2019

Rowan SOM

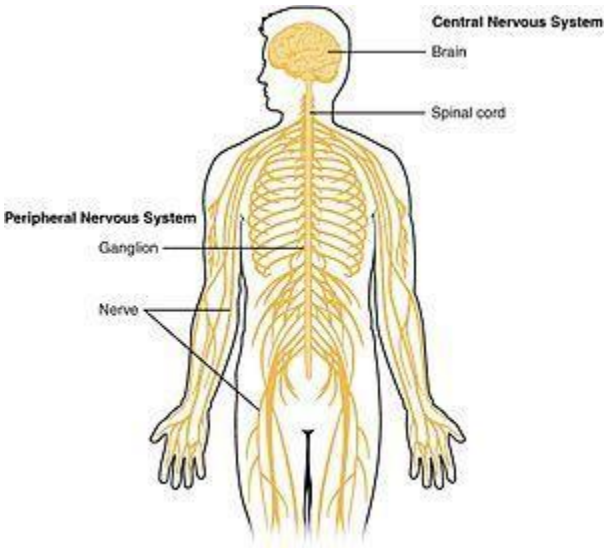
Venkataraman, Venkat
PhD

[INTERMEDIATE BRAIN BEE]

Contains the material needed to prepare for the regional NSF contests

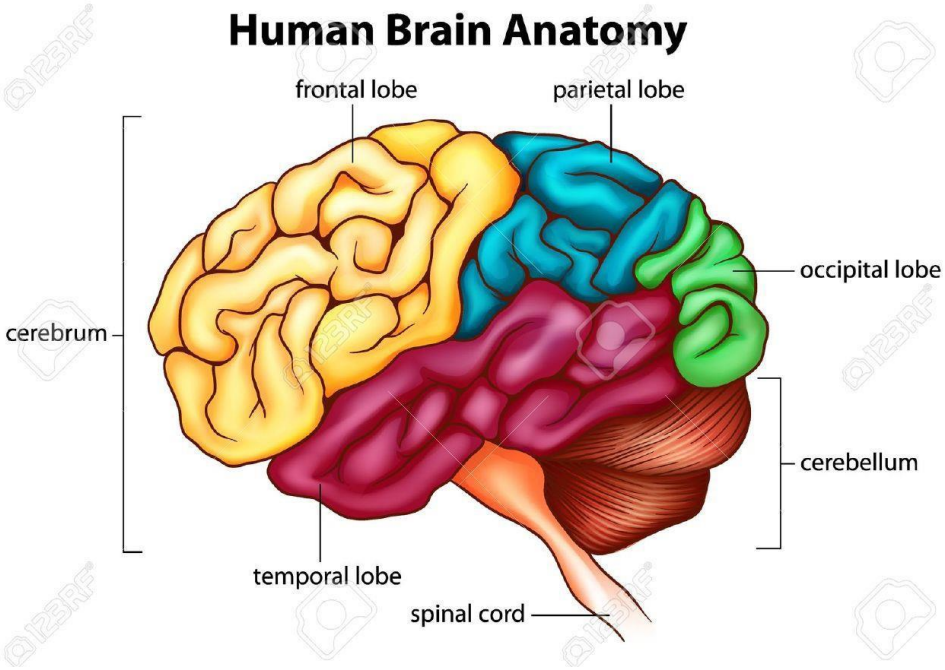
Table of Contents

NERVOUS SYSTEM



- The nervous system is a complex structure (made of neurons and supporting cells) that transmit signals around the body. It is in effect our body's electrical wiring.
- The nervous system of vertebrates (which includes humans and animals that have backbones and spinal columns) has two parts, the central nervous system (CNS) and the peripheral nervous system (PNS).
- The CNS includes the brain, spinal cord and retina of the eyes. Parts of the skeletal system protect the brain and the spinal cord: The brain is protected by the skull and the spinal cord, by the vertebrae.
- The PNS includes all other nervous system structures that sit outside the CNS but that help connect the CNS to areas of the body.
- Nerves are enclosed bundles of long fibers called axons that are parts of nerve cells. Neurons and glial cells have axons.
- Glial (or glia) cells are derived from the Greek word "glue". They are specialized cells that provide structure and support to neurons. They help hold neurons in place, supply nutrients to neurons, destroy germs, remove dead neurons, and direct axons of neurons.
- Some types of glial cells generate a substance called myelin that coat axons and work as electrical insulation to help them quickly and efficiently transmit signals.
- Neurons quickly and precisely send signals as electrochemical waves along axons to other cells. There are two types of neurons: sensory neurons and motor neurons.
- Sensory neurons change light, touch and sound into neural signals which are sent back to our CNS to help our body understand and react to its surroundings.
- Motor neurons transmit neural signals to activate muscles or glands.
- There are approximately 100 billion neurons in the human brain and 13.5 million neurons in the human spinal cord.
- The nervous system can transmit signals at speeds of 100 meters (328 feet) per second.
- The field of science that focuses on the study of the nervous system is called neuroscience. Neurology is the medical branch of study and treatment of the nervous system. Doctors and surgeons in this field are called neurologists and neurosurgeons.
- Nerves in our body can be vulnerable to both physical damage and damage through diseases. Damage to nerves can cause great pain, loss of feeling, or loss of muscle control.
- Physiatrists help rehabilitate patients with nervous system damage.

BRAIN



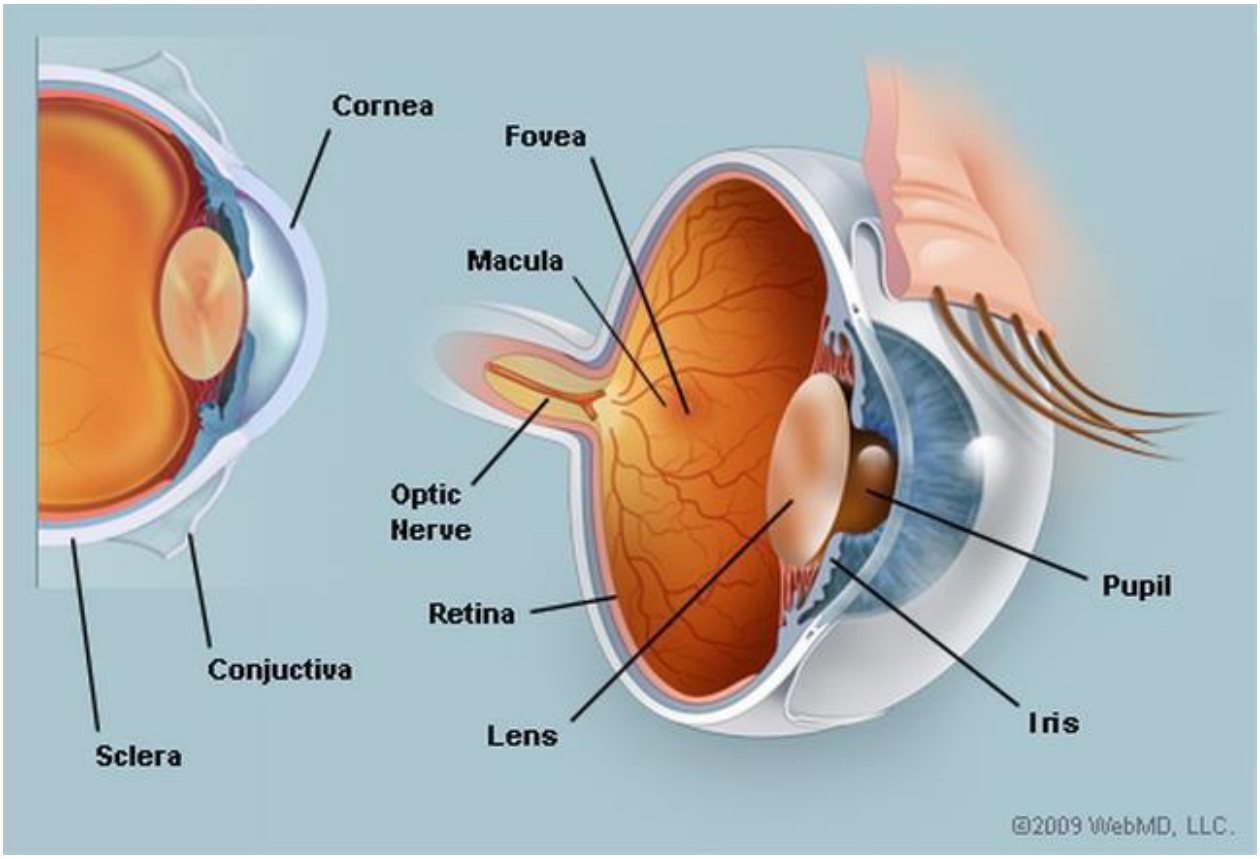
- The human brain is like a powerful computer that stores our memory and controls how we as humans think and react. It has evolved over time and features some incredibly intricate parts that scientists still struggle to understand.
- The brain is the center of the human nervous system, controlling our thoughts, movements, memories and decisions.
- With evolution, the human brain has become more and more complicated. Many of its interesting properties are still not well understood by scientists.
- The brain contains billions of nerve cells that send and receive information around the body.
- The human brain is over three times as big as the brain of other mammals that are of similar body size.
- Each side of the brain interacts largely with just one half of the body, but for reasons that are not yet fully understood, the interaction is with opposite sides, the right side of the brain interacts with the left side of the body, and vice versa.
- The largest part of the human brain is called the cerebrum. Other important parts include corpus callosum, cerebral cortex, thalamus, cerebellum, hypothalamus, hippocampus and brain stem.
- The human brain is protected by the skull (cranium), a protective casing made up of 22 bones that are joined together.
- The brain of an adult human weighs around 3 pounds (1.5 kg). Although it makes up just 2% of the body's weight, it uses around 20% of its energy.
- The brain is effectively floating in liquid (Cerebrospinal fluid) that acts as both a cushion to physical impact and a barrier to infections.
- Diseases of the brain include Alzheimer's disease, Parkinson's disease and multiple sclerosis. Diseases such as these can limit the normal function of the human brain.
- Most strokes result from a blood clot in the brain that blocks the local blood supply, which causes the damage or destruction of nearby brain tissue and a wide range of stroke symptoms.

SENSES

- Senses are a collection of sensory organs or cells in the body that respond to particular physical occurrences. Senses send information collected to various parts of the brain where the data is interpreted, and an appropriate response signal returned.
- The exact number of senses humans have is disputed due to the various definitions of what a 'sense' is. However, it is widely agreed that there are five main human senses: sight, hearing, taste, touch and smell.
- SIGHT/VISION results from the ability of the eye to detect and focus on images of visible light with photoreceptors found in the retina of the eye. Electrical nerve impulses are generated for different colors, hues and brightness. The two types of photoreceptors are rods and cones. Rods are functional in dim light, while cones identify different colors in bright light.
- HEARING is a sense that detects the vibrations of sound. Mechanoreceptors in the inner ear, in the form of tiny bones and hair-like fibers, turn motion or sound waves from the air into electrical nerve pulses that the brain can then interpret.
- TOUCH is activated by neural receptors such as hair follicles found in the skin, but also pressure receptors on the tongue and throat.
- TASTE is detected by sensory cells called taste buds located on top of the tongue. There are five basic tastes: sweet, bitter, sour, salty and savory.
- SMELL, like taste, is deemed to be a chemical sense. There are hundreds of olfactory receptors or sensory cells in our nasal passage, each of which will bind itself to a different molecular smell feature.

- Around 80% of what we think is taste is actually smell. Flavor is a combination of taste and smell perception. Test this yourself by holding your nose closed the next time you eat something: can you taste it very well?
- Other perceived human senses are debatable but generally include, the ability to detect temperature, pain, balance and kinesthetic (which is the relative positions of our body parts - test this sense by closing your eyes and touching your nose with a finger).
- There are many internal body stimuli that may be perceived as senses too. For example, chemoreceptors for detecting salt and carbon dioxide concentrations in the blood and stretch receptors in the lungs which control our breathing rate.
- Compared to animals, humans have a quite weak sense of smell.
- Animals have differences in how their receptors sense the world around them. For example, dogs and sharks have a terrific sense of smell, while cats can see very well in dim light.
- Some animals have receptors in places that seem very unusual to us. Flies and butterflies, for example have taste organs on their feet, so they can taste anything they land on and catfish have taste organs across their entire bodies.
- Other animals have sense receptors we can only dream off. Some snakes have sensory organs that can detect infrared light, birds and bees can see ultraviolet light. Bats and dolphins use sonar to interpret their surroundings.
- Certain fish and rays can detect changes in nearby electrical fields and many bird species use the Earth's magnetic fields to determine the direction they are flying.

