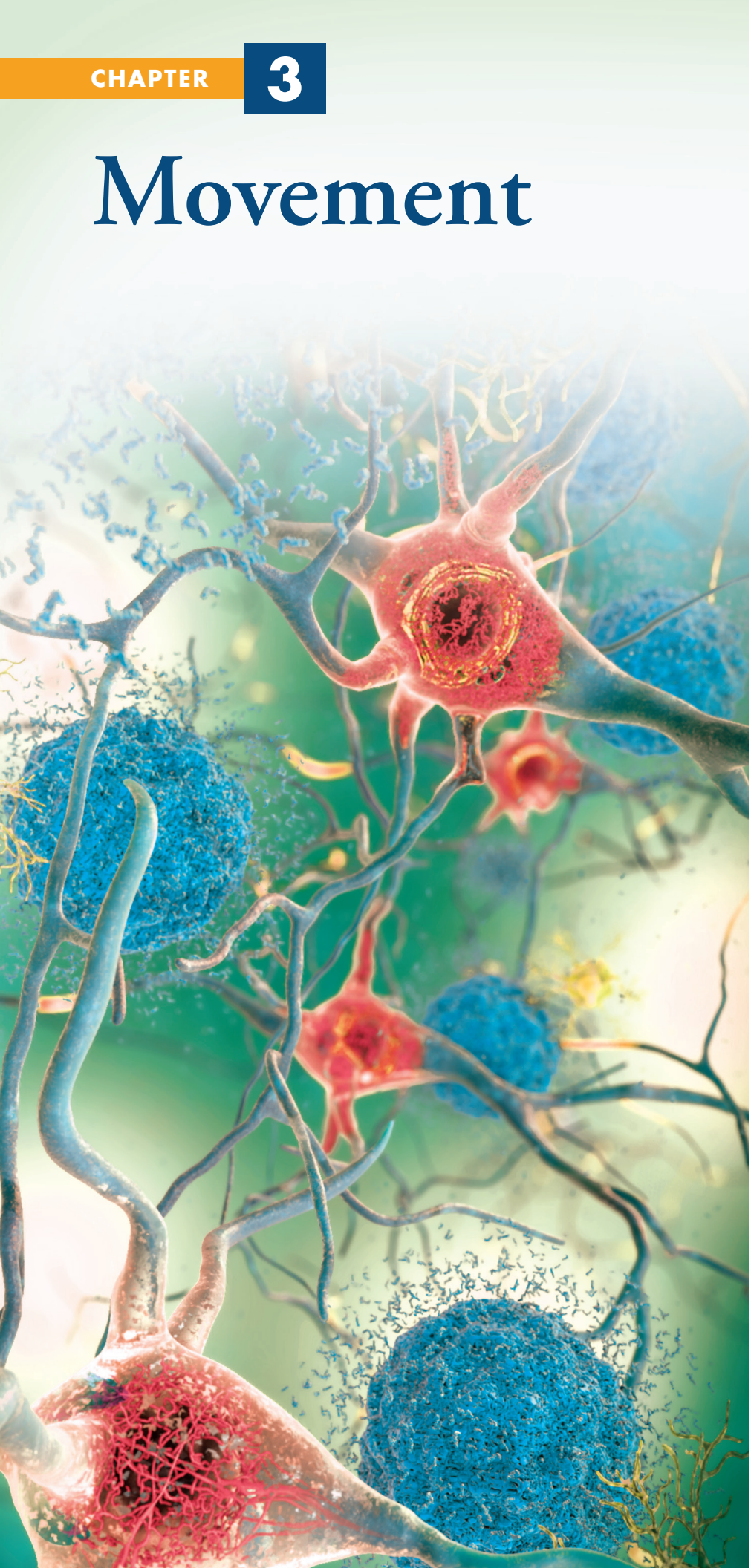
Why do different people, when exposed to the same pain stimulus, experience the pain differently? How itchy or painful something feels obviously depends on the strength of the stimulus, but also on a person's emotional state and the setting in which the injury occurs. When pain messages arrive in the 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.

