BrainFacts

A PRIMER ON THE BRAIN AND NERVOUS SYSTEM

Pages 36-95

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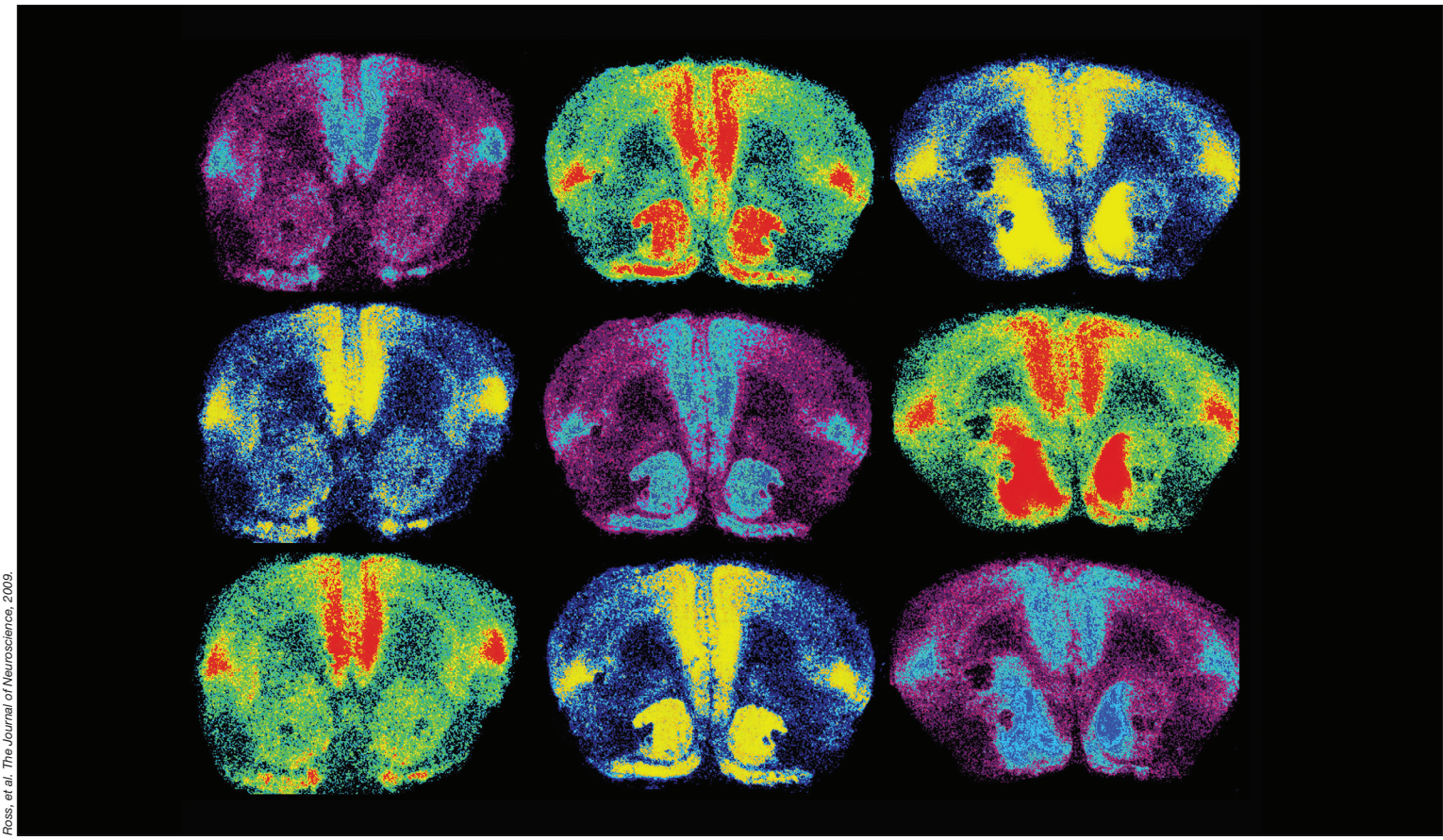


Ross, et al. The Journal of Neuroscience, 2009.

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

EMOTIONS

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

Anatomy of Emotion

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

The amygdala integrates emotions, emotional behavior, and motivation. It interprets fear, helps distinguish friends from foes, and identifies social rewards and how to attain them. One very familiar type of learning is dependent on the amygdala: classical conditioning, which associates a stimulus with reward or punishment.

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

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

Motivation: Affective Decision-Making

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

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

Motivation: Dopamine and Reward Pathways

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

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

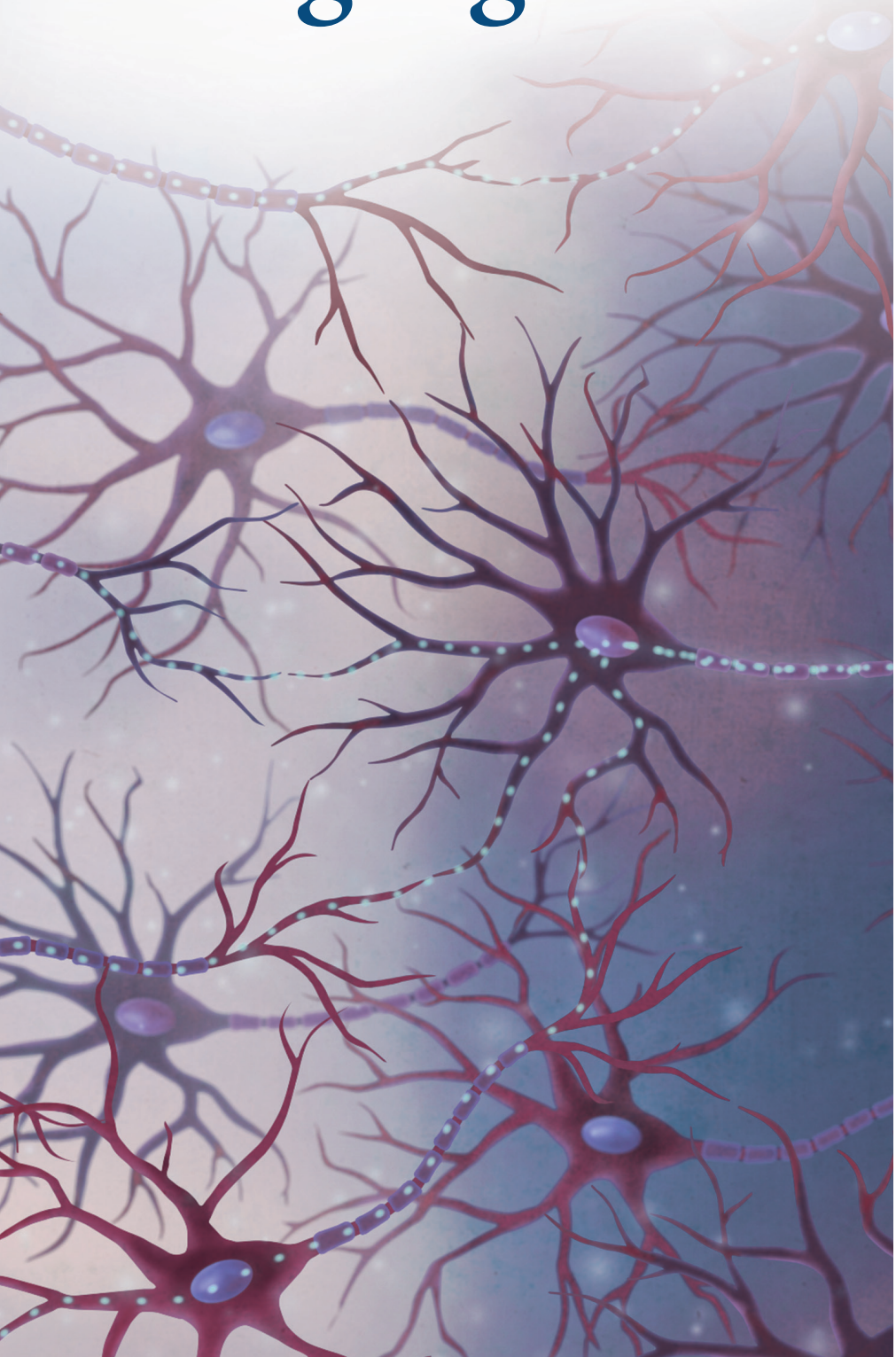
Surprisingly, it's not the reward itself, but the expectation of a reward that most powerfully influences the emotional reaction. Reward learning occurs in response to something unexpected — when the actual reward differs from what was predicted. If a reward is greater than anticipated, dopamine signaling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

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

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

CHAPTER 5

Thinking, Planning & Language



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

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

Constructing Representations

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

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

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

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

Consider the case of D.B.O., a 72-year old man who suffered multiple strokes. In tests run by researchers, D.B.O. could identify only 1 out of 20 different common objects by sight. He also struggled when he was asked to take a cup and fill it with water from the sink. He approached several different objects — a microwave, water pitcher, garbage can, and roll of paper towels — saying "This is a sink … Oh! This one could be a sink … This is also a sink," before finally finding the real sink and filling the cup. But in striking contrast, he could easily identify objects when he closed his eyes and felt them; he could also name things that he heard, such as a rooster's "cock-a-doodle-doo."

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

Regional Specialization and Organization

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

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

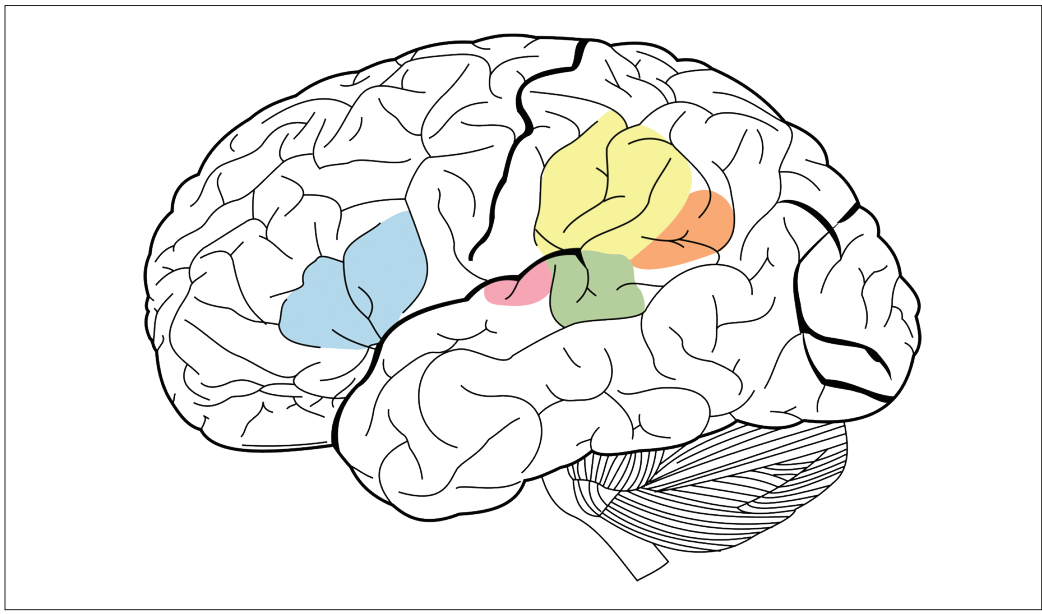
Within these brain areas, information is organized into hierarchies, as complex skills and representations are built up by integrating information from simpler inputs. One example of this organization is the way the brain represents words. Regions that encode words include the posterior parietal cortex,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

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

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

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

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



James.mcd.nz

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

LANGUAGE PROCESSING

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

After Leborgne died, Broca performed an autopsy and found a large damaged area, or lesion, in a portion of the frontal lobe. Since then, we have learned that damage to particular regions within the left hemisphere produces specific kinds of language disorders, or aphasias. The portion of the frontal lobe where Leborgne's lesion was located is still called Broca's area, and it is vital for speech production. Further studies of aphasia have greatly increased our knowledge about the neural basis of language.