EYE

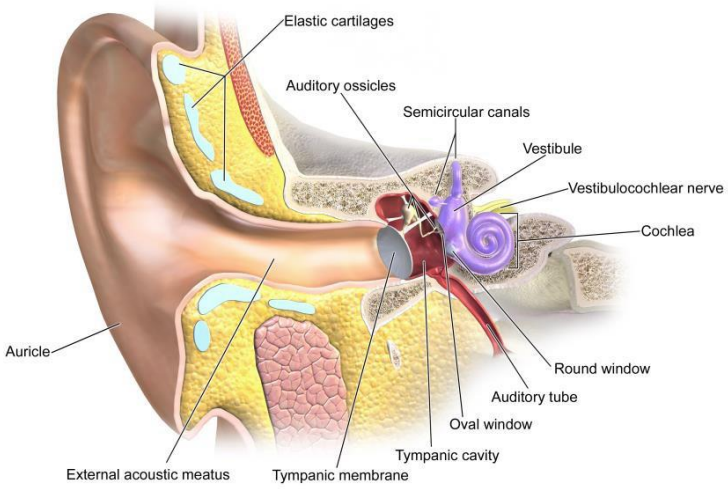


Eyes detect light and allow us to see.

- The information our eyes receive is sent to our brain along the optic nerve. This information is then processed by our brain and helps us make appropriate decisions. For example, if you can see an object flying in your direction then you will probably move quickly out of the way.
- Around 95% of animals have eyes. Some are very simple, just picking up light and dark conditions while others are more complex, allowing for the recognition of shapes, color and depth.
- Like humans, some animals have eyes placed close together that allow for improved depth perception, others have eyes spread further apart (often on opposite sides of their head, as in horses) to allow for a greater field of view and an early warning against potential predators.
- The light sensitive tissue lining the inner surface of your eye is known as the retina, acting similar to a film in a traditional camera.
- Cone cells in the retina detect color in bright light while rod cells detect low light contrasts.
- The part of the eye that allows us to focus on different things in known as the lens, it changes shapes so we can focus on objects at various distances.
- The cornea is the transparent covering of the iris and pupil; along with the lens, it refracts light so that images can be projected onto the retina.
- The central opening of the eye is known as the pupil. It changes size depending on the amount of light.
- The colored area around the pupil is called the iris. It controls the size of the pupil and can be colored brown, blue, green or other colors and shades depending on the person.

- Scientists believe that animal eyes evolved around 500 million years ago, beginning in simple form (perhaps just distinguishing light and dark) but giving a distinct advantage. This advantage led to eyes evolving quickly amongst animals (by evolutionary standards) in the struggle for existence.
- Throughout the animal kingdom there are many different types of eyes: the human eye is very different from the compound eye of a fly which is better at detecting fast movements.
- Human eyes contain a small blind spot where the optic nerve passes through the retina. Our brains use information from the other areas to fill in the vision gap; so it is rarely, if ever, noticed.
- Glasses and other protective equipment are often worn by humans to protect the eyes from UV rays or during other dangerous activities such as welding.
- Glasses and contact lenses are worn to correct common sight conditions such as short and long sightedness (myopia and hypermetropia).

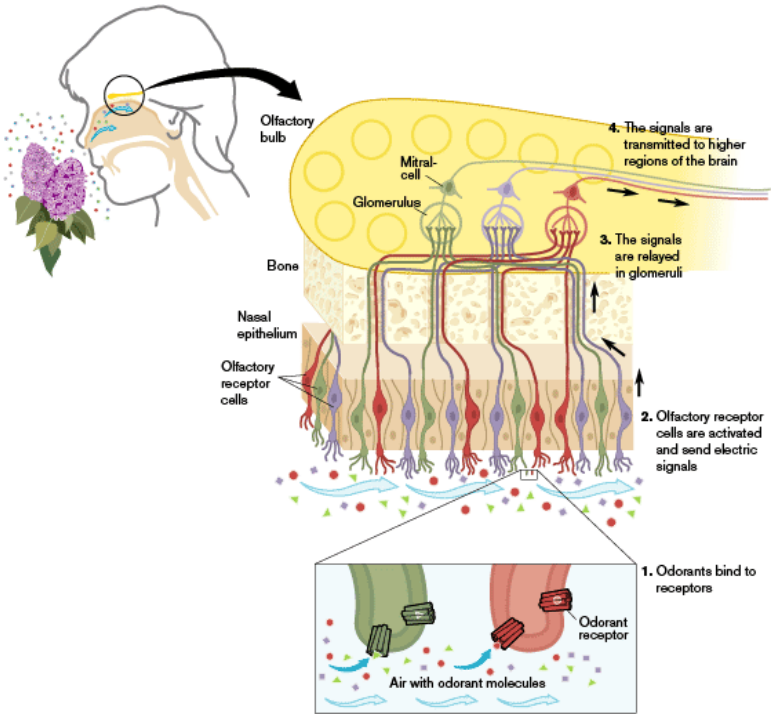
EAR



The Anatomy of the Ear

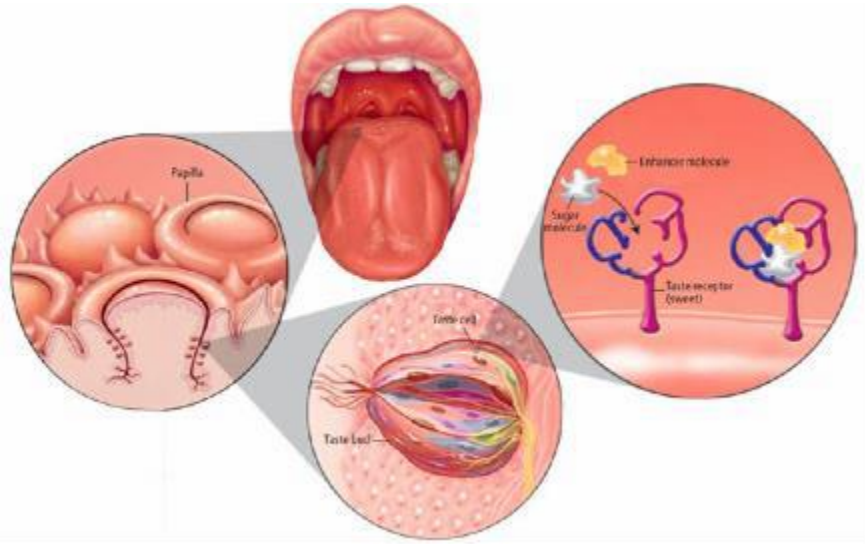
- Our ears help us detect sound. They convert sound waves into nerve impulses that are sent to the brain.
- While your ears pick up the sound, it is your brain that does the hard work of making sense of it all.
- There is much more to the ear than the part you can see on the outside of your head.
- The middle part of the ear (behind the ear drum) amplifies sound pressure. The middle ear also contains the Eustachian tube which helps equalize pressure and drain mucus.
- Ear infections are more common in children because of their developing immune systems and differences between their Eustachian tubes and those of adults.
- The inner ear is found inside the temporal bone, the hardest bone in the human body. It contains the spiral shaped hearing organ called the cochlea as well as the vestibule and semicircular canals which help with balance.
- Sounds waves are passed from air to liquid in the inner air. The inner air also contains tiny hair cells which react to sound waves, triggering chemicals that are sent to the brain as nerve impulses. Abnormalities in the inner ear of humans can cause deafness.
- Skin glands in the ear canal produce ear wax which helps protect the ear by lubricating it and cleaning it of dirt and dust.
- Excessive ear wax can impair hearing, especially if it is pressed hard against the eardrum.
- Ear wax normally comes out of your ear naturally so it's not a good idea to try and remove it yourself unless it is causing health problems (best to see your doctor first).

NOSE



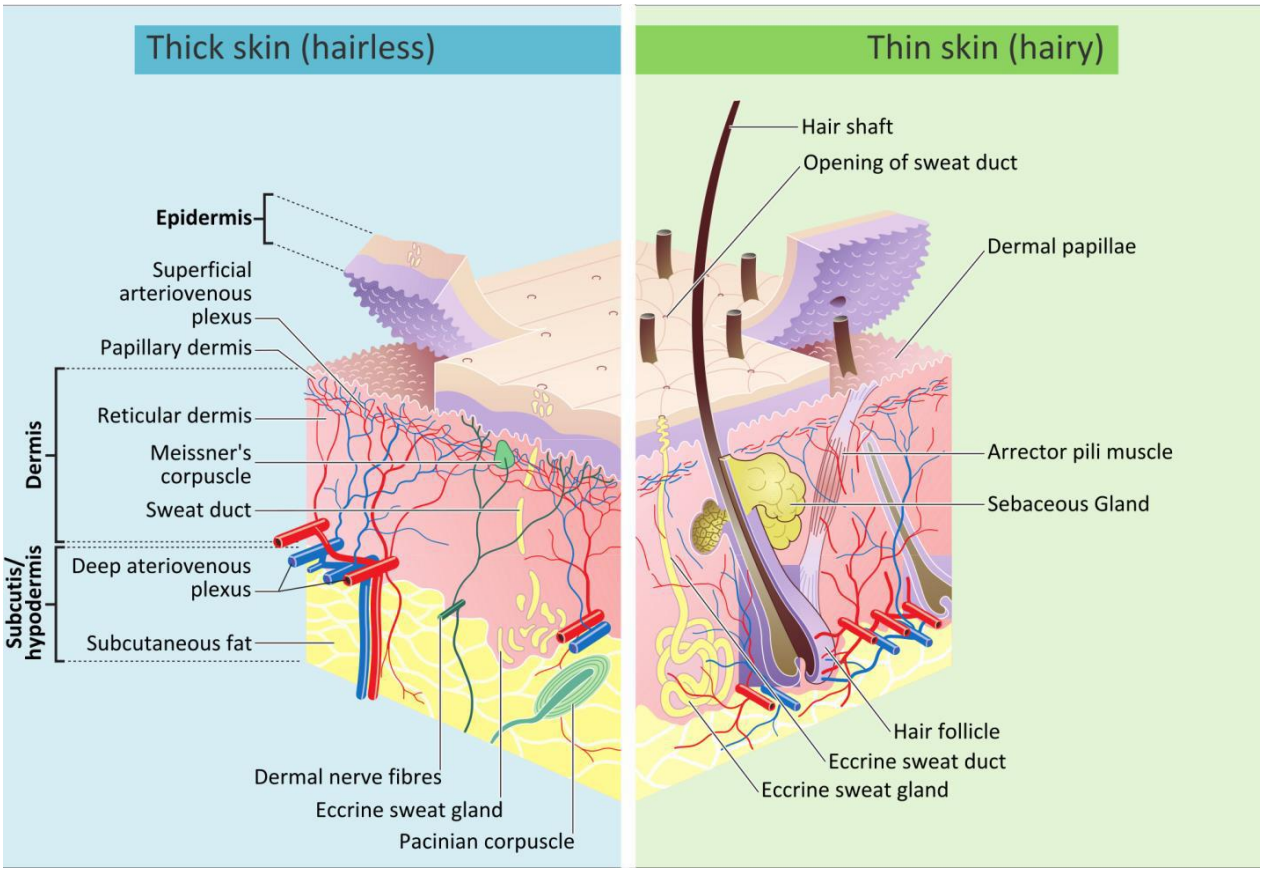
- The nose has special cells which help us smell.
- The technical term for sense of smell is 'olfaction'.
- Your nose can help detect dangerous chemicals in the air.
- The human nose can smell many different odors but is far less sensitive than other animals such as dogs.
- The human nose has 2 nostrils divided by the nasal septum. The nasal septum is made up mostly of cartilage, a tissue that is stiffer than muscle but more flexible than bone.
- Found at the roof of the nose, the ethmoid bone separates the nasal cavity and brain. The ethmoid bone is also one of the bones that make up the orbit of the human eye.
- The nasal cavity is a large space found inside the head, above and behind the nose.
- Air passing through the nasal cavity is warmed to match body temperature (or cooled if it is very hot).
- Dust and other particles are removed in the nasal cavity by short hairs. The floor of the nasal cavity is also the roof of the mouth.
- 'Anosmia' is the inability to smell.
- 'Dysosmia' is when things don't smell as they should.
- 'Hyperosmia' is having a very strong sense of smell.
- On average, men have larger noses than women.
- It is traditional for Maori people in New Zealand to press noses (hongi) as a greeting.
- Plastic surgery involving the nose is called 'rhinoplasty'.