CHAPTER 3

Movement



Have 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.

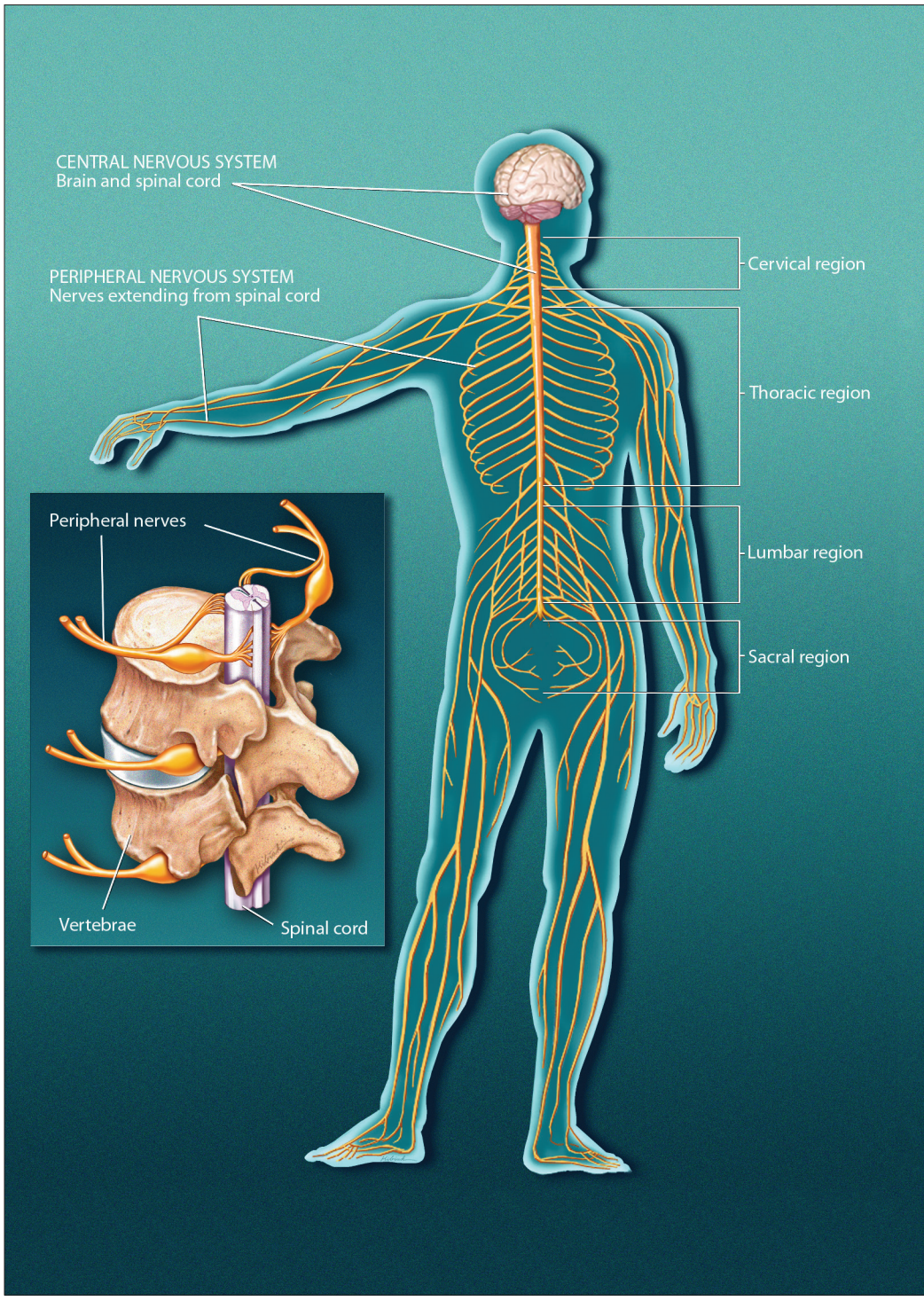
VOLUNTARY MOVEMENTS

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

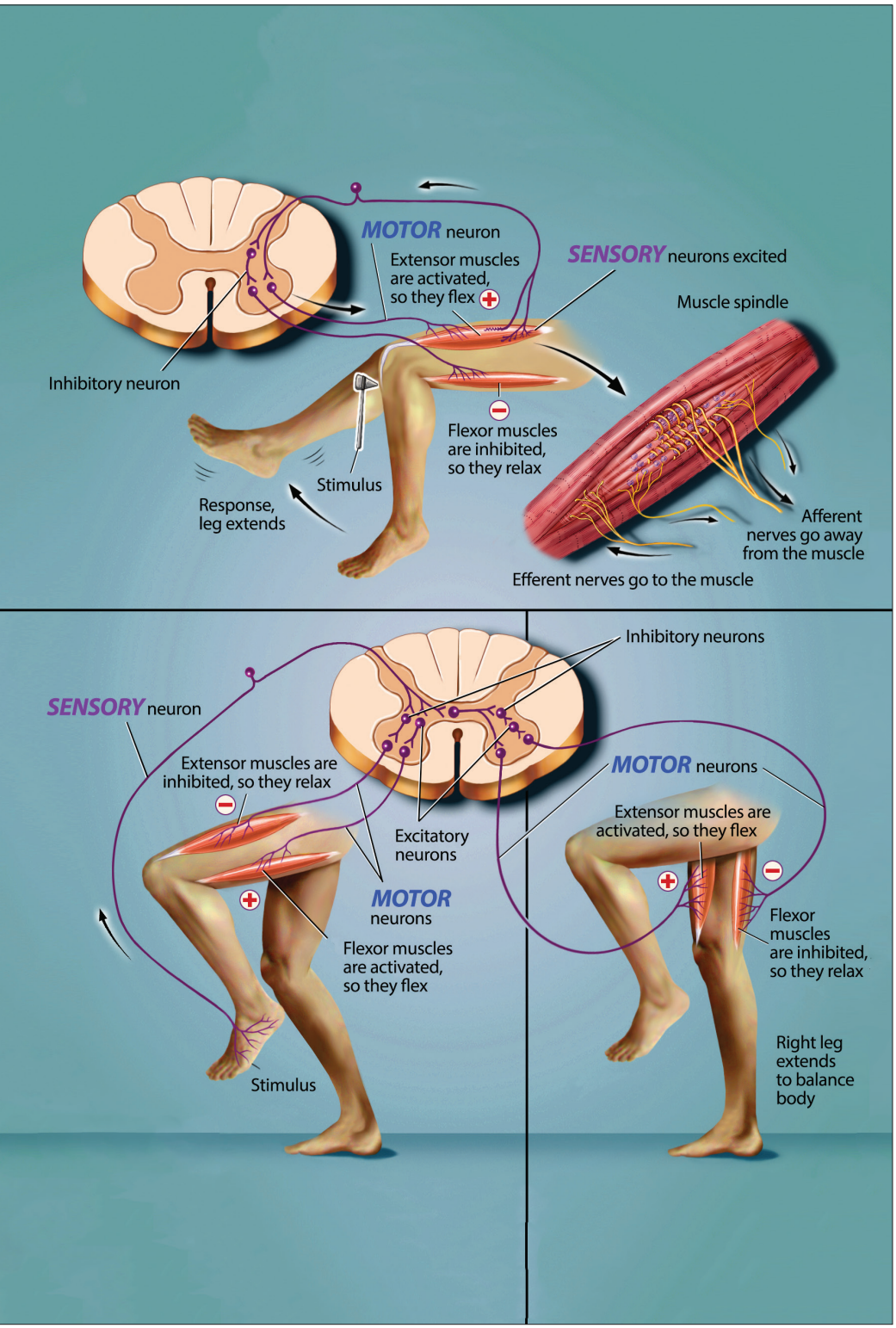
called extensors. Flexors and extensors work in opposition, so when one set of muscles contracts, the other relaxes. For example, bending the elbow requires contraction of the biceps (a flexor) and relaxation of the triceps (an extensor). For such motions, the muscles that promote the movement are called 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.