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

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

Unlike patient Leborgne, S.A. could speak fluently, but her utterances made no sense: she offered absurd answers to questions, used made-up words, and had difficulty naming familiar items. After her death, Wernicke determined that she had damage in her left temporal lobe. This caused her difficulty in comprehending speech, but not producing it, a deficit that is now known as "Wernicke's aphasia," or "fluent aphasia." Fluent aphasic patients might understand short individual words, and their speech can sound normal in tone and speed, but it is often riddled with errors in sound and word selection and tends to be unintelligible.

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

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

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

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

New Insights in Language Research


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

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

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

Functional imaging studies have also identified brain structures not previously known to be involved in language. For example, portions of the middle and inferior temporal lobe participate in accessing the meaning of words. In addition, the anterior temporal lobe is under intense investigation as a site that might participate in sentence-level comprehension. Recent work has also identified a sensory-motor circuit for speech in the left posterior temporal lobe, which is thought to help communication between the systems for speech recognition and speech production. This circuit is involved in speech development and is likely to support verbal short-term memory.

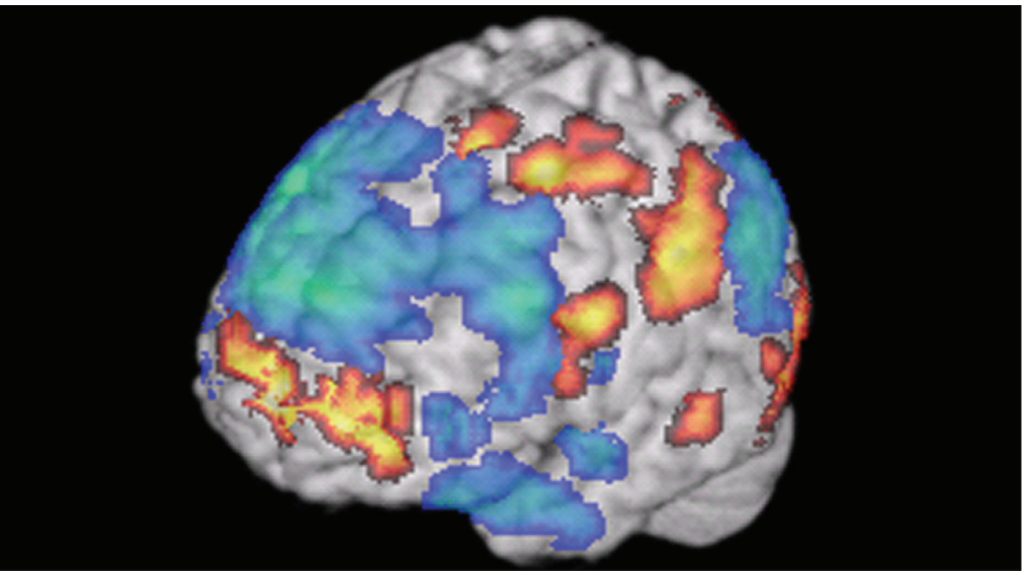
COGNITION AND EXECUTIVE FUNCTION

Executive Function

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

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

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



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

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

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

Executive function can be considered a blend of three core skills: inhibition, working memory, and shifting. Inhibition is the ability to suppress a behavior or action when it is inappropriate — such as calling out loudly when one is in an audience or classroom. Even toddlers demonstrate hints of a developing inhibition ability, as shown in their ability to delay (for at least a short period of time) eating a treat placed in front of them. By the time children reach preschool, they can tackle more complex inhibition tasks, such as "Lucia's hand game," in which they are told to make a fist when shown a finger and a finger when shown a fist. This test, which requires inhibiting their more automatic imitation of adults, is very hard for three-year-olds, but four-year-olds perform significantly better. As people grow older, they wield this ability ever more skillfully.

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

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

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

Decision-Making

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

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

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

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

Social Neuroscience

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

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

An obvious way that we understand the mental states of others is by observing their actions. This requires the brain to see and recognize others' movements and facial expressions, and then draw inferences about the feelings and intentions that drive them. Scientists have learned how brain activity drives these processes by scanning people's brains with fMRI as subjects watch video clips of other people.

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

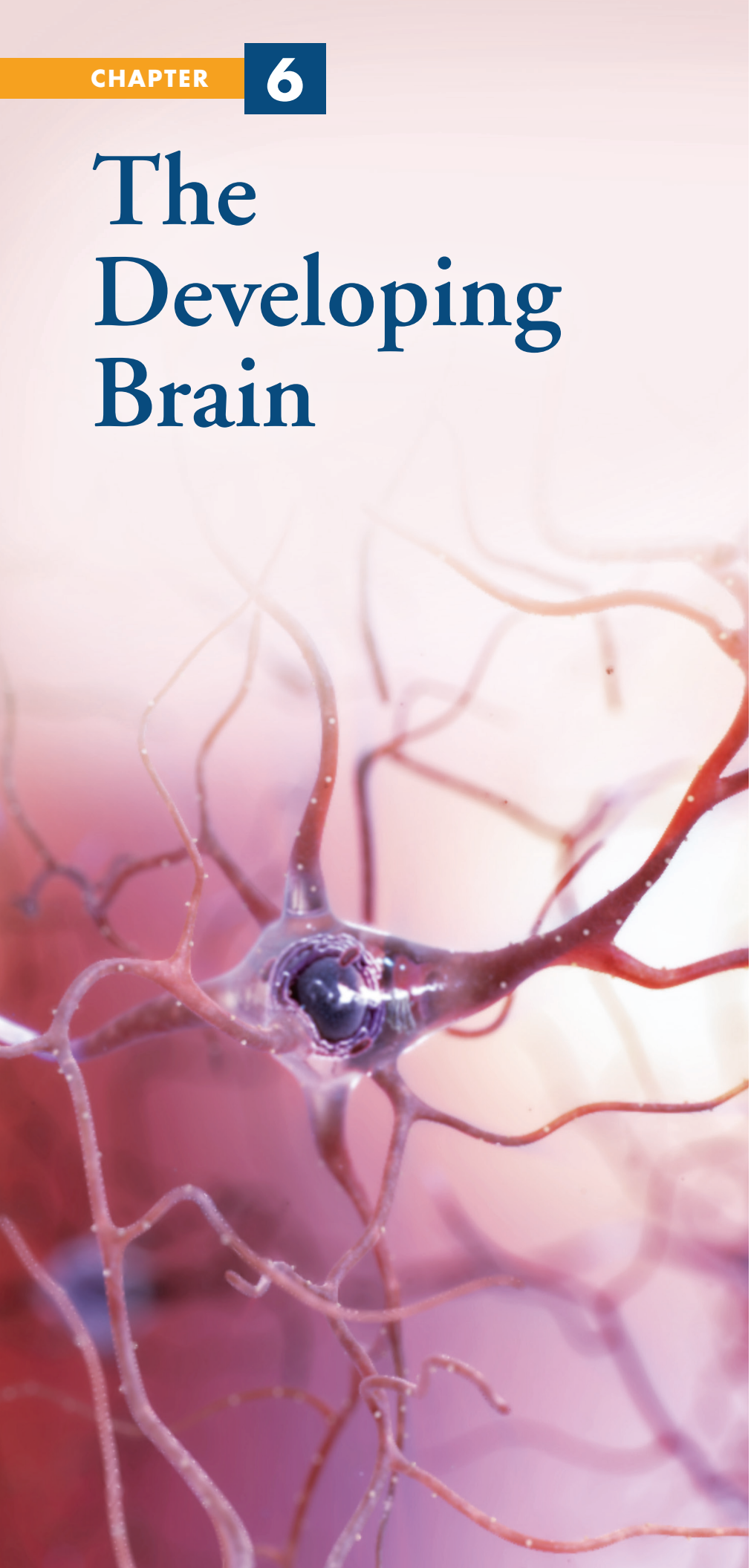
A popular, though controversial, theory of social cognition centered on the discovery of "mirror neurons." In the 1990's, scientists identified neurons in the motor cortex of rhesus macaques that fired when the monkeys performed a specific action. They were astonished to find these neurons also fired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

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

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

CHAPTER 6

The Developing Brain

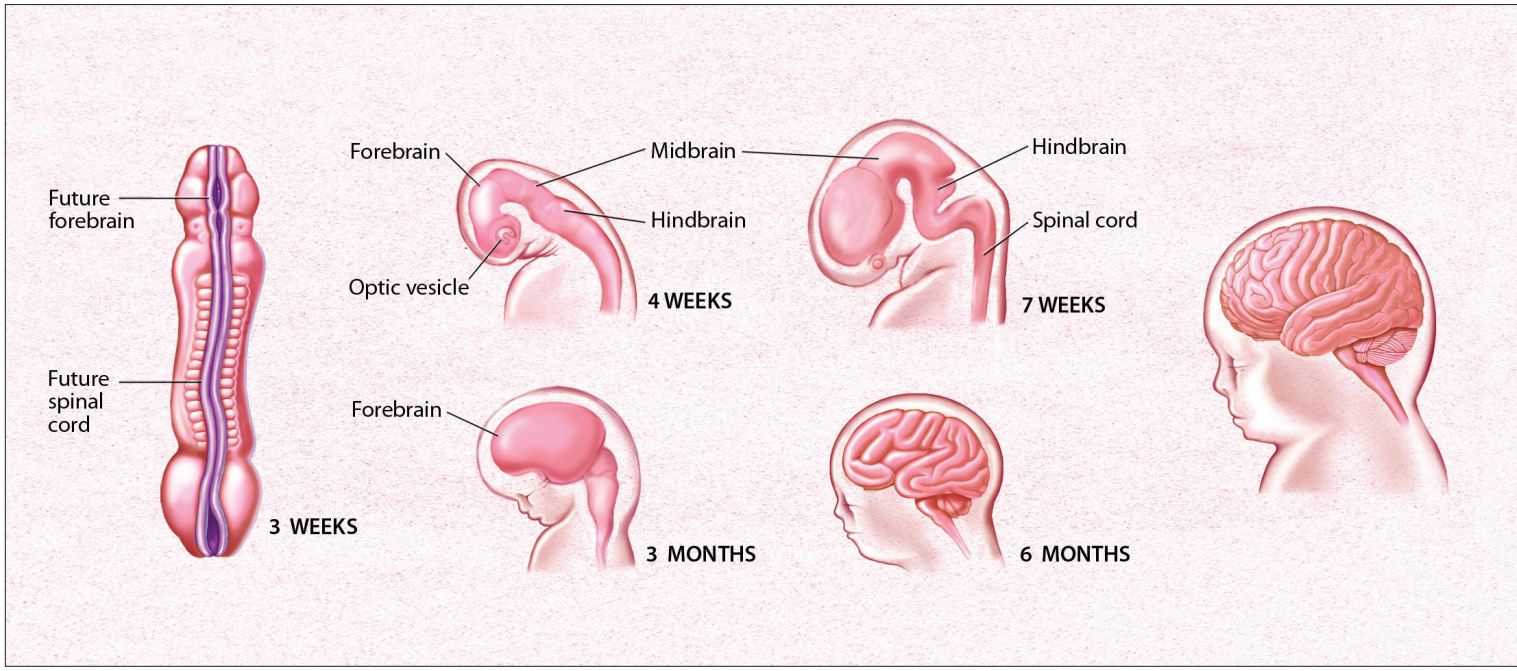


Neurons develop through delicate and carefully choreographed processes that take place while an embryo grows. Signaling molecules "turn on" certain genes and "turn off" others, initiating the formation of immature nerve cells. During the next stage — cell division, also called proliferation — the pool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