TONGUE



- The tongue is a muscular structure attached to the floor of the mouth. It is the main sensory organ of taste.
- The upper surface of a tongue is covered with taste buds which contain taste receptors.
- The human tongue has on average 3,000 - 10,000 taste buds.
- The bumps we can see on the tongue are called papillae. Taste buds sit on top of these papillae but are not visible to the human eye.
- There are five elements of taste perception: salty, sour, bitter, sweet, and umami (or savory).
- Humans also use the tongue for speech where it helps with changes in sound.
- On average, women have shorter tongues than men.
- The human tongue is divided into two parts the anterior and the posterior.
- The anterior part of the tongue is the visible part at the front and is about two-thirds of the tongue's length.
- The posterior tongue area is closest to the throat, and roughly one-third of length.
- There are eight muscles in the human tongue. They can be classified as intrinsic or extrinsic.
- There are four intrinsic muscles which are not attached to any bone, they are the muscles that allow the tongue to change shape, such as point, roll, tuck etc.
- There are four extrinsic muscles which are attached to bone, they allow the tongue to change position, such as poke out, retract, side-to-side movement.
- The average length of the human tongue from the back to the tip is 10 cm (4 in).
- The blue whale has the largest tongue of all animals. Its tongue weighs around 2.7 metric tons (425 stone).
- Taste receptors cannot actually taste food until saliva has moistened it. We usually taste salty things first as salt dissolves quickly in moisture.
- Sticking your tongue out at people is seen as childish or rude in many countries, however, in Tibet it is considered a greeting.
- Dogs and cats often use their tongues to clean their fur and body. The very rough texture of their tongue allows them to remove oils and parasites.
- Have you ever wondered why a dog's tongue hangs out of its mouth after a lot of exercise? Well a dog's tongue increases in size as it exercises due to greater blood flow, moisture on the tongue works to cool this blood flow, cooling the dog.
- Some animal tongues are specially designed to catch prey. Chameleons, frogs, and anteaters have tongues that can extend out of their mouth and grab insects.

SKIN



Skin is the human body's largest organ (an organ is a group of tissues that work together to perform functions in your body. Others include your brain, heart and lungs).

- Your skin performs a range of different functions which include physically protecting your bones, muscles and internal organs, protecting your body from outside diseases, allowing you to feel and react to heat and cold and using blood to regulate your body heat.
- The layers of mammal skin include the epidermis, dermis and subcutis.
- The outer layer of your skin is the epidermis, it is found thickest on the palms of your hands and soles of your feet (around 1.5mm thick). (Think why!)
- The subcutis (or hypodermis) is the deepest layer of your skin. In addition to storing fat, it also contains blood vessels, hair follicle roots and nerves.
- If skin is severely damaged, it may try to heal by forming scar tissue. Scar tissue is not the same as normal skin tissue; it often appears discolored and lacks sweat glands and hair.
- The color of human skin depends on the amount of pigment melanin that the body produces. Small amounts of melanin result in light skin while large amounts result in dark skin.
- Areas that experience repeated friction or pressure can form tough, thick skin known as a callus. Common examples of calluses can be seen on the hands of tennis players and the fingertips of guitarists.
- A large amount of the dust in your home is actually dead skin!
- All mammals have some hair on their skin, even if it isn't always easy for you to see.
- Rhinocereses are protected by thick skin which can be between 1.5cm and 5cm deep.

- Although polar bears have both white and transparent (see through) fur, their skin is actually black.
- Amphibians such as frogs have unique skin. Rather than drinking water, frogs actually soak it into their body through their skin. They also use their skin to absorb around half the air they need.
- Snakes have smooth, dry skin.
- A number of different sea creatures, such as sea lice and barnacles, attach themselves to the skin of whales, making it their home.
- Some fruits and vegetables are known to have 'skins', these include bananas, oranges, apples and potatoes.

BrainFacts

A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

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.

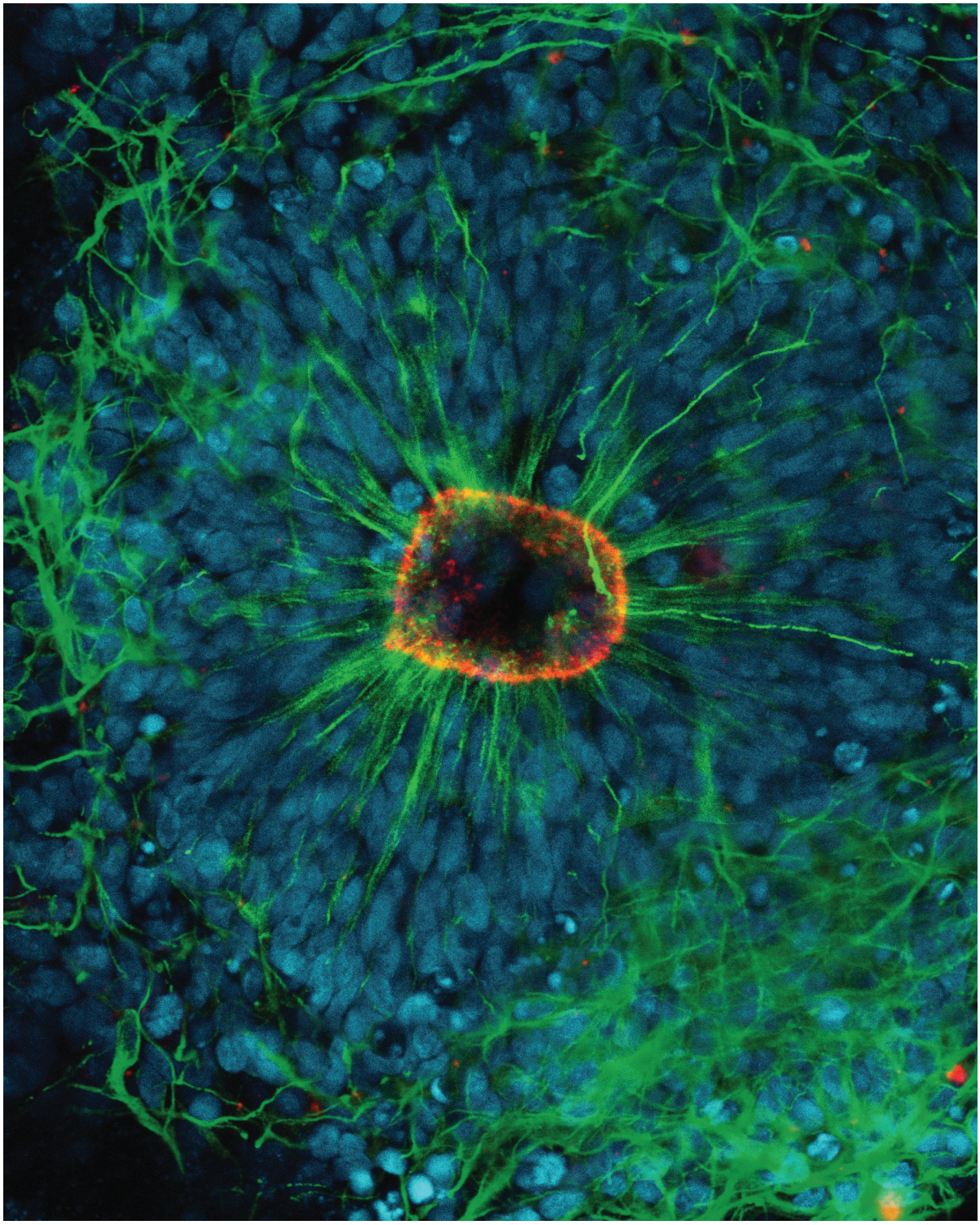
How Research Benefits Human Health

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.



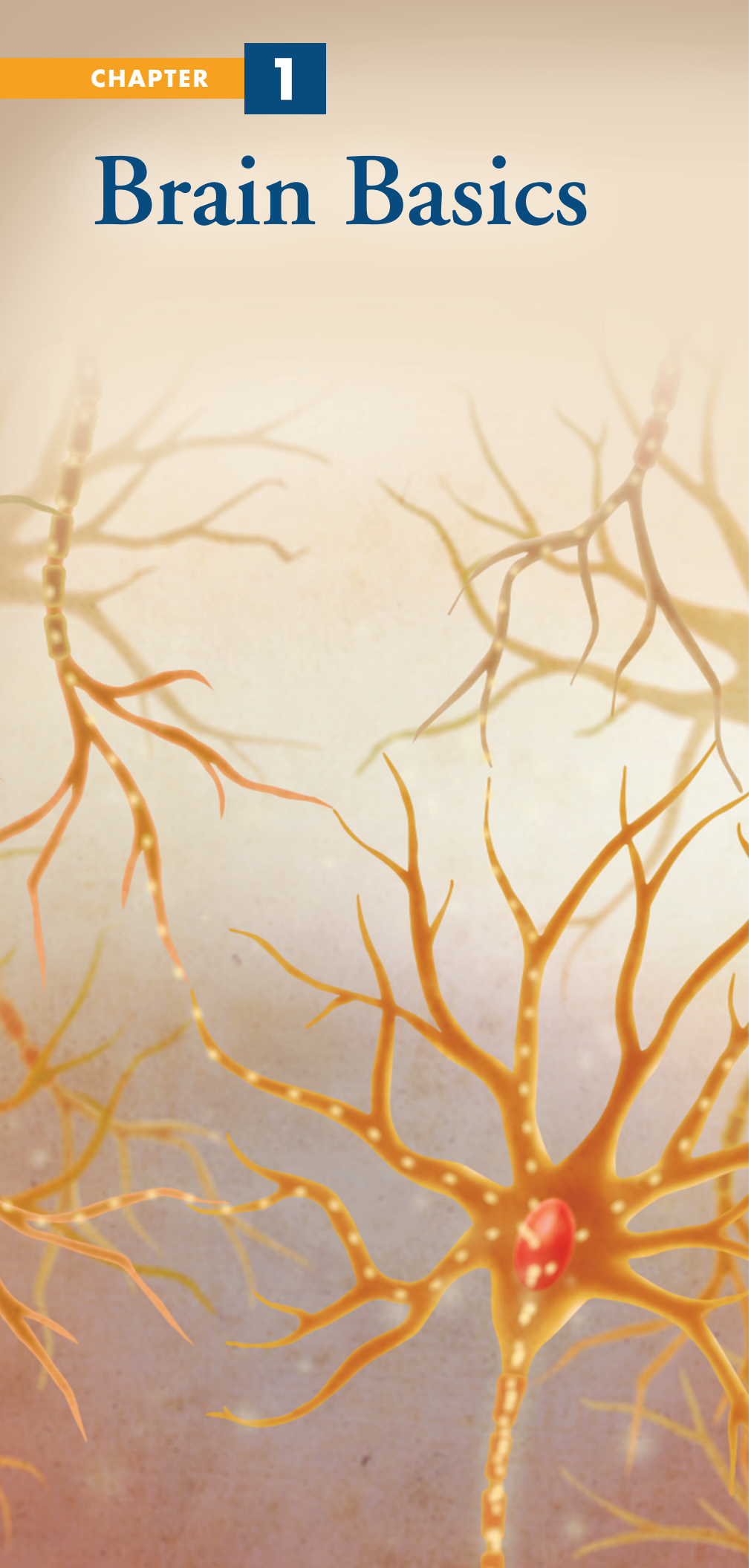
Coulthard, et al. Journal of Neuroscience, 2017.

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.