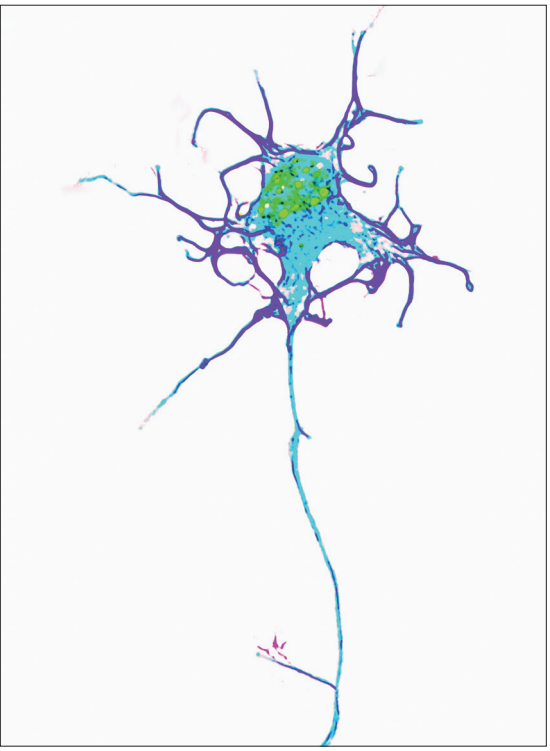
One of the best-known reflexes is the "knee jerk" response, a stretch (myotatic) reflex that occurs when a physician strikes the tendon just below the knee with a small rubber hammer. This tap produces a slight stretch of the knee extensor muscle, which is "sensed" by receptors within the muscle called 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.

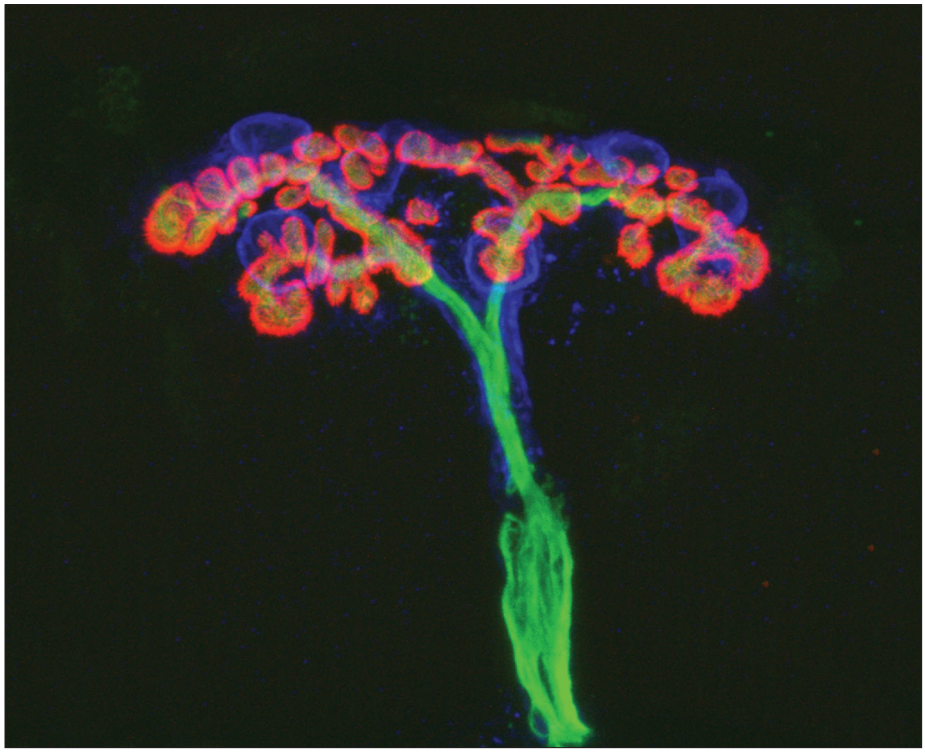
Many reflexes protect you from injury. When you're seated in a doctor's office, the "knee jerk" reflex simply makes your lower leg swing briefly forward. However, if you were to jump off a chair (or perform an even more dramatic gymnastic dismount) this same reflex would promote the contraction of the 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 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 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.