THE JOURNEY OF NERVE CELLS

Formation and Induction

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



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

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

Proliferation

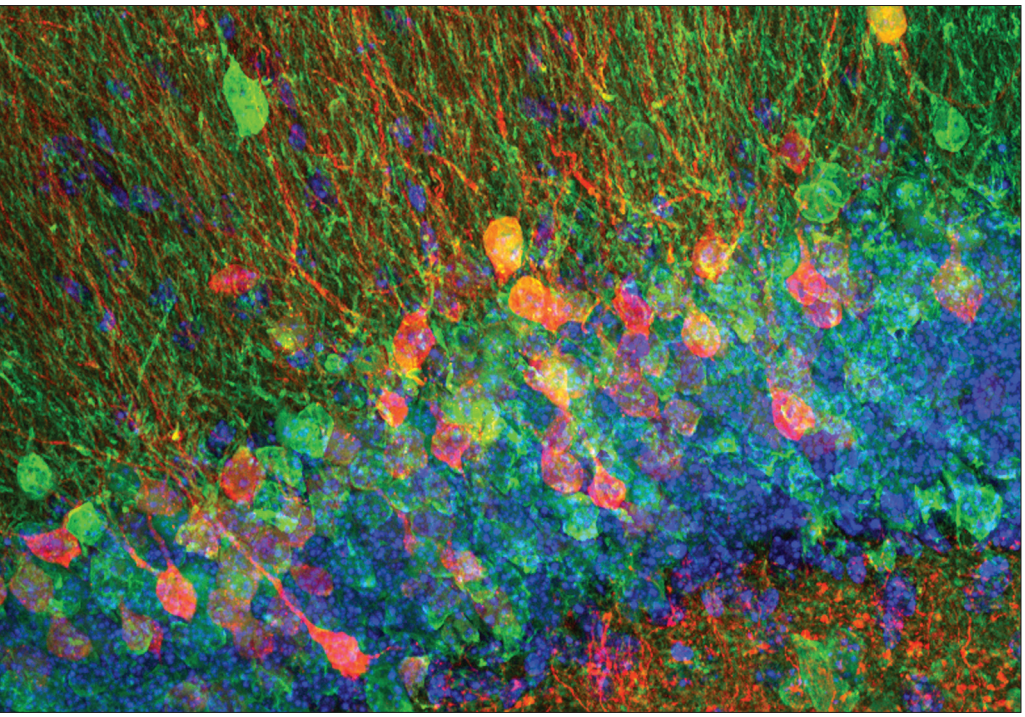
In the brain, neurons arise from a fairly small pool of neural stem and progenitor cells, special cells that can divide and become a variety of mature cell types. Before achieving their mature cell fate, this pool of cells undergoes a series of divisions — increasing the number of cells that will ultimately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

This proliferative process permits rapid growth during early development of the brain, with billions of cells being produced in a matter of weeks. After that series of divisions is complete, only a few neural stem and progenitor cells remain within the brain, and neurogenesis in adulthood is limited to a few regions of the brain, such as those involved with memory.

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

Migration

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



Winkle, et al. The Journal of Neuroscience, 2016

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

process is called migration, and it begins three to four weeks after a human baby is conceived. At this time, the ectoderm starts to thicken and build up along the midline of the embryo. As the cells continue to divide, a flat neural plate grows, followed by the formation of parallel ridges, somewhat resembling the creases in a paper airplane, that rise along either side of the midline. These ridges extend from the "head end", where the future brain will form, along the length of the embryo where the future spinal cord will develop. Within a few days, the ridges fold toward each other and fuse into a hollow neural tube. The head end of the tube thickens into three bulges that form the hindbrain, the midbrain, and the forebrain. Later in the process, at week 7 in humans, the first signs of the eyes and the brain's hemispheres appear. As new neurons are produced, they move from the neural tube's ventricular zone, which lies along the inner surface of the tube, toward the border of the marginal zone, or outer surface. After neurons stop dividing, they form an intermediate zone where they gradually accumulate as the brain develops. A variety of guidance cue neurons to migrate to their final destinations.

The most common guidance mechanism, accounting for about 90 percent of migration in humans, is the radial glia, which project radially from the intermediate zone to the cortex. Neurons use these glia as scaffolding, inching along glial projections until they reach their final destinations. This process of radial migration occurs in an "inside-out" manner; that is, the cells that arrive the earliest (the oldest ones) form the deepest layer of the cortex, whereas the late-arriving (youngest) neurons form the outermost layer. Through a different mechanism, other neurons migrate sideways, or tangentially (rather than radially), moving parallel to the brain's surface and across the radial cortical columns.

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

Making Connections

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

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

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

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

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

Synapse Formation

Once axons reach their targets, a specialized connection called a synapse begins to form. At the synapse, only a tiny space separates the signaling portion of the axon from the receiving portion of the dendrite. Electrical signals that travel down the axon trigger the release of chemical messages called neurotransmitters, which diffuse across this space and are received by receptors on the target dendrite. Such chemical cues can either promote or hinder the generation of a new electrical signal in the receiving neuron. The combined effects of such cues from thousands of synapses ultimately determine how a receiving neuron responds. A human brain contains trillions of these synapses, which gives rise to the brain's astounding capacity for information processing.

For this processing to occur properly, the formation of synaptic connections must be highly specific. Some specificity is the result of the mechanisms that guide each axon to its proper target. Additional molecules mediate target recognition when the axon reaches the proper location. Dendrites are also actively involved in initiating contact with axons, and both sides produce proteins that span the space between them and anchor the synapse together.

Once initial contact is established, a synapse continues to differentiate. On the presynaptic side, the tiny axon terminal that contacts the dendrite becomes specialized for releasing neurotransmitters, stocking itself with neurotransmitter packets, and proteins that enable those packets to be held in place and then released. On the dendritic — or postsynaptic — side, receptors that respond to those neurotransmitters begin to dot the membrane. Both processes ensure that a synapse can transmit signals quickly and effectively.

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

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

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

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

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

Myelination

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

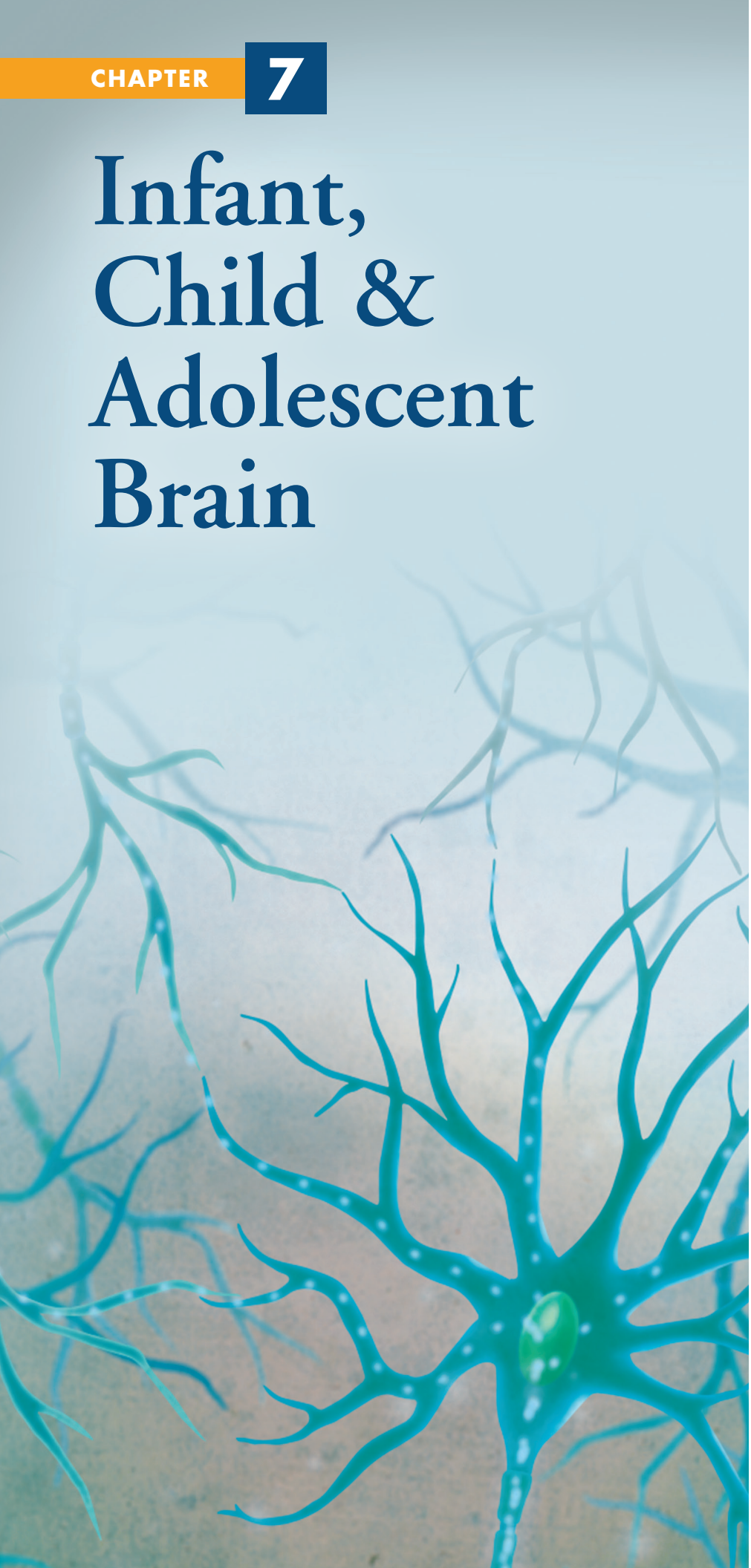
Paring Back

After its initial growth, the neural network is pared back, creating a more efficient system. In fact, only about half the neurons generated during development survive to function in an adult. Entire populations of neurons are removed through apoptosis, a process of programmed cell death initiated in the cells. Apoptosis is activated if a neuron fails to receive enough life-sustaining chemical signals called trophic factors, which are produced in limited quantities by target tissues. Each type of trophic factor supports the survival of a distinct group of neurons. For example, nerve growth factor is important for the survival of sensory neurons. It has recently become clear that apoptosis is maintained into adulthood but constantly held in check. Based on this, researchers have found that injuries and some neurodegenerative diseases kill neurons not by directly inflicting damage but by activating the cells' own death programs. This discovery — and its implication that death need not follow insult — have led to new avenues for therapy.