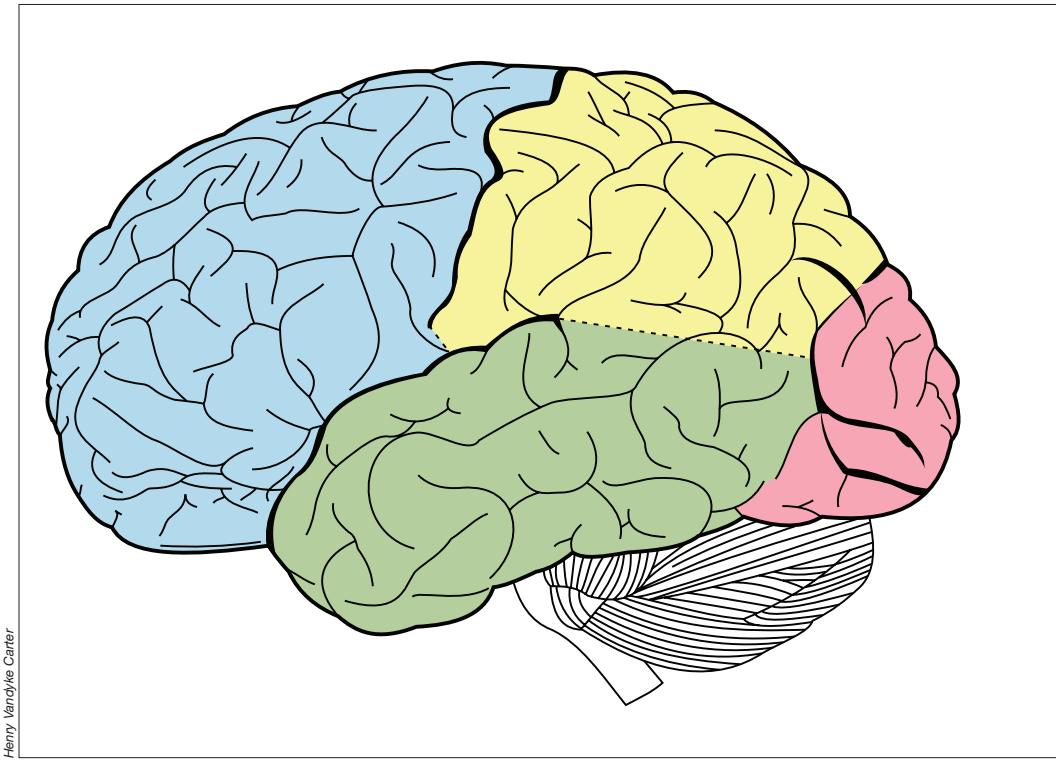
The parietal lobes are located at the top of the brain, immediately behind the frontal lobes. They integrate sensory signals from the skin, process taste, and process some types of visual information.

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.

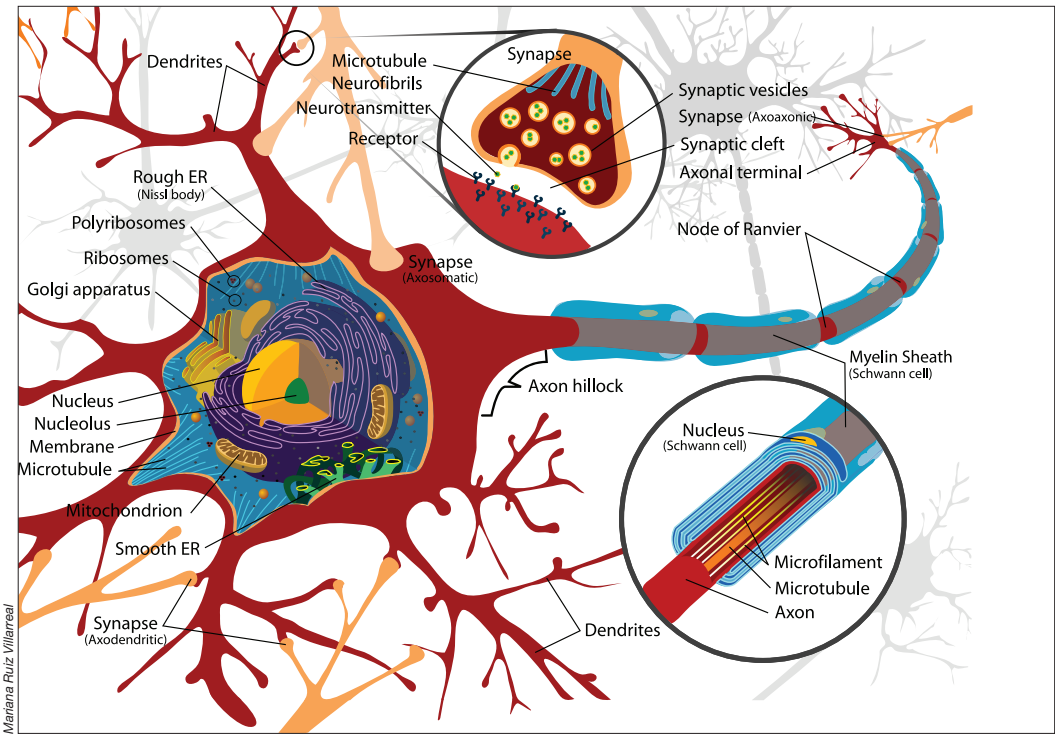
Neuroscientists think each column in the cortex is dedicated to one very specific processing task. But a column's final output can be influenced by the activity of nearby circuits. Every neuron in a circuit has other connections to neurons in neighboring columns. Since every neuron behaves like a microprocessor,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

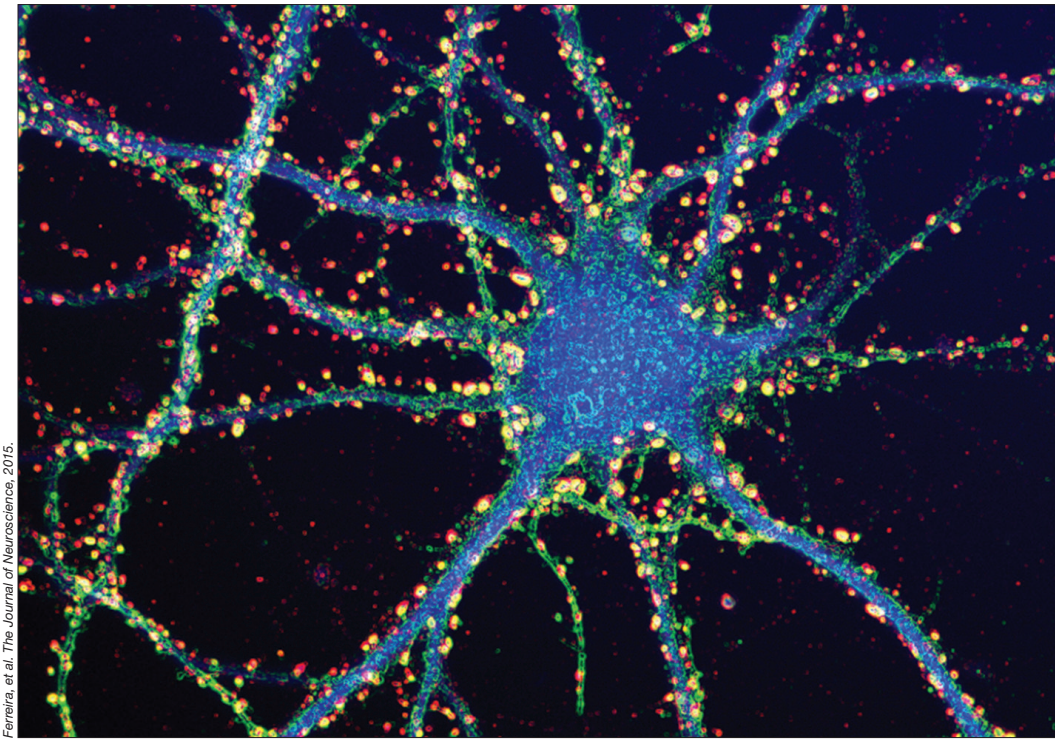
In mammals, the voltage difference across the membrane of a resting neuron is around -70 millivolts (mV), more negative inside the cell than on its outer surface. That membrane potential is affected by signals arriving from other neurons in its circuit, which can make the membrane potential less negative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

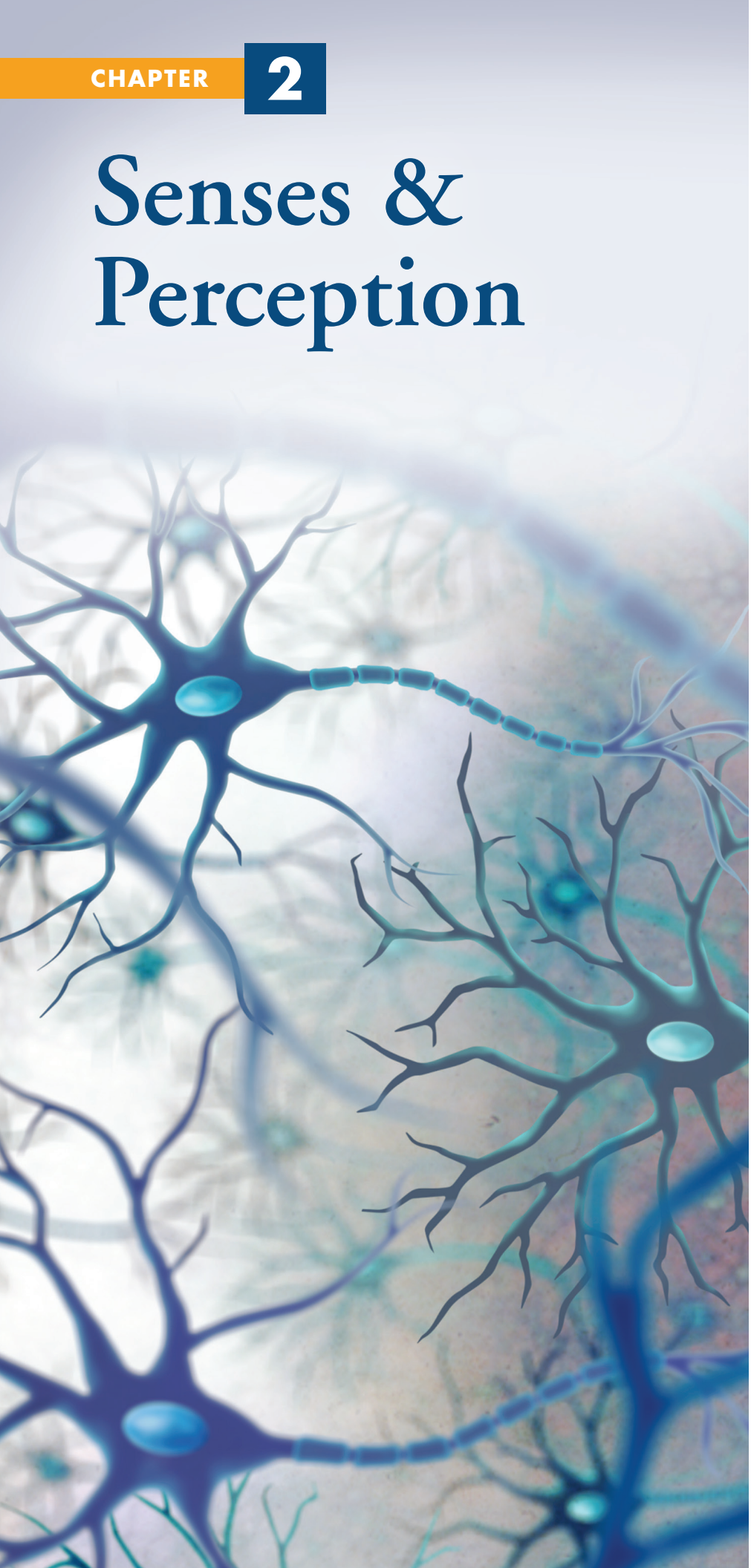
All cells in your body, including neurons, contain the same DNA housing the same genes. Differences among your neurons result from differences in which genes direct cellular activities, a process called gene expression. Each cell (or cell type) builds proteins from a slightly different subset of genes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

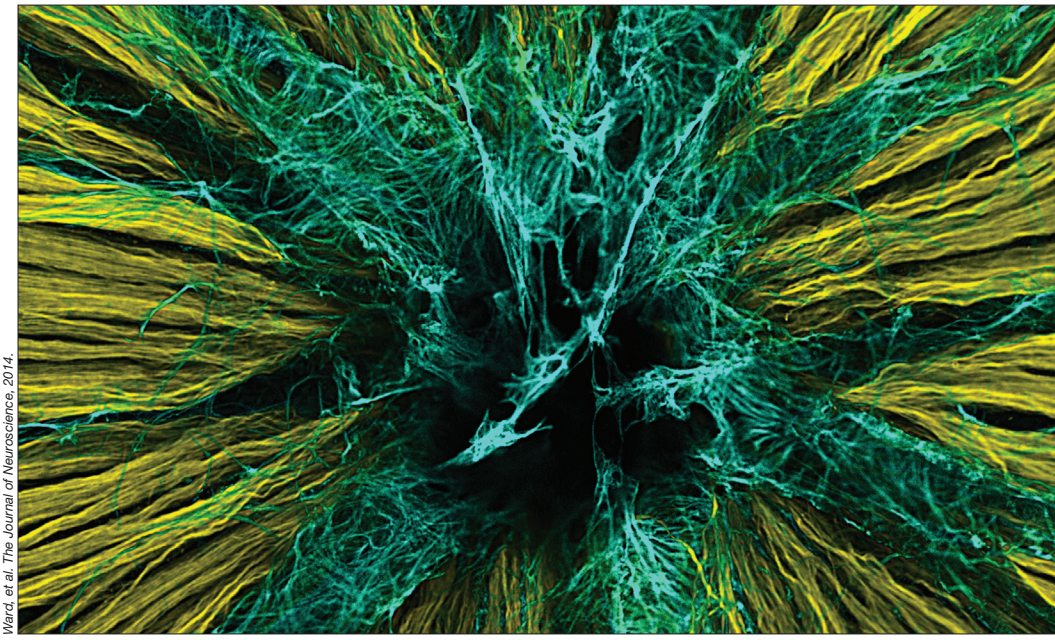
The Three-Layered Retina

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.