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

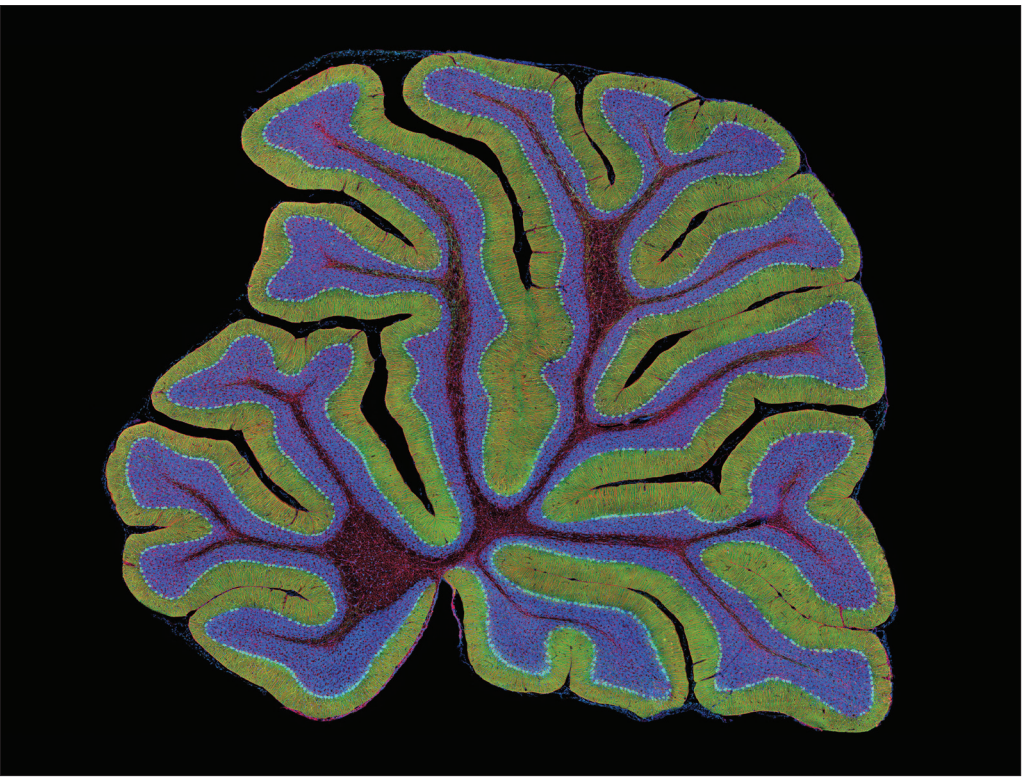
The most complex movements that you perform, including those requiring conscious planning, involve input from the brain. These higher brain regions initiate voluntary motion, coordinate complex sequences of movement, and tailor behavioral output to suit a given situation. Successful execution of these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



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

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, from controlling limb movements to eye movement to grip force.