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

CHAPTER 7

Infant, Child & Adolescent Brain



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

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

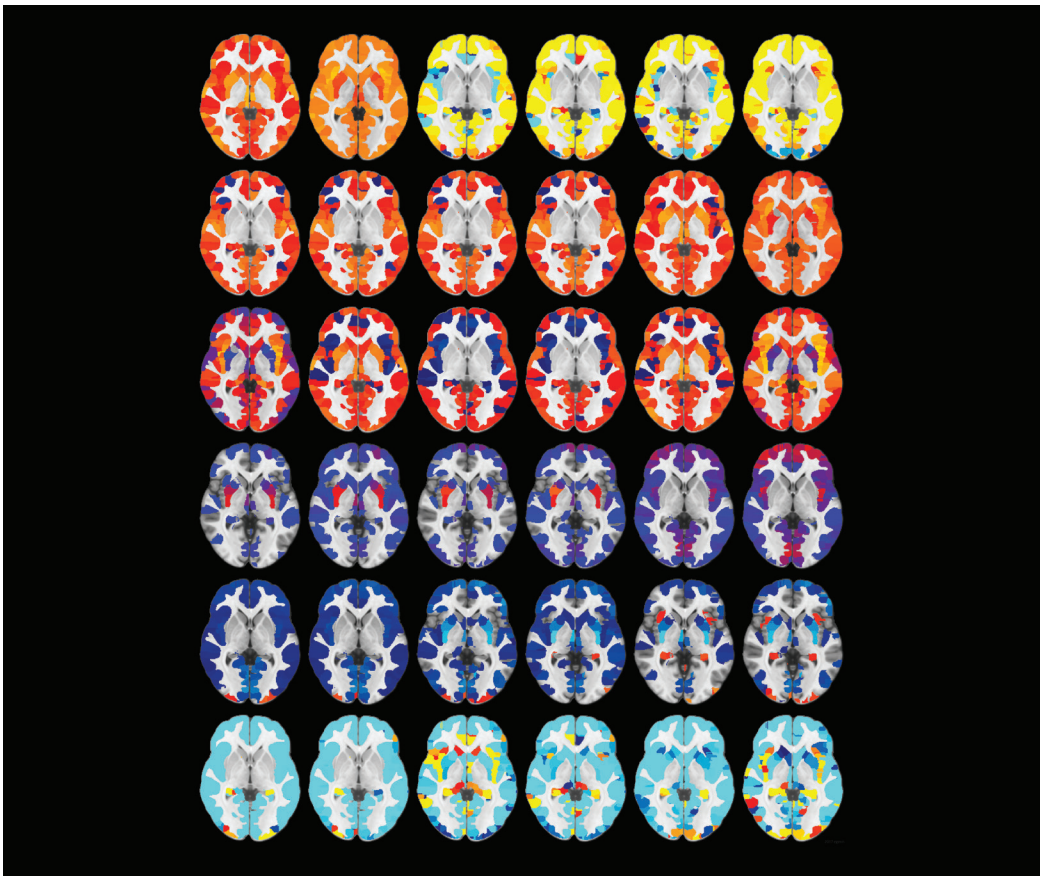
Knowing how the brain was first constructed is an essential step toward understanding its later ability to reorganize in response to external influences or injuries. As the brain develops from the embryo to the adult, unique attributes evolve during infancy and childhood that will influence people's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

THE FIRST YEARS OF LIFE

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

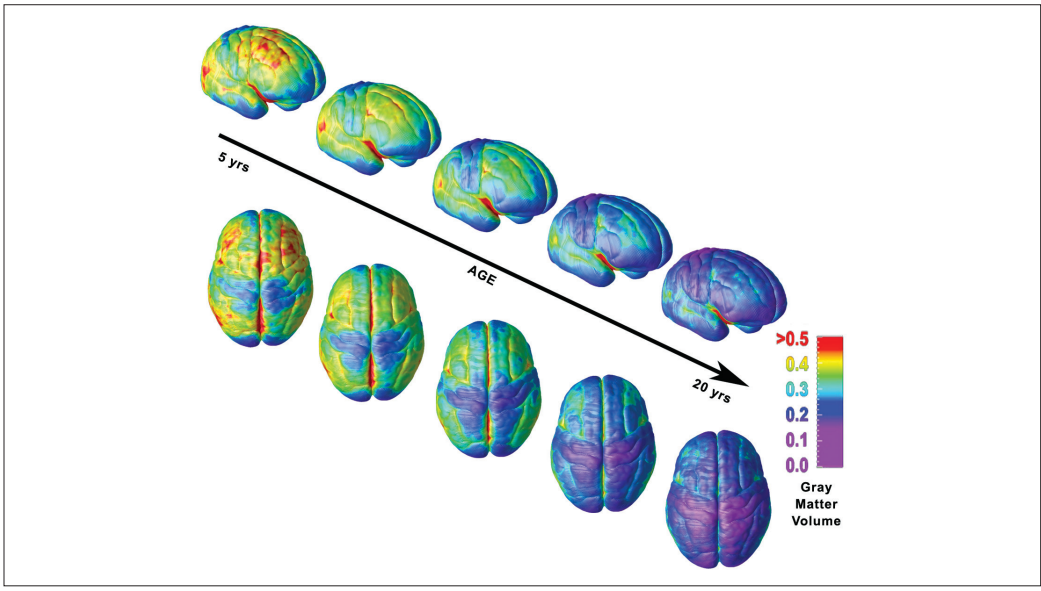
development in the womb? After birth, the baby's brain continues to grow and develop. The average brain-weight of a newborn human baby is about 370 grams (or 13 ounces), just slightly less than a pound. Compare that to the average weight of an adult brain: 3 pounds, with about 86 billion neurons. The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

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



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

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



NIH.

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

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

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

EXPERIENCE SHAPES THE BRAIN

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

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

INTO ADOLESCENCE

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

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

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

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

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

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

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

PLASTICITY

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

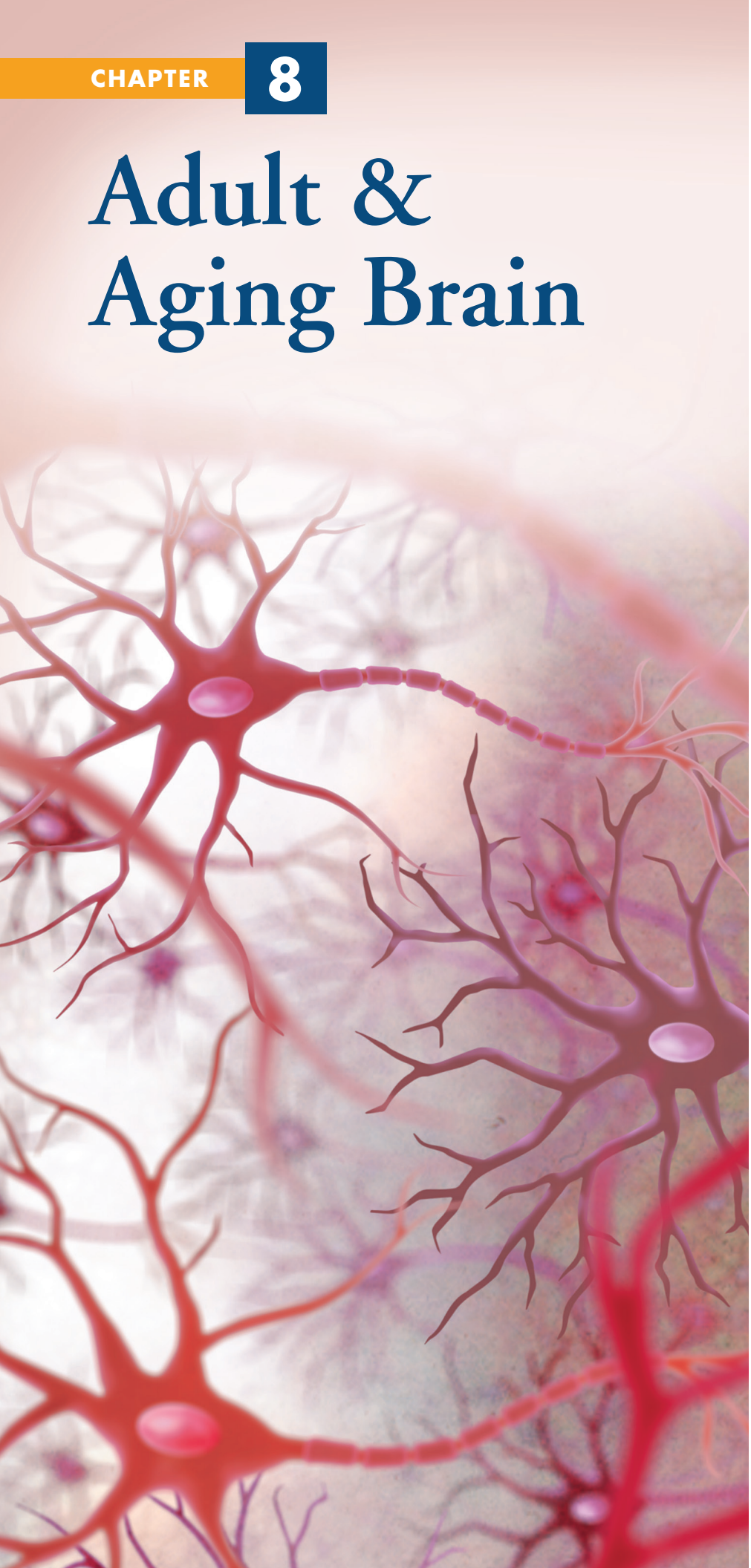
Experience-expectant plasticity refers to integrating environmental stimuli into normal developmental patterns. Being exposed to certain common or universal environmental experiences — for example, hearing language, seeing faces, or being held — during limited critical, or sensitive, periods of development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