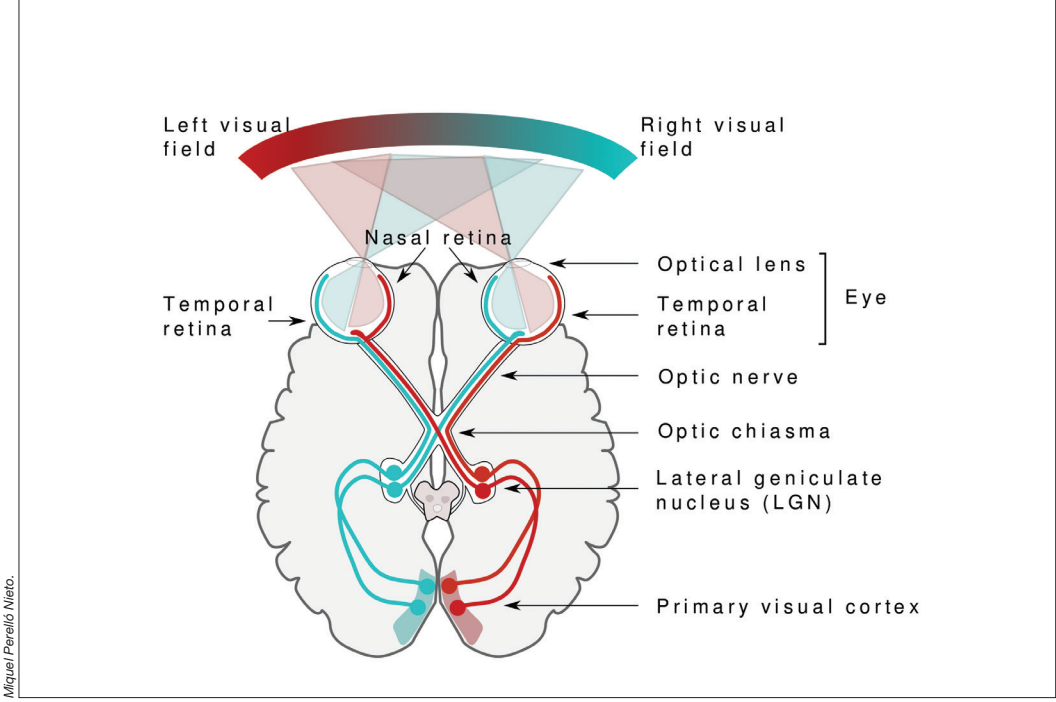
Here, in the back of the eye, is one of the first stops visual information makes on its way to the brain. In this image of a mouse retina, axons of nerve cells are labeled in yellow. They extend through a small opening in the back of the eye — labeled in black — through the optic nerve to higher vision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

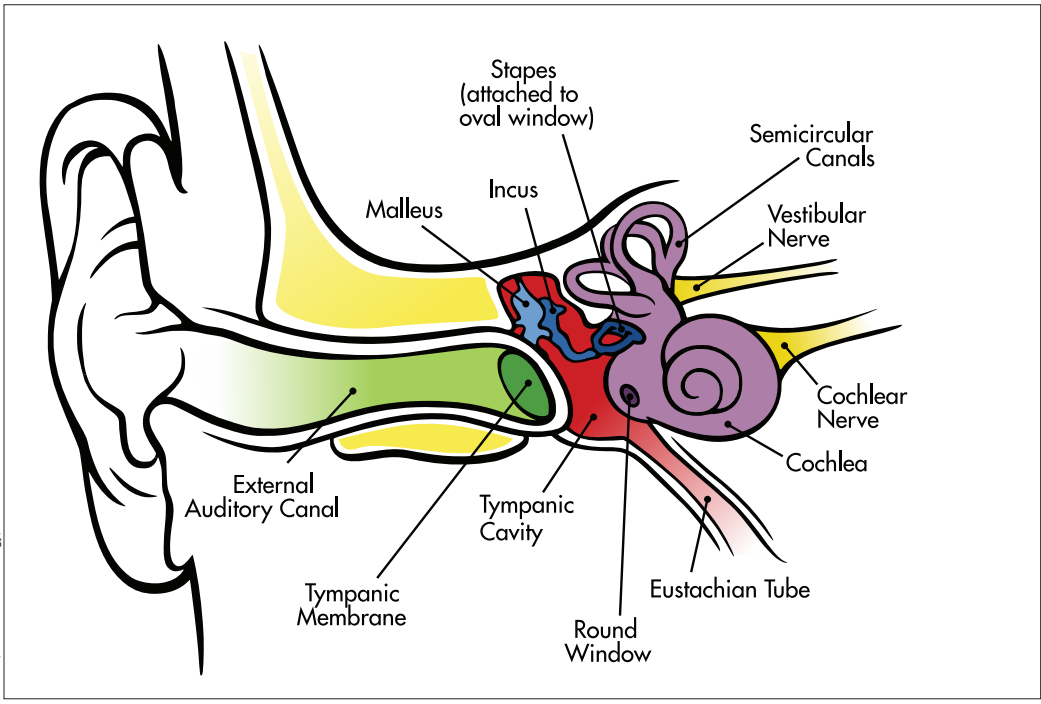
Although sound is processed on both sides of the brain, the left side is typically responsible for understanding and producing speech. Someone with damage to the left auditory cortex (particularly a region called Wernicke's area), as from a stroke, is able to hear a person speak but no longer understands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

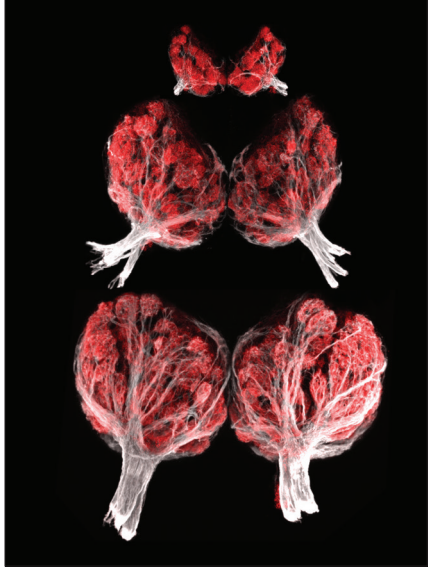


Chittka, et. al. PLoS Biology, 2005.

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.

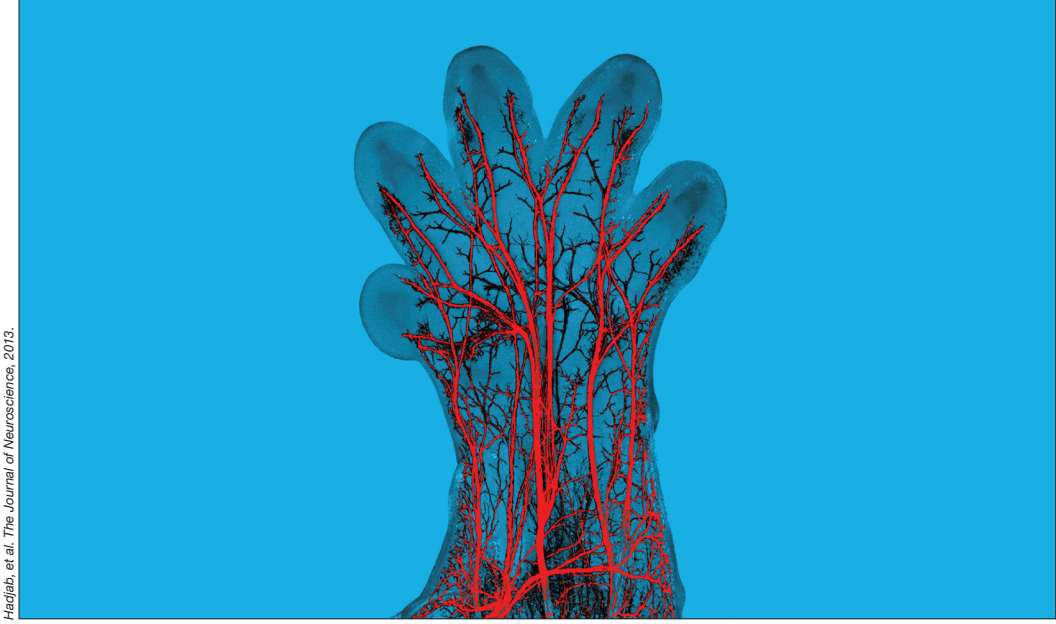
We have around 1,000 different types of olfactory cells, but can identify about 20 times as many smells. The tips of olfactory cells are equipped with several hair-like cilia that are receptive to a number of different odor molecules, and many cells respond to the same molecules. A specific smell will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

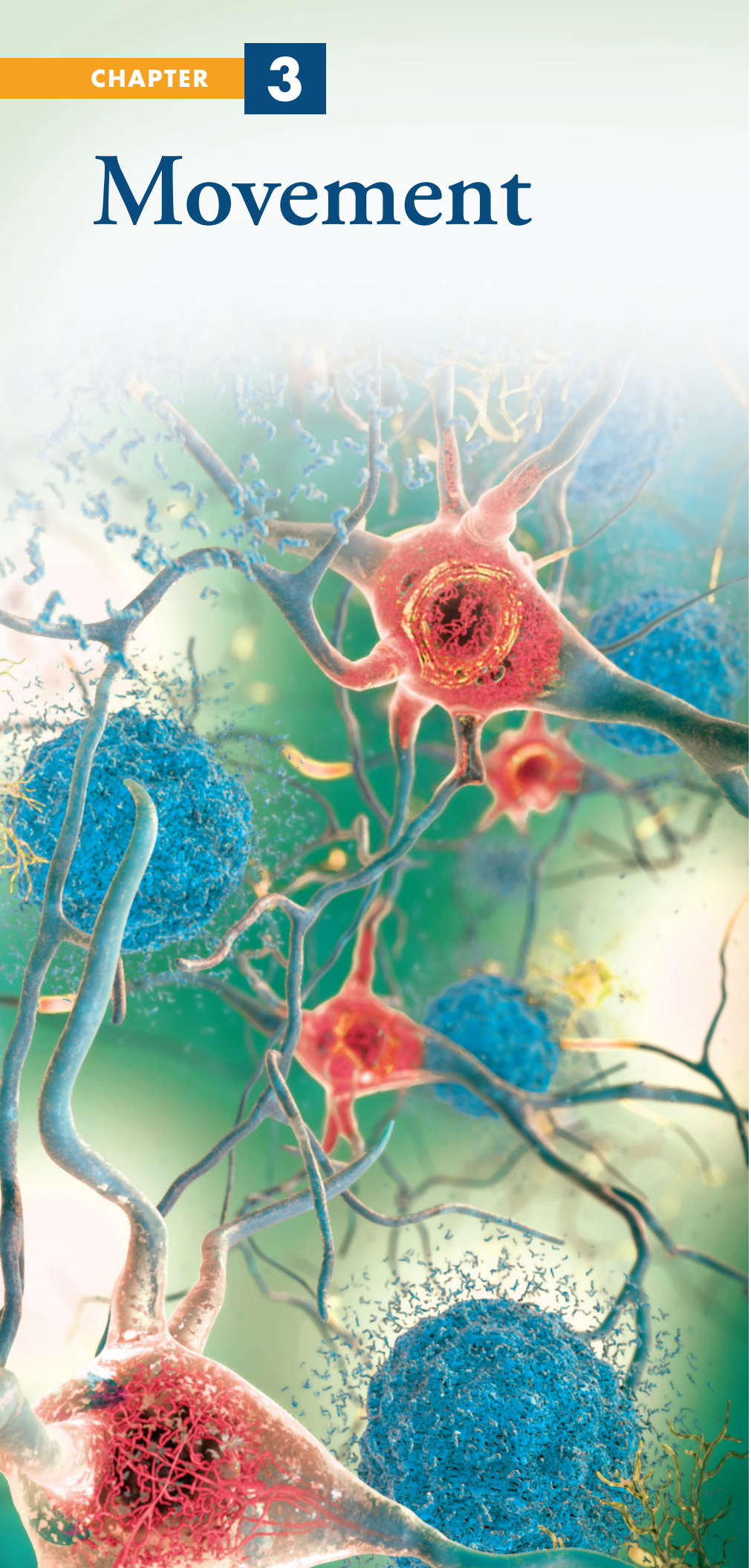
Why do different people, when exposed to the same pain stimulus, experience the pain differently? How itchy or painful something feels obviously depends on the strength of the stimulus, but also on a person's emotional state and the setting in which the injury occurs. When pain messages arrive in the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