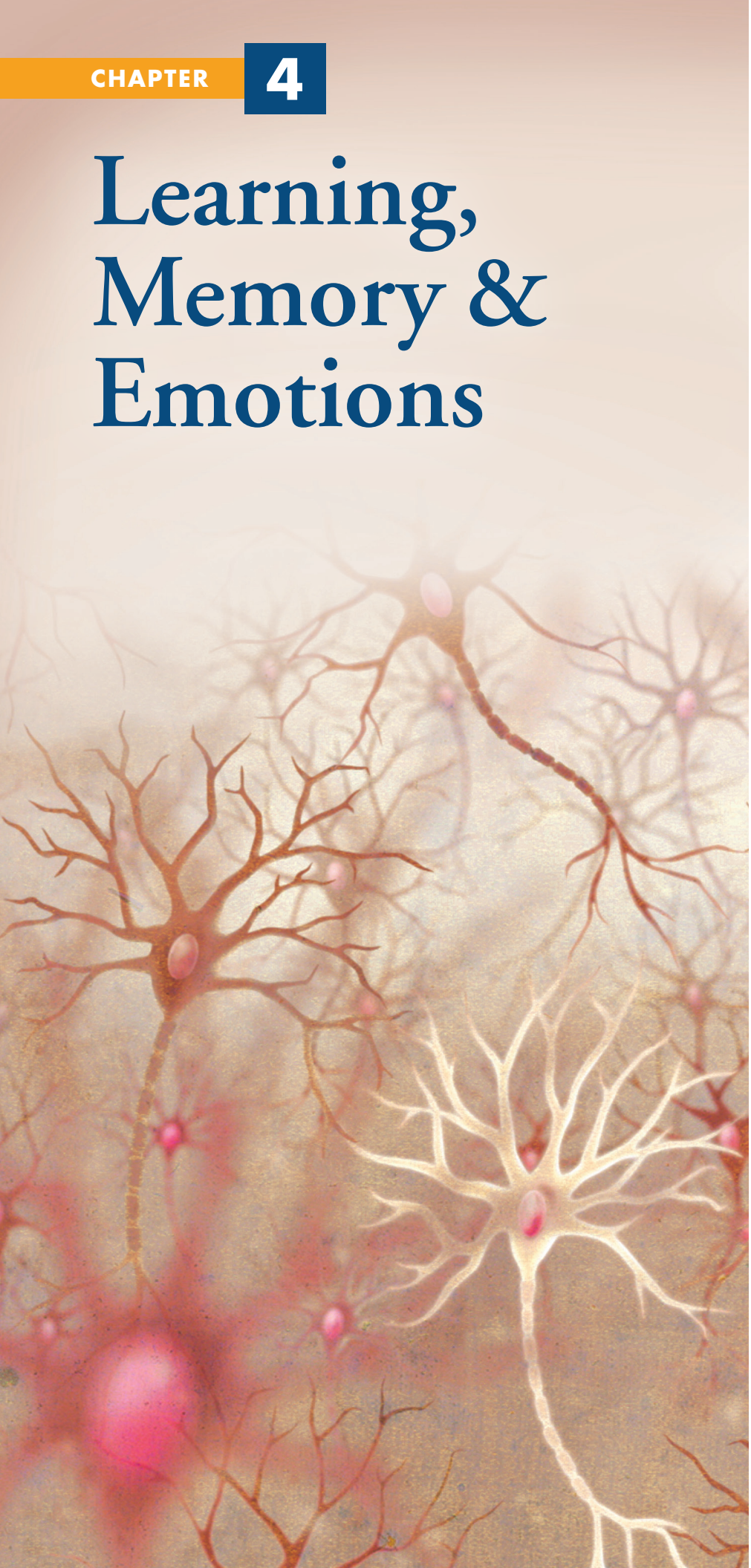
Disturbance of cerebellar function leads to poor coordination, disorders of balance, and even difficulties in speech, one of the most intricate forms of movement control. Long-term alcohol abuse is a common cause of acquired cerebellar degeneration. Typical symptoms are poor coordination, an unsteady 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.