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

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

CHAPTER 8

Adult & Aging Brain



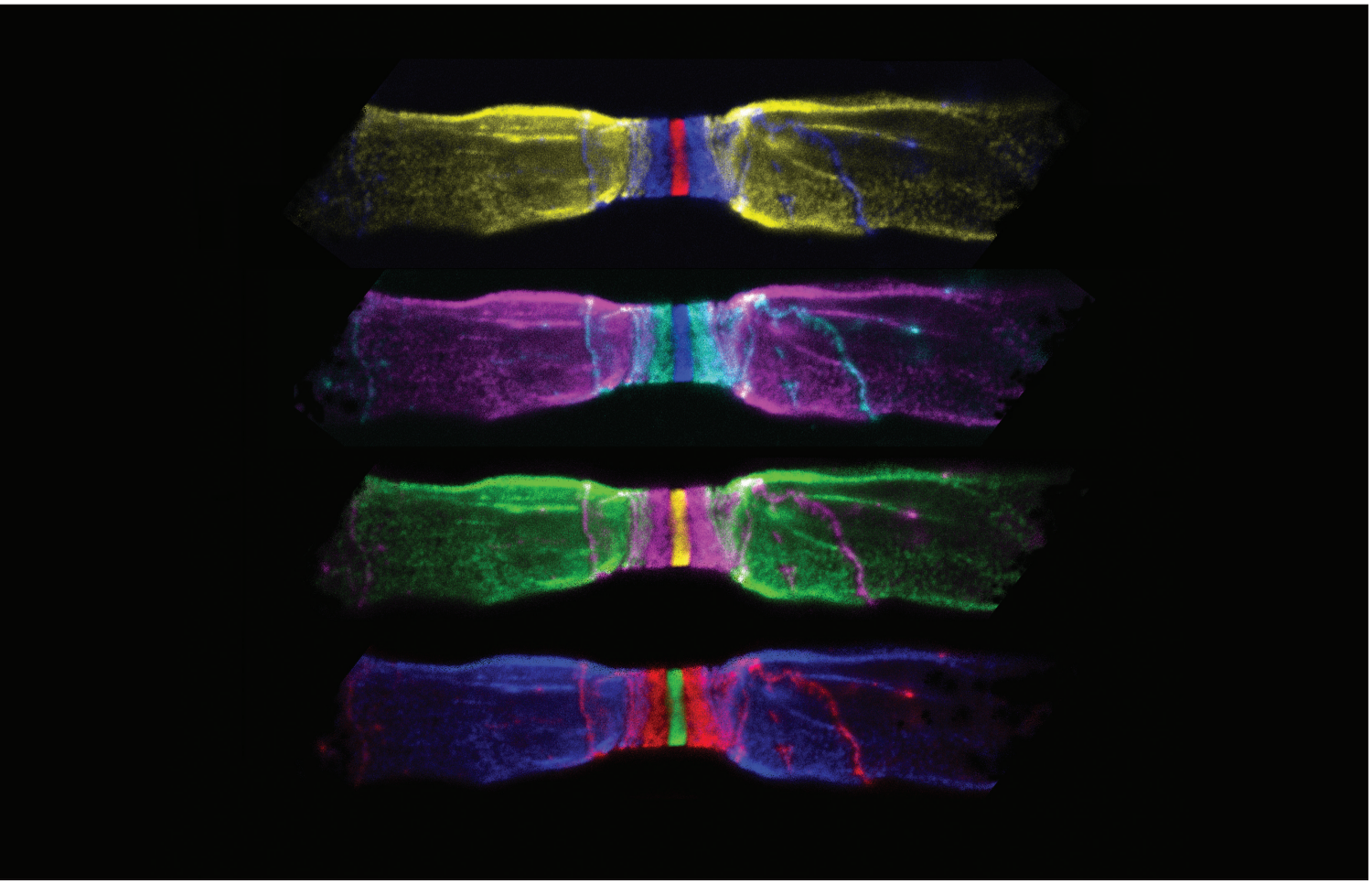
The previous chapter described how your brain changes as you grow — in overall size, number of cells, myelination, and synapse formation — even continuing to develop well beyond your teenage years. In fact, recent research suggests that maturation is still occurring in the third decade of your life.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

THE ADULT BRAIN

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

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

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



Desmazieres, et al. Journal of Neuroscience, 2014

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

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

Intelligence also peaks during early to middle adulthood, roughly ages 25 to 60. However, different cognitive abilities have distinctive patterns of maturation. Fluid intelligence, which includes abilities like solving problems and identifying patterns, peaks around age 30. By contrast, crystallized intelligence, which deals with vocabulary and knowledge of facts, increases until about age 50. Some scientists speculate that there is no single age at which all (or even most) of our cognitive functions are at their peak.

WHAT IS AGING?

Normal vs. Pathological Aging

Aging is a dynamic, gradual process. While it can be characterized by resilience in both physical and neurological health, too often aging increases the risk of injury and disease. One such risk is dementia, a decline in cognitive ability that interferes with a person's day-to-day functioning. While aging is inevitable, dementia and disability are not. In fact, neuroscientists believe our brains can remain relatively healthy as we age. Pronounced decline in memory and cognitive ability, once thought to be part of normal aging, are now recognized as separate disease processes in the aging brain. Although the brain loses some neurons as we age, a widespread and profound loss of neurons is not part of normal aging.

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

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

HOW THE BRAIN CHANGES

Cognitive Changes

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

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

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

Certain aspects of attention can also become more difficult as our brains age. For example, it might be harder to focus on what friends are saying when we're in a noisy restaurant. The ability to focus on a particular stimulus and filter out distractions is called selective attention. Another type of attention, divided attention, refers to the ability to focus on two tasks at the same time. Activities that require this type of split focus — such as holding a conversation while driving — also become more challenging with age.

Structural Changes

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

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

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

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

Neuronal Changes

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

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

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

Finally, the formation of new neurons also declines with age. Although neurogenesis was once believed to halt after birth, we now know of two brain regions that continue to add new neurons throughout life: the olfactory bulbs and the dentate gyrus of the hippocampus. Studies suggest that the rate of neurogenesis plummets with age in mice, but recent human studies suggest a more modest decline. It is not yet clear whether neurogenesis appreciably affects cognition in the aging human brain, but mouse studies indicate that strategies that boost neurogenesis can enhance cognitive function.

Chemical Changes

The amount of neurotransmitters and the number of their receptors might also decline with age. Several studies have reported that less dopamine is synthesized in the aged brain, and there are fewer receptors to bind the neurotransmitter. Less robust evidence indicates that the amount of serotonin might also decline with age.

WHY DOES THE BRAIN AGE?

From cortical thinning to the loss of dendritic spines, you've seen how the brain ages. But what causes these changes? Many different theories have been advanced to explain why neurons, and cells in general, age. One possibility is that changes in gene expression play a role. Researchers have found that genes important for synaptic plasticity are expressed less in the brains of older people than in the brains of younger adults. The underexpressed genes also showed more signs of damage.

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

Oxidative Stress and DNA Damage

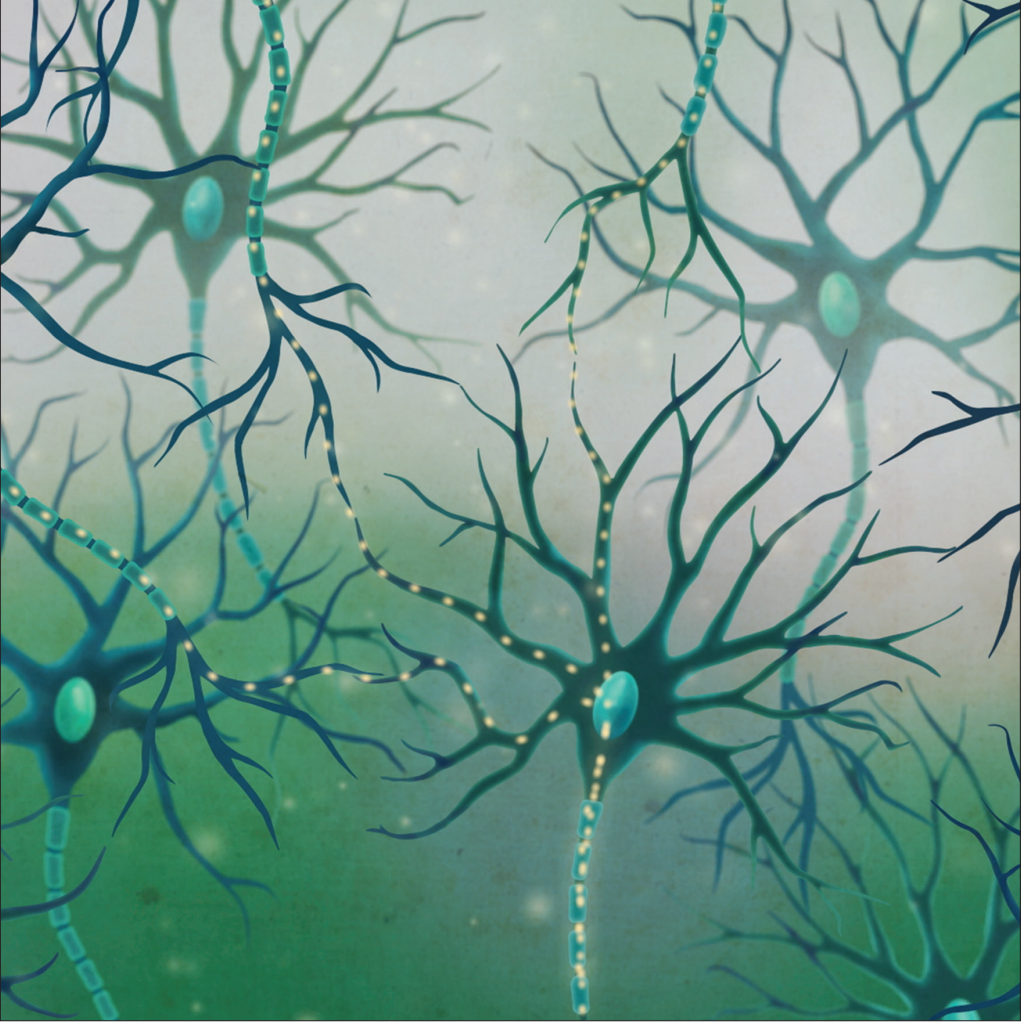
DNA damage that accumulates over a lifetime could contribute to aging processes throughout the brain and body, and DNA damage due to oxidative stress has received a great deal of attention. Every cell in your body contains organelles called mitochondria, which function a bit like cellular power plants, carrying out chemical reactions that provide energy for cell use. Some of these metabolic reactions produce harmful byproducts called free radicals, highly reactive molecules which, if left unchecked, can destroy fats and proteins vital to normal cell function and can damage DNA as well.

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

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

Immune Dysfunction

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



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

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

Impaired Protein Recycling

We know that excessive buildup of abnormal proteins in the brain contributes to age-related neurodegenerative diseases like Alzheimer's and Parkinson's. Buildup of proteins and other cell components can also contribute to cellular degeneration in the healthy brain. Cells normally break down and recycle damaged proteins and molecules, using a process that is usually efficient but not perfect. Over time, damaged molecules can build up in cells and prevent them from functioning normally. Because neurons in the brain are not replaced as often as cells in other parts of the body (for example, bone marrow, intestinal lining, hair follicles), brain cells might be even more vulnerable to this buildup of damaged molecules. Also, the cellular machinery involved in breakdown and recycling processes degrades with age, reducing the efficiency of the "waste removal" systems.

Finally, remember that changes in the aging brain occur within the context of other changes throughout the body. Researchers speculate that worsening cardiovascular health, for example, could contribute to, or even drive, many changes seen in the aging brain.

HEALTHY AGING

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

Diet and Exercise

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

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

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

improved cognitive health as well as a longer lifespan.

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

Exercise exerts its neuroprotective effects in the brain by improving neuroplasticity — the brain's ability to form and reorganize connections between neurons in response to changes in behavior and environment. Scientists also believe that exercise increases neurogenesis (the formation of new nerve cells) which, in turn, enhances neuroplasticity. Evidence from rodent studies confirms that exercise increases neurogenesis: Older mice allowed to run on a wheel have higher rates of neurogenesis in the hippocampus than sedentary mice, and they perform better on learning and memory tests. Exercise can also improve blood flow and increase production of neurotrophic factors that support new neurons and synapses. For humans, starting exercise later in life can be beneficial, but the studies suggest that adopting an exercise program earlier in life could yield even more neuroprotective benefits.