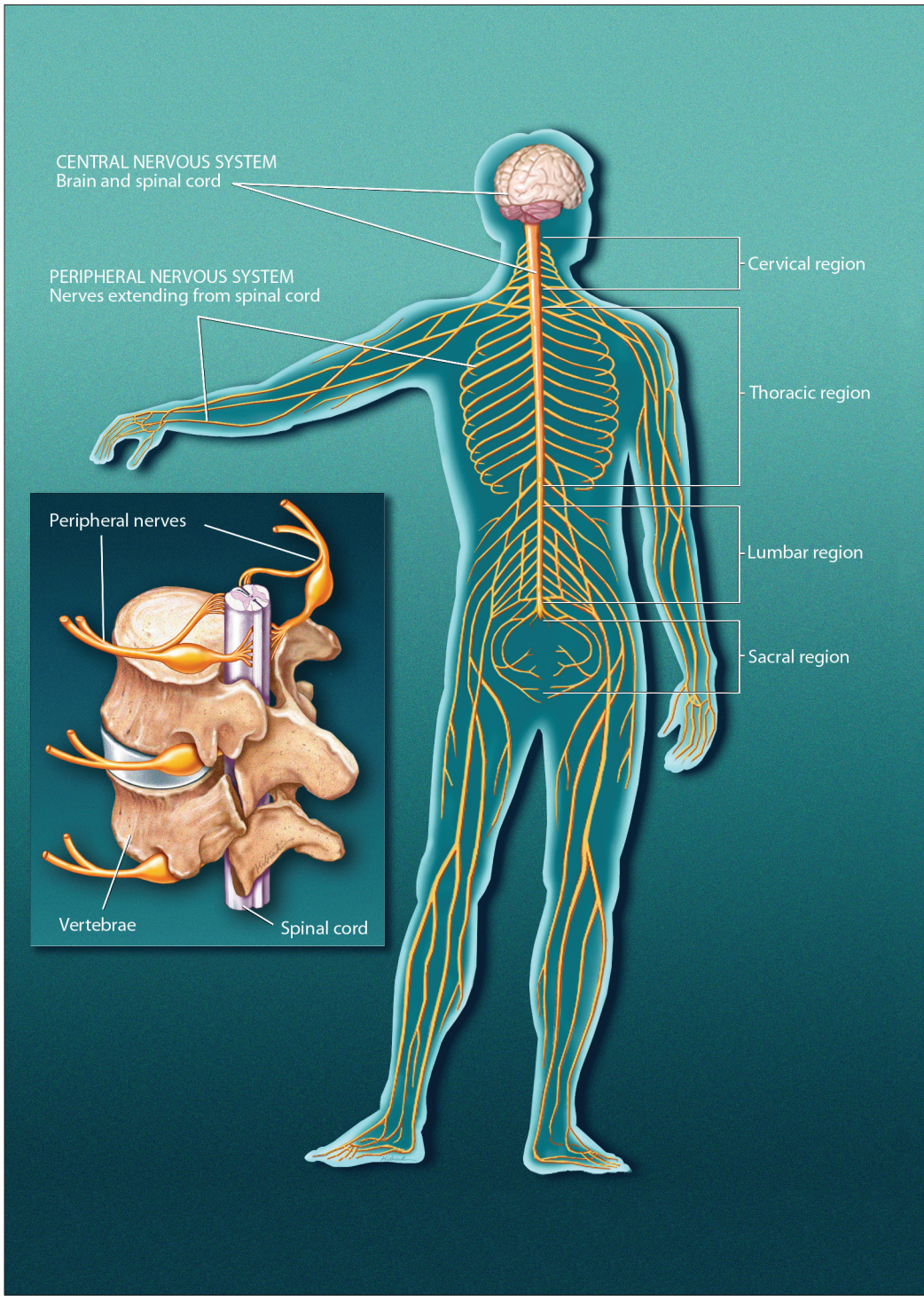
VOLUNTARY MOVEMENTS

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

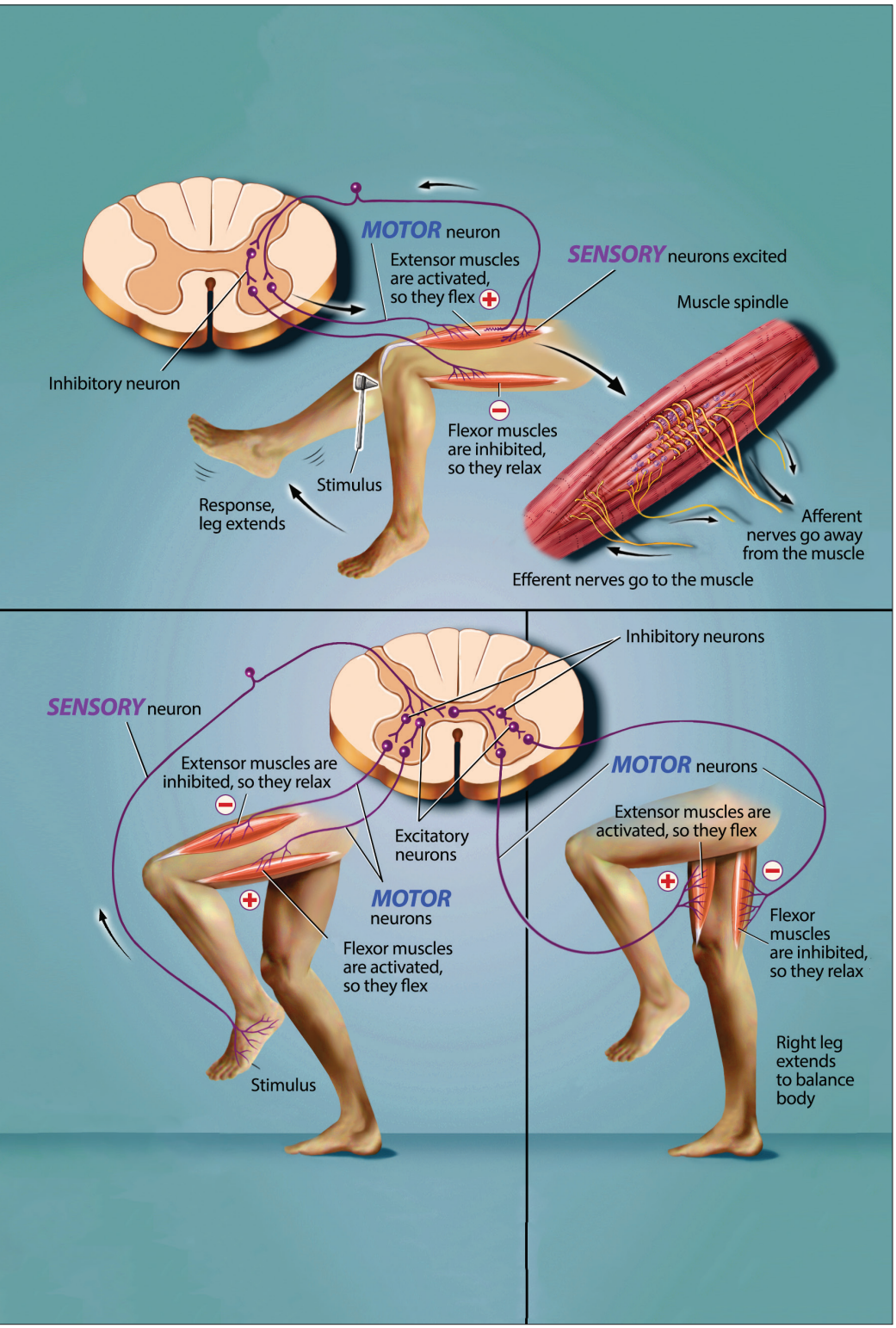
called extensors. Flexors and extensors work in opposition, so when one set of muscles contracts, the other relaxes. For example, bending the elbow requires contraction of the biceps (a flexor) and relaxation of the triceps (an extensor). For such motions, the muscles that promote the movement are called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

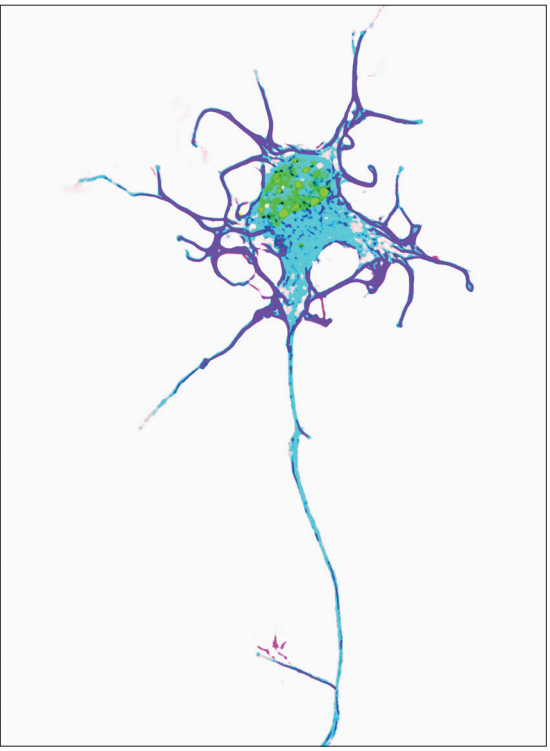
One of the best-known reflexes is the "knee jerk" response, a stretch (myotatic) reflex that occurs when a physician strikes the tendon just below the knee with a small rubber hammer. This tap produces a slight stretch of the knee extensor muscle, which is "sensed" by receptors within the muscle called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