CHAPTER 4

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

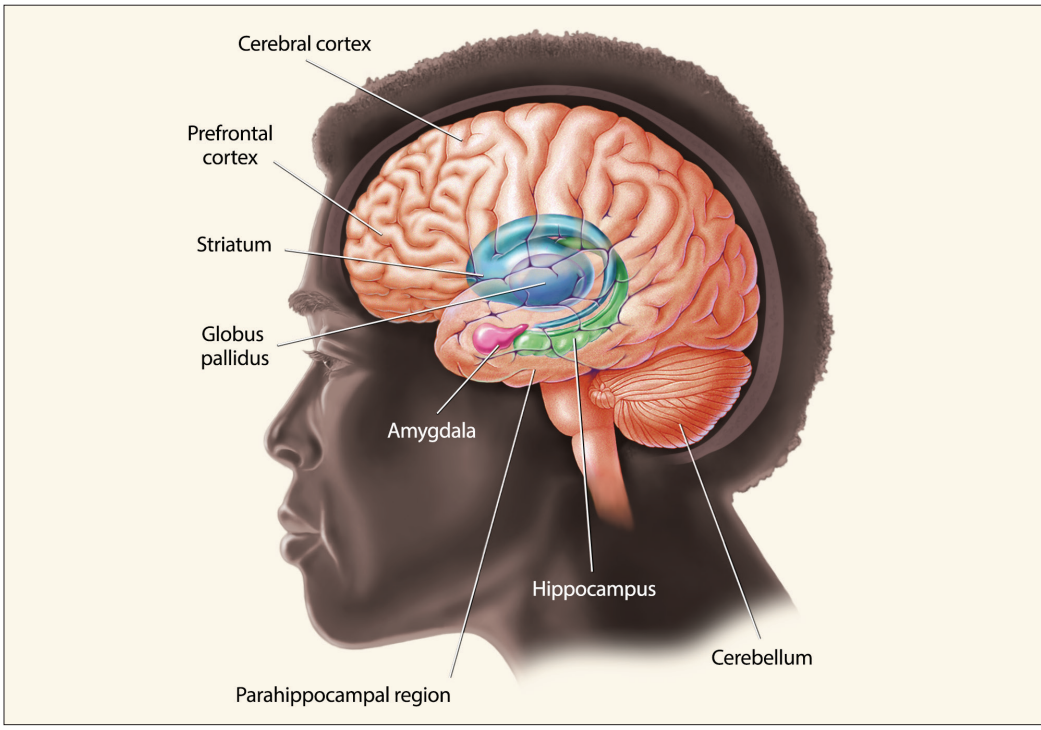
Our understanding of how humans learn and remember is far from complete, but researchers are uncovering intriguing new details about the mechanisms, limits, and architecture of memory formation.

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.

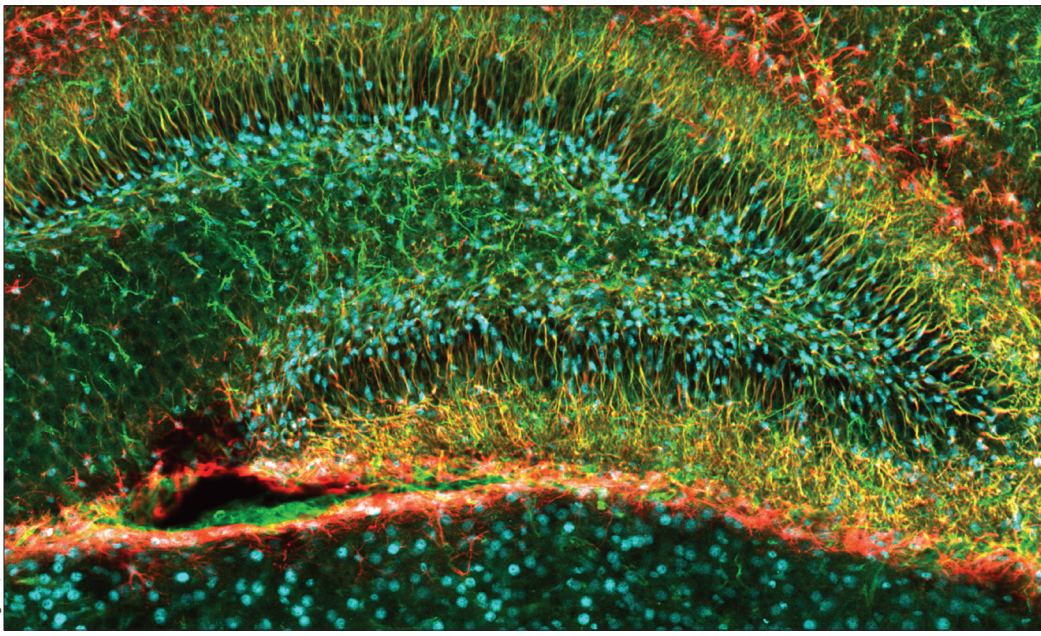
Declarative Memory

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.



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

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 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 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 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 navigating 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.

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.

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 (α-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.