Mental Stimulation and Social Networks

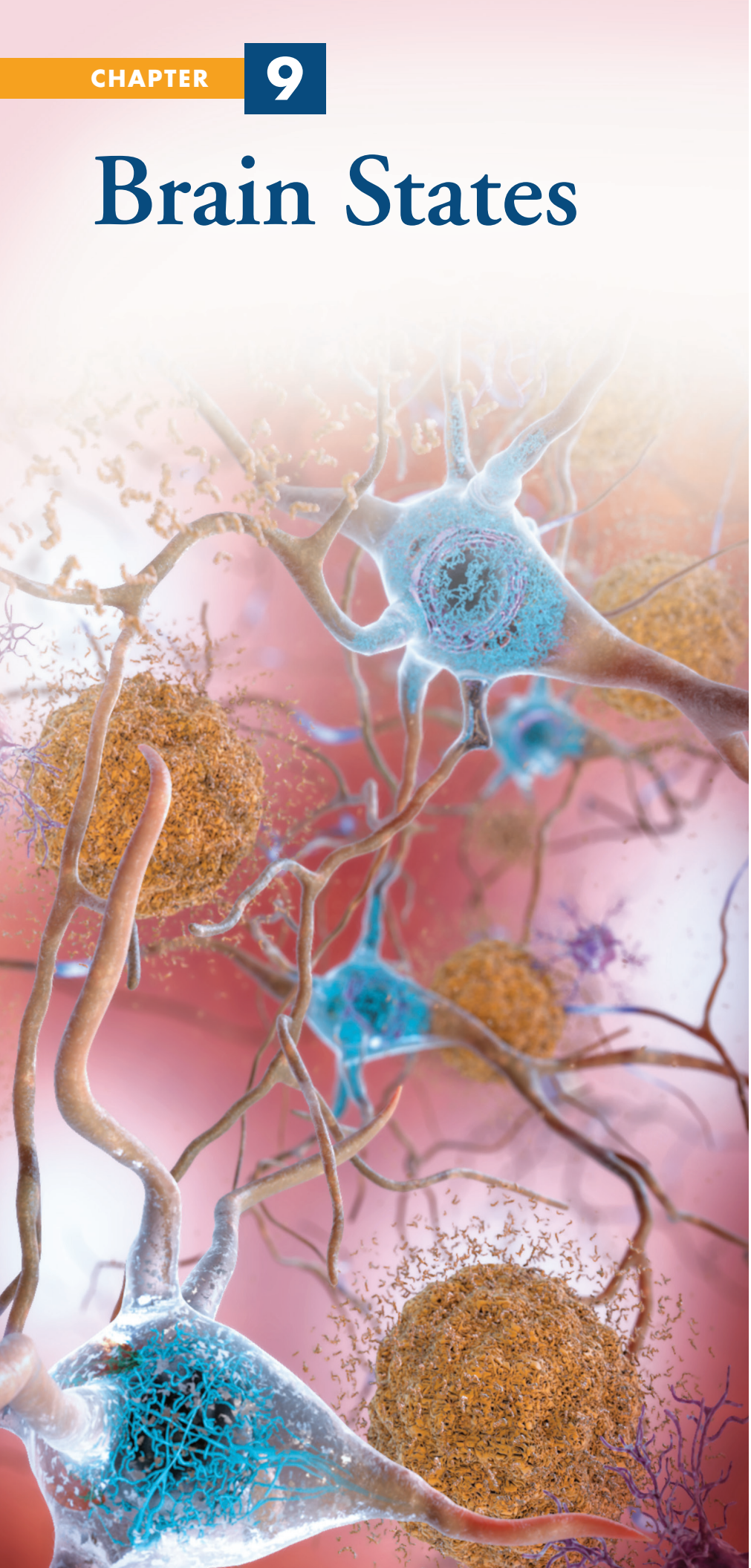
Mental stimulation and large social networks can also improve cognitive function in aging. In lab studies, mice housed in cognitively stimulating environments with many opportunities for social interaction perform better on learning and memory tests as they age compared to mice housed in standard cages.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

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

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

CHAPTER 9

Brain States

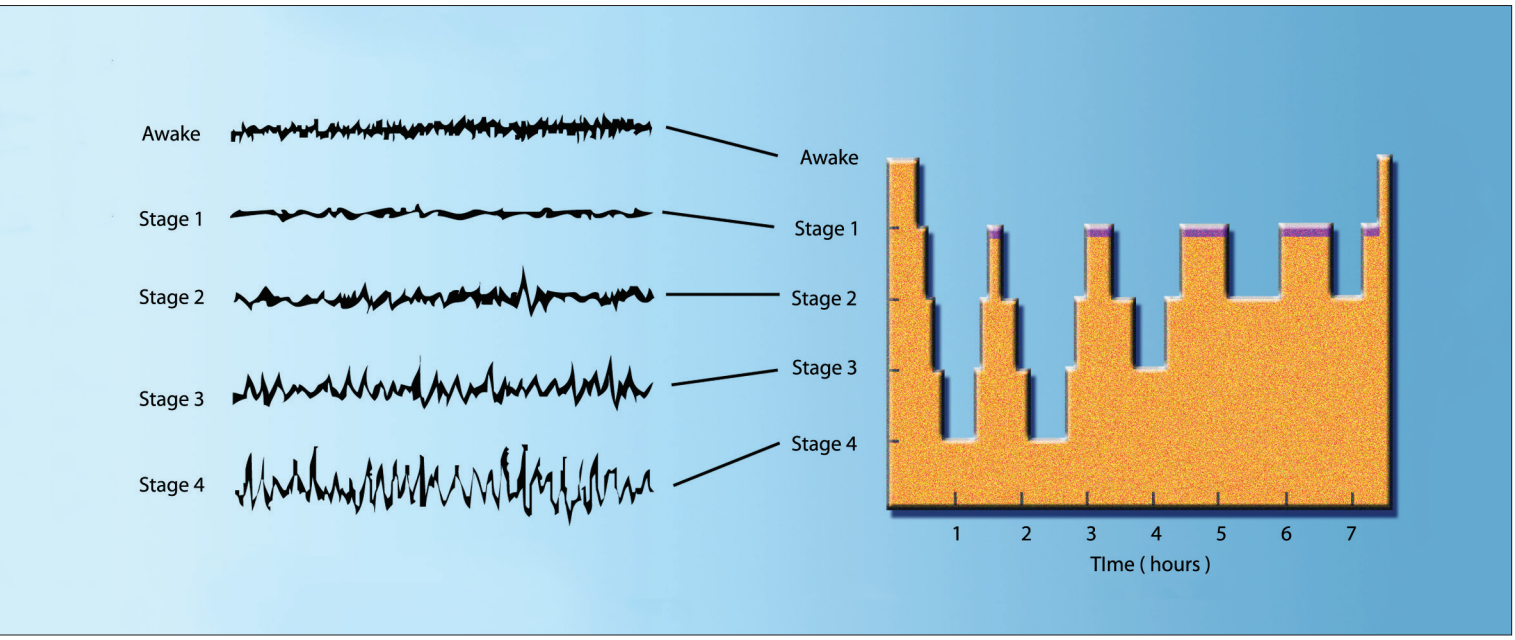


Have you ever considered the ups and downs that occur during your day? Speaking literally, you are up and awake during the day and lying down sleeping at night. Speaking figuratively, ups and downs could mean that you experience periods of elevated alertness and arousal compared with your mood when you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

SLEEP

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

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



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

Brain Activity During Sleep

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

SWS gets its name from the high amplitude, low frequency, brain waves in EEG recordings. The high amplitude of slow waves indicates that many cortical neurons are switching their activity in a synchronized way from a depolarized (more excitable) state to a hyperpolarized (less excitable) state and back again. These slow waves appear to be important to sleep function — the longer a person stays awake, the more slow waves they will experience during the SWS state. Slow waves become less frequent the longer the person is asleep. If awakened during SWS, most people recall only fragmented thoughts, not active dreams.

Have you ever seen a cat dreaming — twitching its whiskers or paws while it sleeps? Dreaming happens mainly during REM sleep, which takes its name from the periodic rapid eye movements people make in this state. Brain activity recorded during REM looks very similar to EEGs recorded while awake. EEG waves during REM sleep have much lower amplitudes than the SWS slow waves, because neuron activity is less synchronized — some nerve cells depolarize while others hyperpolarize, and the "sum" of their electrical states is less positive (or negative) than if they acted in synchrony. Paradoxically, the fast, waking-like EEG activity during REM sleep is accompanied by atonia, a loss of muscle tone causing the body to become temporarily paralyzed. The only muscles remaining active are those that enable breathing and control eye movements. Oddly enough, the neurons of our motor cortex fire as rapidly during REM sleep as they do during waking movement — a fact that explains why movements like a kitten's twitching paws can coincide with dreams.

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

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

Sleep Regulation

How does the brain keep us awake? Wakefulness is maintained by the brain's arousal systems, each regulating different aspects of the awake state. Many arousal systems are in the upper brainstem, where neurons connecting with the forebrain use the neurotransmitters acetylcholine, norepinephrine, serotonin, and glutamate to keep us awake. Orexin-producing neurons, located in the hypothalamus, send projections to the brainstem and spinal cord, the thalamus and basal ganglia, as well as to the forebrain, the amygdala, and dopamine-producing neurons. In studies of rats and monkeys, orexin appears to exert excitatory effects on other arousal systems. Orexins (there are two types, both small neuropeptides) increase metabolic rate, and their production can be activated by insulin-induced low blood sugar. Thus, they are involved in energy metabolism. Given these functions, it comes as no surprise that orexin-producing neurons are important for preventing a sudden transition to sleep; their loss causes narcolepsy, as described below. Orexin neurons also connect to hypothalamic neurons containing the neurotransmitter histamine, which plays a role in staying awake.

The balance of neurotransmitters in the brain is critically important for maintaining certain brain states. For example, the balance of acetylcholine and norepinephrine can affect whether we are awake (high acetylcholine and norepinephrine) or in SWS (low acetylcholine and norepinephrine). During REM, norepinephrine remains low while acetylcholine is high, activating the thalamus and neocortex enough for dreaming to occur; in this brain state, forebrain excitation without external sensory stimuli produces dreams. The forebrain becomes excited by signals from the REM sleep generator (special brainstem neurons), leading to rapid eye movements and suppression of muscle tone — hallmark signs of REM.

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

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

Sleep-Wake Cycle

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

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

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

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

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

Simon Fraser University

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

Sleep Disorders

The most common sleep disorder, and the one most people are familiar with, is insomnia. Some people with insomnia have difficulty falling asleep initially; others fall asleep, then awaken part way through the night and can't fall back asleep. Several common disorders, listed below, disrupt sleep and prevent people from getting an adequate amount of sleep.