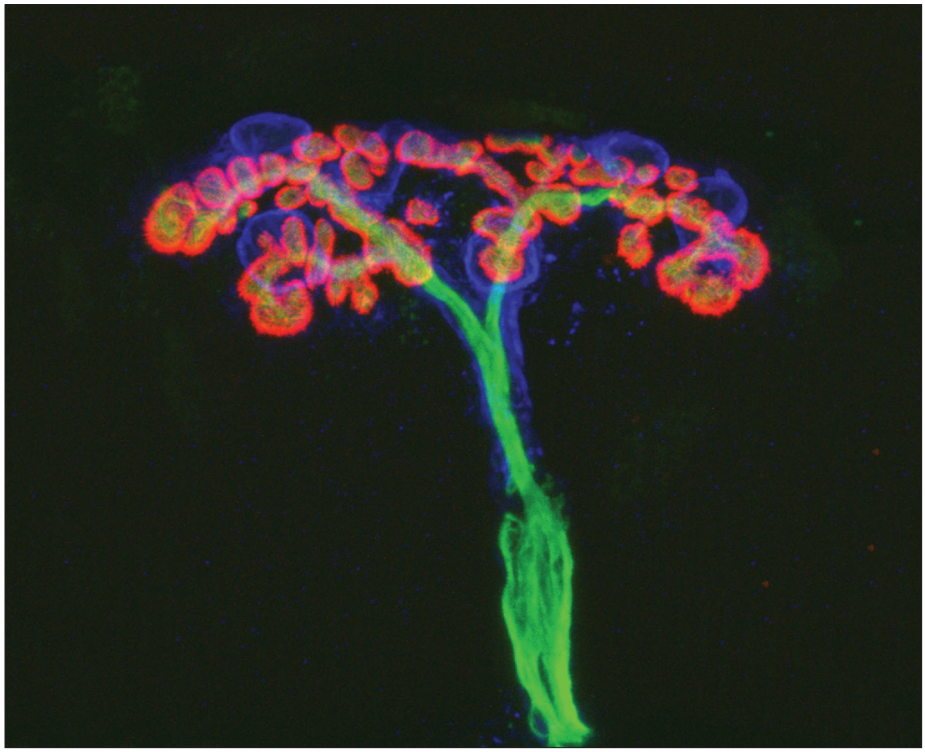
Many reflexes protect you from injury. When you're seated in a doctor's office, the "knee jerk" reflex simply makes your lower leg swing briefly forward. However, if you were to jump off a chair (or perform an even more dramatic gymnastic dismount) this same reflex would promote the contraction of the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

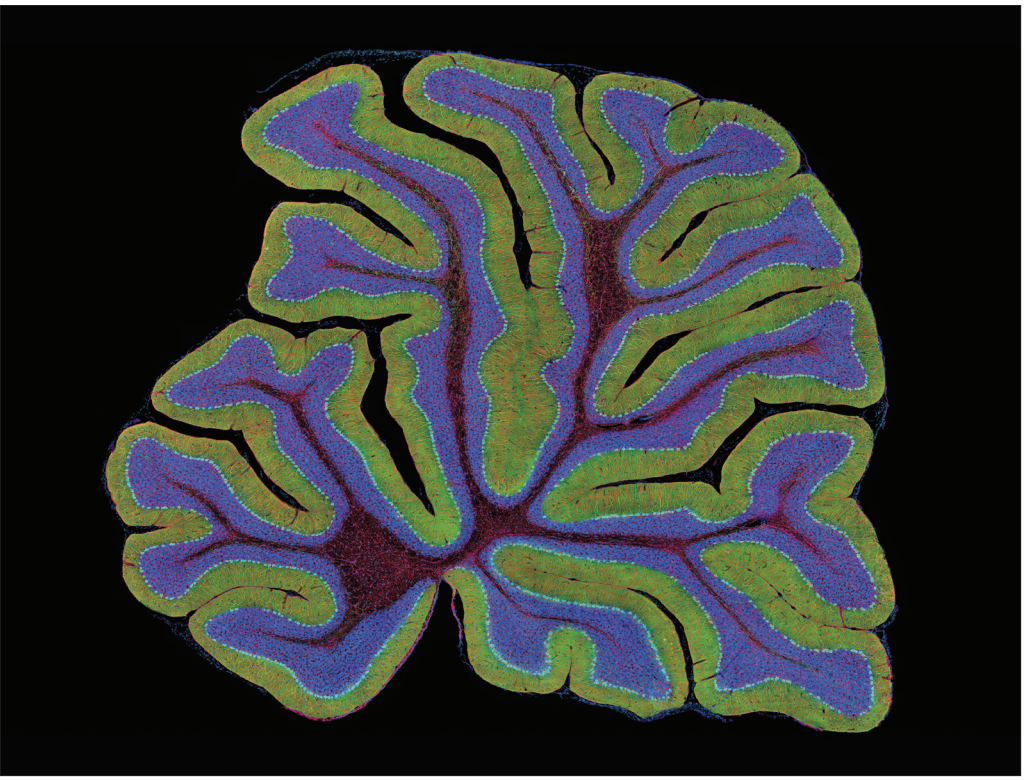
The most complex movements that you perform, including those requiring conscious planning, involve input from the brain. These higher brain regions initiate voluntary motion, coordinate complex sequences of movement, and tailor behavioral output to suit a given situation. Successful execution of these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

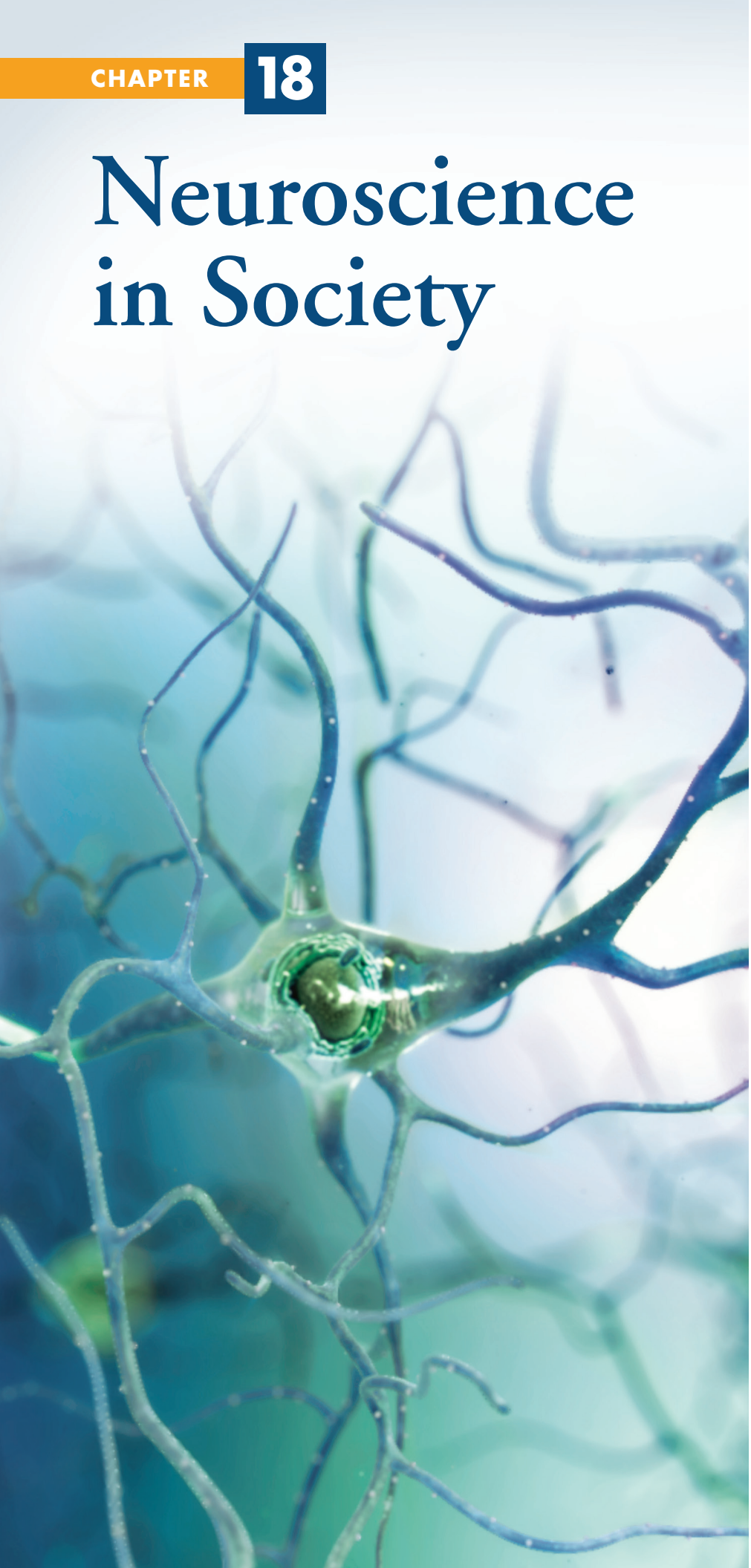
Disturbance of cerebellar function leads to poor coordination, disorders of balance, and even difficulties in speech, one of the most intricate forms of movement control. Long-term alcohol abuse is a common cause of acquired cerebellar degeneration. Typical symptoms are poor coordination, an unsteady 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 18

Neuroscience in Society



By this time, you've learned a great deal about your brain and how complicated it is. The preceding chapters have mostly looked at the brain as a part of a thinking, behaving, and feeling individual.

But you rarely live your life as an isolated individual. In fact, you probably interact with a wide variety of people every day, from bus drivers to store clerks to your best friend. Those interactions, along with the interactions of people around you, form the basis of our society. It makes sense that what you've learned about the brains of individuals can help you understand groups of individuals — human societies — and how they function.

Neuroscientists constantly discover new things about the forces that drive the brain. If insights into questions like "How do I make decisions?" or "What causes addiction?" can change one person's life, they can have an even greater influence on groups of people, sometimes even inspiring them to transform the societies in which they live.

Many questions require critical thinking about how the human mind works: "Who decides what the law should be?" "What makes laws fair?" "How can we design the economy, and what groups of people does it leave behind?" Answering these questions requires a thoughtful understanding of the workings of the human mind. Neuroscience can provide evidence-based arguments for how to build a society, rooted in a solid understanding of brain science.

It might sound like science fiction, but the more we discover about the brain, the greater its potential to transform human society. Scientists need to grapple with the ethical dimensions of their work, engaging in conversations with sociologists, lawyers, politicians,

economists, and philosophers to determine the best ways to build on their groundbreaking revelations about the human brain.

NEUROLAW

In earlier chapters, you learned all about decision-making, but many decisions have more drastic consequences than whether to buy a taco or stir fry for lunch. Behind every crime that makes the news is a decision — or a series of decisions — that may have individuals facing the legal consequences of breaking the law. As with so many things (including the brain), the more closely you look at this issue, the more complicated it gets.

Take addiction, for example. In the last few decades, the American prison population has grown by about 500 percent, largely because of drug-related arrests. In this book, you've learned how drug use affects the brain and is associated with significant changes to the prefrontal cortex (PFC), a part of the brain that oversees impulse control and suppressing cravings. Those changes in the PFC make resisting drug use much more difficult. Seen this way, ongoing drug use looks less like a bad decision and more like a symptom of a disease: addiction.

Now lawyers, judges, and scientists have to decide how drug users should be treated by the criminal justice system. Should they continue to be jailed, as a punishment for their decision to break the law? Or should they receive therapy or rehabilitation to treat, and help them recover from their altered brain states? Or should they receive some combination of both? What is the perfect balance?

Many examples muddy the waters of decision-making and punishment. In one famous case, an individual who had brain surgery to remove a tumor suddenly developed a compulsion to view child pornography. During his trial, the man's doctor provided evidence that the surgery had damaged a part of the brain that typically suppresses such dark urges. Personality changes after brain surgeries are not uncommon — was it possible that his terrible fixation was a side effect of his life-saving surgery? If so, what should his punishment be? If the behavior wasn't his "fault," what does a just society owe his victims?

These are not easy questions to answer. They require us to temper our notions of fairness and justice with new scientific knowledge. The more neuroscience reveals to us about the mechanisms underlying memory, personal responsibility, and behavior, the more we must accommodate our social structure to the ramifications of these new discoveries.

For another example, consider eyewitness testimony, a common tool in the courtroom. Studies have found that the testimony of people who actually witnessed a crime is very convincing to juries — more convincing than many types of forensic evidence. But recent research has shown that human memory is far from perfect, especially as time passes after a crime. As witnesses recall their memories, they introduce errors, which are then reconsolidated into new memories. This is true of even the most memorable events. In a study of New York City residents one year after the 9/11 terrorist attacks, their memories of the event differed in 40 percent of the details. This doesn't mean that eyewitness testimony is useless, but neuroscience has demonstrated that it is far from infallible. Judges and lawyers must now come to terms with this change of perspective.

The more neuroscience reveals to us, the more we must accommodate our social structure to the ramifications of these new discoveries.

Nor is this the first time that neuroscience has helped to change the way the courts work. Polygraph tests, once a staple of television crime dramas, have been rejected in many courts (including the United States Supreme Court) as being unreliable. This decision was based on the work of many scientists, who showed that the physiological reactions measured by polygraph tests (sweating, increased heart rate, etc.) are *not* definitively linked to guilt or lying.