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

Sleep apnea occurs when the airway muscles of the throat relax during sleep, to the point of collapse, closing the airway. People with sleep apnea have difficulty breathing and wake up without entering the deeper stages of SWS. This condition can cause high blood pressure and may increase the risk of heart attack. Treatments for sleep apnea focus on reducing airway collapse during sleep; simple changes that may help include losing weight, avoiding alcohol or sedating drugs prior to sleep, and avoiding sleeping on one's back. However, most people with sleep apnea require breathing machines to keep their airway open. One such device, called a continuous positive airway pressure or "CPAP" machine, uses a small mask that fits over the nose to provide an airstream under pressure during sleep. In some cases, people need surgery to correct their airway anatomy.

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

Narcolepsy: An Example of Sleep Disorder Research

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

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

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

AROUSAL

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

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

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

Neurotransmitters

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

Sensory Input

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

Autonomic Nervous System

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

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

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

Sexual Arousal

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

ATTENTION

If you are paying attention right now, there should be detectable changes in your heart rate, breathing, and blood flow. If that sounds familiar, it's because those same physiological changes occur during arousal, which is necessary for being alert and paying attention. As mentioned previously, the state of arousal calls for reactions to the environment. To make decisions about what to do, you need to focus on what's happening in the environment, especially involving anything relevant to your goals. For example, if your goal is to run away from an angry bear, you need to be alert and pay attention to where you're running so you don't trip and fall. Scientists have theorized that the state of arousal speeds processing and improves comprehension of environmental details. Otherwise, your brain would need an infinite amount of time and energy to process all of its sensory inputs (sounds, sights, smells, and other feelings), because the environment is always changing.

Focus

Even with multitasking, it is impossible for the brain to process all its sensory inputs. Instead, people focus their attention on one thing at a time. Attention is a fascinating ability, because it enables you to have so much control and the ability to fine-tune your focus to different locations, times, and topics. Consider the page you are reading right now. Although you can see the whole page, you focus on only one line at a time. Alternatively, you can turn your attention to the past — just minutes ago when you were reading about arousal. Or you can ignore the sentences altogether and focus on the number of times the word "you" occurs on this page. Scientists recognize two types of attention, which involve different brain processes: voluntary (endogenous) attention and involuntary (exogenous) attention.

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

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

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

Disorders of Attention

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

Between 50–82 percent of patients who suffer stroke in the right hemisphere experience hemineglect syndrome, also known as spatial neglect and unilateral neglect. In these cases, patients with neglect ignore the left side of their visual field. Sometimes they ignore the left side of the body and the left side of individual objects, as well. Diagnosis of hemineglect syndrome can be done with a pen and paper. For example, patients can be instructed to draw a copy of a picture like a butterfly or a castle, and those patients with hemineglect usually draw only the right half of the picture or leave out details of the left side. Research on patients with hemineglect syndrome contributes to our understanding of rehabilitation after stroke, as well as the role of the right parietal cortex in attention and perception.

REST: DEFAULT MODE NETWORK

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

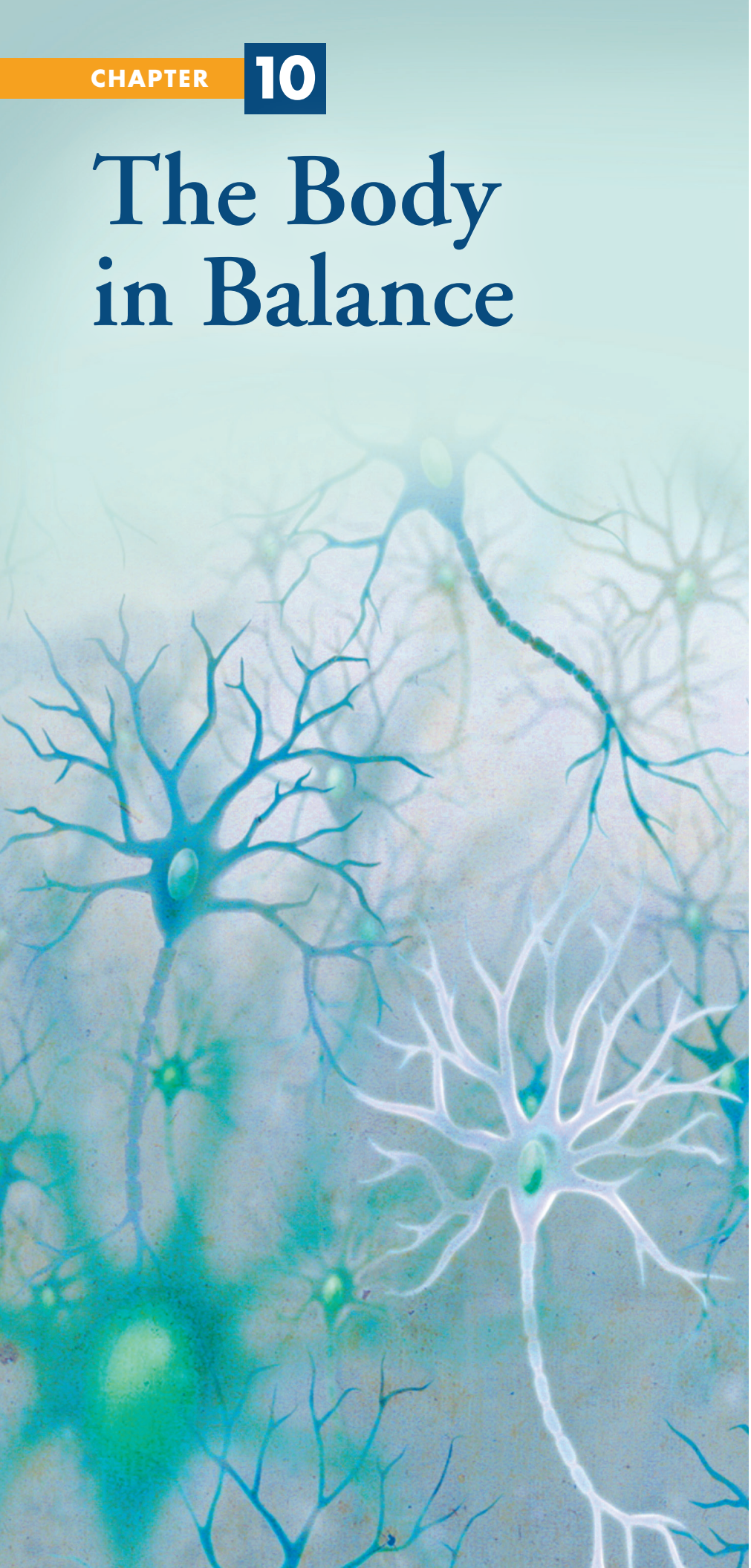
Although the exact role of the default mode network is unclear, the functions of its "participating" brain regions provide hints about its purpose. Studies on emotion have revealed that activity in the ventromedial PFC is directly related to how anxious a subject feels while performing a task — suggesting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

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

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

CHAPTER 10

The Body in Balance



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

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

CIRCADIAN RHYTHMS

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

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

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

An autonomic neural pathway ties the daily rhythmic activity of the SCN directly to other clocks in the body. Neurons in the SCN stimulate an adjacent region of the brain called the paraventricular nucleus (PVN), which in turn sends signals down a chain of neurons through the spinal cord to the peripheral organs of the body. You've already learned how signals in part of this neural pathway stimulate orexin neurons to regulate the body's sleep/wake cycle. Related pathways also govern the secretion of melatonin, a hormone that influences sleep behaviors. Specifically, electrical activity originating in the SCN enters the PVN's neural network and sends signals up to the pineal gland, a small pinecone-shaped gland embedded between the cerebral hemispheres. The pineal gland secretes melatonin into the bloodstream at night. Melatonin binds to cells in many tissues, and although it has no direct effect on clock gene expression in the SCN, its systemic effects seem to reduce alertness and increase sleepiness. Light exposure triggers signals that stop melatonin secretion, promoting wakeful behaviors.

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

Desynchronizing the body's physiological clocks can cause noticeable and sometimes serious health effects. You might have experienced a familiar example of circadian rhythm disturbance: jet lag. After crossing many time zones in a short time period, a person's patterns of wakefulness and hunger are out of sync with day and night. Exposure to the local day/night cycle resets the brain and body, but it can take several days to get fully resynchronized. Circadian rhythms can also be disturbed by situations like late-shift jobs or blindness, which decouple normal daylight signals from wake/sleep cycles. Long-term circadian disruptions are associated with health problems including weight gain, increased rates of insomnia, depression, and cancers.

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

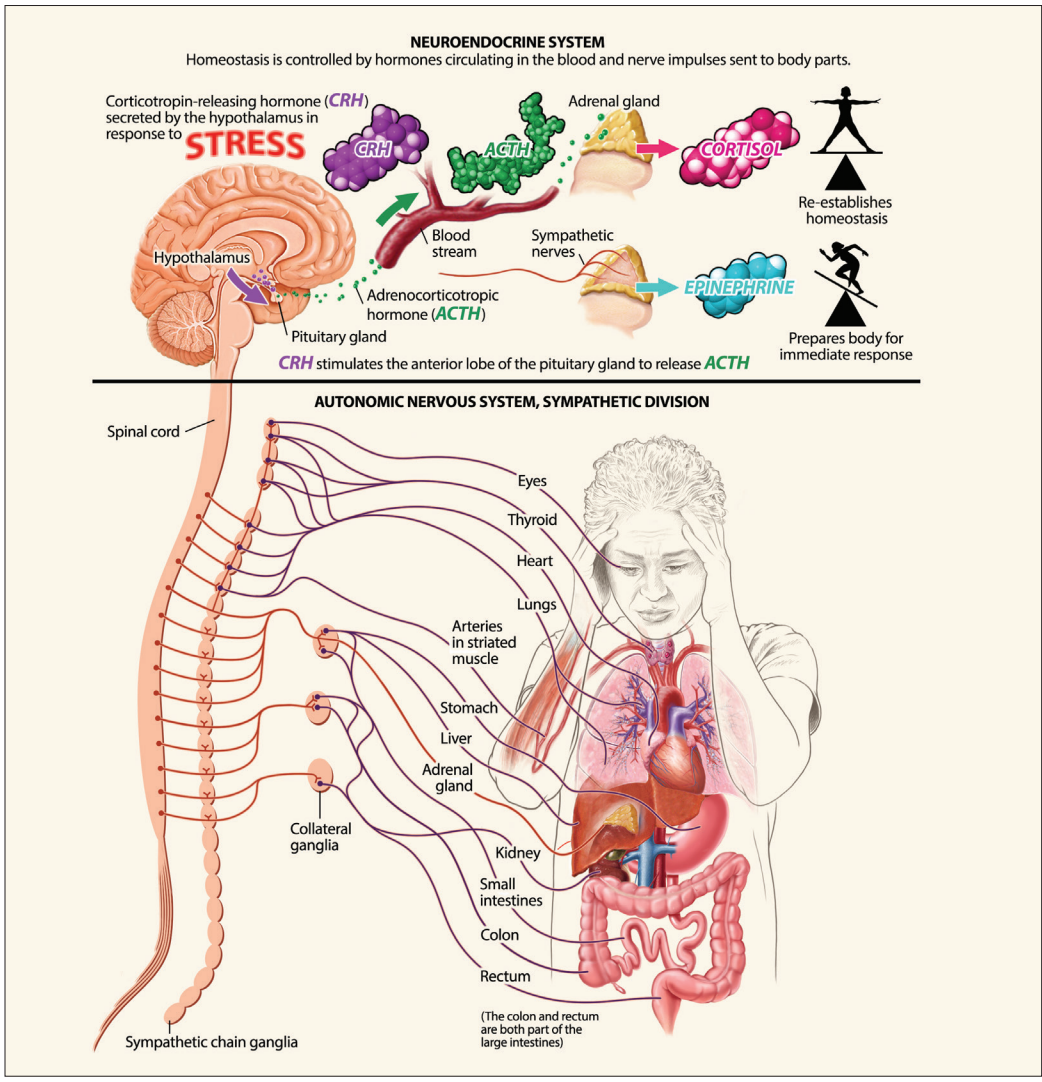
HORMONES, HOMEOSTASIS, AND BEHAVIOR

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

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

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

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



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

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

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

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

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

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

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

Many other hormones are not regulated by the pituitary gland, but are released by specific tissues in response to physiological changes. The brain contains receptors for many of these hormones but, unlike pituitary hormones, it does not directly regulate their secretion. Instead, when these hormones bind to receptors on neurons, they modify the output of neural circuits, producing behavioral changes that have homeostatic effects. One example of this is a pair of hormones called leptin and ghrelin.