After all, dragging an innocent person to the police station to submit to a lie detector test might produce the same symptoms. Reliable lie detection technology might exist one day, but that day is too far in the future to affect current court decisions.

NEUROECONOMICS

You are constantly making financial decisions for yourself. Should you stock up on all of your favorite snacks now that you are at the grocery store, or come back later for the items when there is a big sale? Are you saving enough for college? Do you like that new sports car enough to put up with its poor gas mileage? In recent years, economists and neuroscientists have begun collaborating to investigate the brain processes behind these decisions. This field, called "neuroeconomics," has the potential to significantly alter the way people think about the economy.

A driving force behind modern capitalism is the belief that individuals make rational purchasing decisions — that everyone acting in their own self-interest creates a system in which resources will be distributed as fairly as possible. Yet that theory doesn't explain why so many economic decisions are irrational, or based on gut instinct and rationalized later. Neuroeconomics is especially interested in those situations where choices are less clear-cut or rational and involve unknown (or unacknowledged) factors and risk.

To learn more about these decisions, scientists have measured brain activity as people complete economic tasks — for example, running brain scans as people play a simple double-or-nothing game. When a player decides to risk it all to double winnings, activity increases in a part of the brain called the insular cortex. Scientists hypothesize that networks of the insular cortex interact with other brain areas, including parts of the limbic system that function in learning, memory and emotion, to let the player picture the negative consequences of taking such a risk. Suddenly risking a mortgage payment at the blackjack table might not look so appealing.

Scientists have also discovered that our hormones play a role in economic decisions. In one case, some participants in an investment game were given a dose of oxytocin, a hormone long associated with social bonding. Those who received the oxytocin boost were more trusting with their money and invested larger amounts with a broker. However, if they made investments through a computer program rather than a person, the oxytocin had no effect on their investment strategy. These results suggest that social and neurobiological factors interact to play a role in such decisions, and these kinds of effects are at the heart of many economic decisions. More research in this area could lead to more rational investment strategies.

Another study of male stock traders looked at levels of the hormones testosterone and cortisol. Researchers took saliva samples from a small group of traders every day during a work week, before and after the bulk of their work was done. On days when the traders had higher testosterone levels than average, they took larger risks. However, higher-than-average levels of cortisol (a hormone associated with stress) correlated with risk-averse behavior. With millions of dollars on the line, hormones could be making the difference between a good day at the market and a very bad one.

Research into reward pathways and the way your brain promotes impulsive behavior can help prevent making purchases and decisions that you would regret.

Neuroscience can change our current thoughts about the economy in many other ways. Research on autism spectrum disorders is discovering promising treatments, but also revealing opportunities for workplaces to employ the unique abilities of neurodiverse people. Research into reward pathways and the way your brain promotes impulsive behavior can help prevent making purchases and decisions that you would regret. Scientists are also studying unconscious biases and discrimination, in an effort to help eliminate negative prejudices in hiring

and employment. These are only a few of the practical applications of neuroscience, and more are anticipated. Sometime in the near future, neuroscience could have all the tools needed to design a better, and more inclusive, economic system.

ETHICS AND THE FUTURE OF NEUROSCIENCE

Modern science has the potential to change some of the most fundamental beliefs of our society. Brain science, in particular, has raised many ethical issues. Consider the history of brain research, where early attempts to understand the brain started or exacerbated practices such as phrenology, eugenics, forced sterilization, and unnecessary lobotomies. When the ethical frameworks of science fail, it can incur consequences that affect not only individuals, but society as a whole.

In the future, new technologies that are already on the horizon will raise serious ethical questions. Genetics is one area under intense scrutiny. As you've read in this book, you've seen that many brain diseases have their roots in your genetic code, and scientists are now able to screen for some of these diseases while children are in the womb. Emerging technologies might soon help us identify potential problems and alter a child's genes to prevent it. But is it ethical to alter an unborn child's genetics to cure autism? Other genetic diseases, like Huntington's, will only manifest much later in life. Is it acceptable to "pre-treat" this disease with genetic alterations? What about making children smarter or increasing their chance of getting a perfect math score on their SATs? Some people believe that all children have the right to be genetically enhanced, while others insist that they retain the right *not* to be enhanced.

And who would have access to these enhancements? Will they only be available to children of the rich and powerful, leaving most of us behind? Similar questions can be asked of other therapies, like drugs or devices like transcranial stimulation, which alter the brain in order to treat it.

In the past, these questions were often posed by authors of science fiction. But with the startling technological advances of recent decades, these real-world challenges might be closer than you think. In fact, many scientists and doctors already deal with serious ethical quandaries created by neuroscience. For example, scientists can detect specific biomarkers for disorders such as depression, psychosis, and certain types of chronic pain. Are medical professionals obligated to take steps to treat a disease or disorder that currently shows no symptoms and might never actually materialize? When is the right time to intervene?

There are even thornier questions to consider: When getting permission to treat the brain in some way, the organ that gives consent is the same as the organ being treated. How does that affect the idea of "informed consent" in cases like Alzheimer's disease or a debilitating brain tumor? Should a doctor proceed with treatment when the patient (that is, his or her brain) might not have had the ability to properly consent?

The questions raised in this chapter have no easy answers. Your responses could depend on your religion, your socioeconomic class — and, yes, on the activity of your hormones, your neurotransmitters, and the progressive maturation and aging of your nervous system. The brain is the most complicated structure in the known universe, and investigating its mysteries seems to produce as many questions as answers — and these questions are scientific, ethical, legal and social. But the progress of science has always stirred up "inconvenient" questions about ethical behavior, social conventions, and the proper use of our institutions. Asking those questions early will help researchers and the public work together to create strong ethical frameworks for our evolving society.

Science is an ongoing process. Neuroscience has made many beneficial advances, but facts are also evolving as discoveries emerge. We are only on the very cusp of understanding the billions of cells and trillions of connections that form the human brain. Stay curious about the neuroscience you read in the news, keeping in mind what you have learned in this book to give you context behind the headlines. You are part of science, too. Dialogues between scientists are as vital as dialogues between neuroscientists and society. Creating a forum for debate and discussion holds out the best hope of answering questions in ways that advance our society now and in the future.

BrainFacts.org

FOUNDING PARTNERS

The Kavli Foundation

The Kavli Foundation, established by Fred Kavli, is dedicated to advancing science for the benefit of humanity, promoting public understanding of scientific research, and supporting scientists and their work. The Foundation's mission is implemented through an international program of research institutes in the fields of astrophysics and theoretical physics, nanoscience, and neuroscience, and through the support of conferences, symposia, endowed professorships, journalism workshops, and other activities. The Foundation is also a founding partner of the Kavli Prizes, biennial $1 million prizes that recognize scientists for their seminal advances in three research areas: astrophysics, nanoscience, and neuroscience.

Gatsby Charitable Foundation

Gatsby is a trust set up by David Sainsbury to realize his charitable objectives in plant science research, neuroscience research, science and engineering education, economic development in Africa, public policy research and advice, and the arts.

Gatsby aims to be more than a funder, acting as an enabler for projects, designing, developing, overseeing and, in some cases, delivering activities. Gatsby takes a long-term view as they do not think much can be achieved by short, one-off projects. Gatsby is always looking to increase the impact of its limited funds, and is therefore eager to form partnerships with others who share its goals. Gatsby supports both large- and small-scale work, employing different methods and models depending on the different challenges, but is always ultimately looking to deliver long-term, sustainable change.

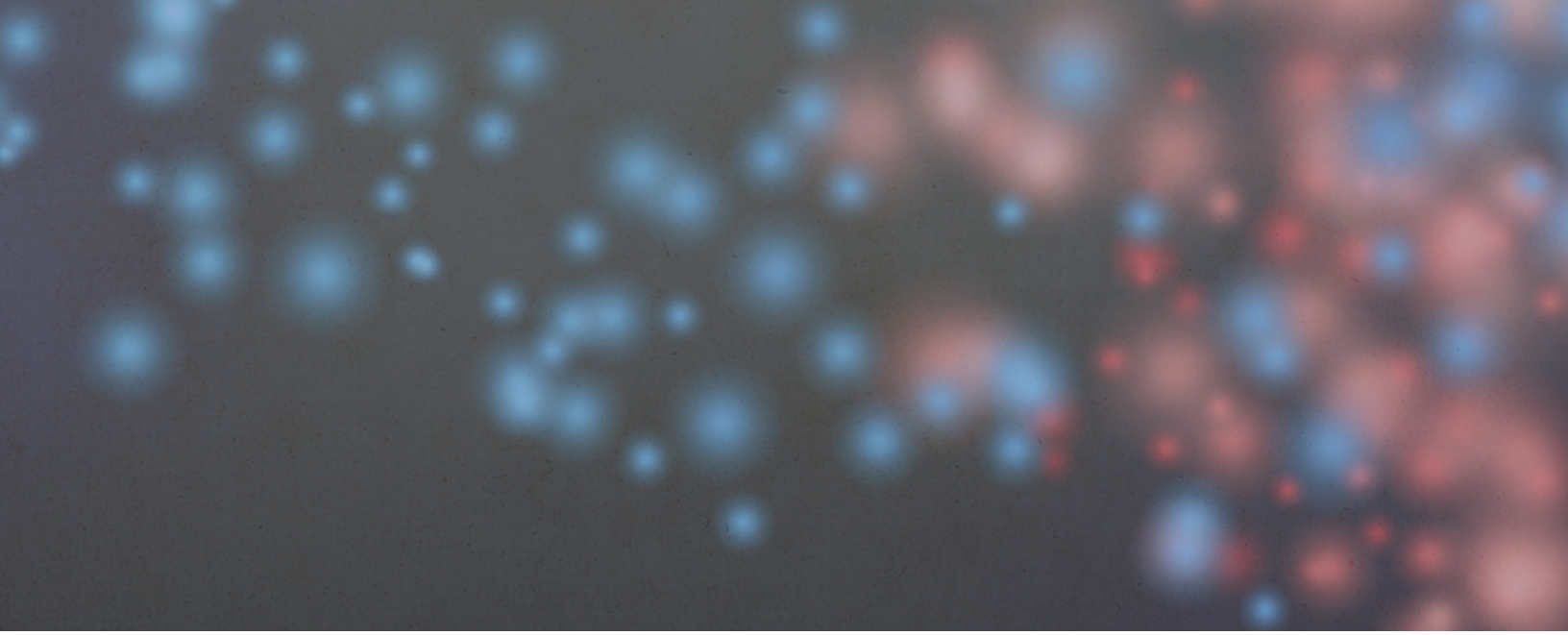
Society *for* Neuroscience

The Society for Neuroscience (SfN) is the world's largest organization of scientists and physicians devoted to understanding the brain and nervous system. The nonprofit organization, founded in 1969, now has nearly 37,000 members in more than 90 countries and over 130 chapters worldwide.

SfN's mission is to:

- Advance the understanding of the brain and the nervous system by bringing together scientists of diverse backgrounds, by facilitating the integration of research directed at all levels of biological organization, and by encouraging translational research and the application of new scientific knowledge to develop improved disease treatments and cures.
- Provide professional development activities, information, and educational resources for neuroscientists at all stages of their careers, including undergraduates, graduates, and postdoctoral fellows, and increase participation of scientists from a diversity of cultural and ethnic backgrounds.
- Promote public information and general education about the nature of scientific discovery and the results and implications of the latest neuroscience research. Support active and continuing discussions on ethical issues relating to the conduct and outcomes of neuroscience research.
- Inform legislators and other policymakers about new scientific knowledge and recent developments in neuroscience research and their implications for public policy, societal benefit, and continued scientific progress.

SfN's mission emphasizes the importance of engaging and inspiring the public about the progress and promise of brain research. BrainFacts.org, a public information initiative of The Kavli Foundation, the Gatsby Charitable Foundation, and SfN, provides trusted, authoritative information to the public about the brain and nervous system.



A Companion Publication to

BrainFacts.org

A PUBLIC INFORMATION INITIATIVE OF:

THE KAVLI FOUNDATION

GATSBY

SfN SOCIETY *for* NEUROSCIENCE

The Society for Neuroscience | 1121 14th Street NW | Suite 1010 | Washington, DC 20005 | (202) 962-4000 | sfn.org