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

STRESS

Your body reacts in stereotyped ways when you feel threatened. You breathe faster, your heartbeat speeds up, your muscles tense and prepare for action. These reactions may have helped our ancestors run from predators, but any stressful situation — arguing with your parents, a blind date, a looming deadline at work, abdominal cramps, discovering your apartment was robbed, trying karaoke for the first time — has the potential to set them off. Scientists call this reaction the stress response, and your body turns it on to some degree in response to any external or internal threat to homeostasis.

The Stress Response

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

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

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

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

It's easy to imagine how (and why) these physiological changes make your body alert and ready for action. But when it comes to stress, your body can't tell the difference between the danger of facing down a bull elephant and the frustration of being stuck in traffic. When stress is chronic, whatever its cause, your adrenal glands keep pumping out epinephrine and glucocorticoids. Many animal and human studies have shown that long-term exposure to these hormones can be detrimental.

Chronic Stress

Overexposure to glucocorticoids can damage a wide range of physiological systems. It can cause muscles to atrophy, push the body to store energy as fat, and keep blood sugar abnormally high — all of these can worsen the symptoms of diabetes. Overexposure to glucocorticoids also contributes to the development of hypertension (high blood pressure) and atherosclerosis (hardening of the arteries), increasing the risk of heart attacks. Because the hormones inhibit immune system function, they also reduce resistance to infection and inflammation, sometimes pushing the immune system to attack the body's own tissues.

Chronic stress can also have specific negative effects on brain tissue and function. Persistently high levels of glucocorticoids inhibit neuron growth inside the hippocampus, impairing the normal processes of memory formation and recall. Stress hormones can also suppress neural pathways that are normally active in decision-making and cognition, and speed the deterioration in brain function caused by aging. They may worsen the damage caused by a stroke. And they can lead to sleep disorders — cortisol is also an important wakeful signal in the brain, so the high cortisol levels due to chronic stress may delay sleep. Stress-induced insomnia can then start a vicious cycle, as the stress of sleep deprivation leads to the release of even more glucocorticoids.

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

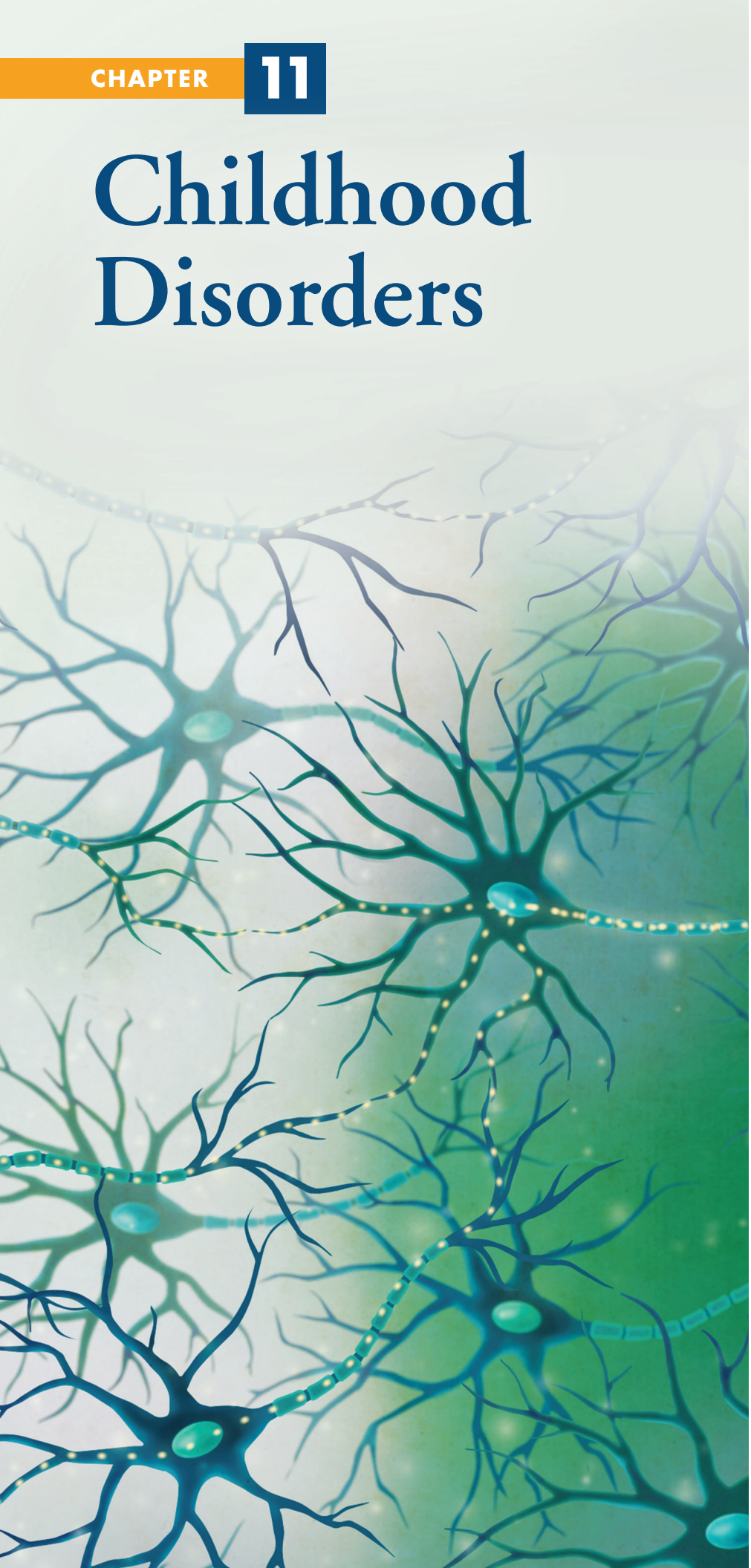
Because metabolic stressors such as starvation induce high glucocorticoid levels, it's been suggested that these hormones might help prepare the fetus for the environment it will be born into. Tough, stressful environments push fetuses to develop stress-sensitive "thrifty" metabolisms that store fat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

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

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

CHAPTER 11

Childhood Disorders



AUTISM SPECTRUM DISORDERS

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

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

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

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

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

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

It appears that many genes, each with a small effect, contribute to the inheritance of most ASDs. But such small effects make these genes hard to identify in genome-wide association studies. Scientists are now looking at the rare variants associated with ASD. These afflict fewer people with ASD, but their effects are larger and easier to detect. Some of these rare mutations are in single genes whose impairment is already known to cause intellectual disability and social dysfunction. These genes include FMR1 (codes for fragile X mental retardation protein, but its non-mutant form is needed for normal cognitive development); PTEN (codes for a tumor suppressor enzyme that regulates cell division, so cells don't divide or grow too fast); and TSC1 or TSC2 (tuberous sclerosis complex 1 and 2), which also code for proteins that help control cell growth and size. Between 50 to 60 percent of people with fragile X syndrome and approximately 40 percent of people with tuberous sclerosis complex have ASD. Children with a variant of the gene NF-1 develop tumors in childhood (neurofibromatosis) and a 2011 study found that nearly 10 percent met the criteria for autism.

Intriguingly, these ASD-related genes influence a major signaling pathway for regulating cell metabolism, growth, and proliferation, the mTOR pathway. This suggests a very real potential for treating autism with drugs that target the mTOR pathway. For example, mouse models with mutations in PTEN show traits similar to humans with these gene variants: altered sociability, anxiety, and repetitive behaviors. These behaviors can be relieved or reversed by drugs that inhibit the mTOR pathway. Clinical trials of these drugs (rapamycin and lovastatin) are underway.

Despite this progress, autism genetics is so complicated that it can't be used to diagnose the condition. And unlike diabetes, kidney disease, or thyroid disease, there are no biochemical or other biomarkers of autism. Currently, autism diagnosis is based on behavioral analysis, but efforts are underway to use more objective criteria such as tracking eye movements and functional neuroimaging, which can even be done in infants.

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

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

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

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

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

ATTENTION DEFICIT HYPERACTIVITY DISORDER

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

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

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

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

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

DOWN SYNDROME

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

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

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

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

There is no real treatment for Down syndrome, nor any clear explanation of what occurs in the brain. Poor connections among nerve cells in the hippocampus, the part of the brain involved in memory (and the first brain area affected by Alzheimer's disease), are believed to be a key factor in brain or intellectual differences in Down syndrome. Dysfunction in the mitochondria, the cell's power plants, might also play a role in development of related disorders that involve energy metabolism, such as diabetes and Alzheimer's.

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

DYSLEXIA

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

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

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

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

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

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

EPILEPSY

If someone has two or more seizures that cannot be explained by a temporary underlying medical condition such as a high fever or low blood sugar, their medical diagnosis will be "epilepsy" — from the Greek words meaning to "seize," "attack," or "take hold of." About 1 percent of American children and 1.8 percent of adults have been diagnosed with this brain disorder. Seizures result from irregular activities in brain cells that can last five or more minutes at a time. Some seizures look like staring spells, while others cause people to collapse, shake, and become unaware of what is going on around them. The pattern of symptoms and after-seizure brain recordings using EEGs are used to distinguish between different types of epilepsy and determine whether the true cause of the seizures is epilepsy or a different medical condition.

Seizures are classified by where they occur in the brain. Generalized seizures affect both sides of the brain. They include absence or *petit mal* seizures, which can cause rapid blinking or a few seconds of staring into space, and tonic-clonic or *grand mal* seizures, which can make someone fall, have muscle spasms, cry out, and/or lose consciousness. Focal or partial seizures are localized to one area of the brain. A simple focal seizure can cause twitching or a change in sensation, triggering strange smells or tastes. Complex focal seizures can leave a person confused and unable to answer questions or follow directions. A person can also have so-called secondary generalized seizures, which begin in one part of the brain but spread to become generalized seizures. In some patients with severe epilepsy, multiple types of seizure can occur at the same time.

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

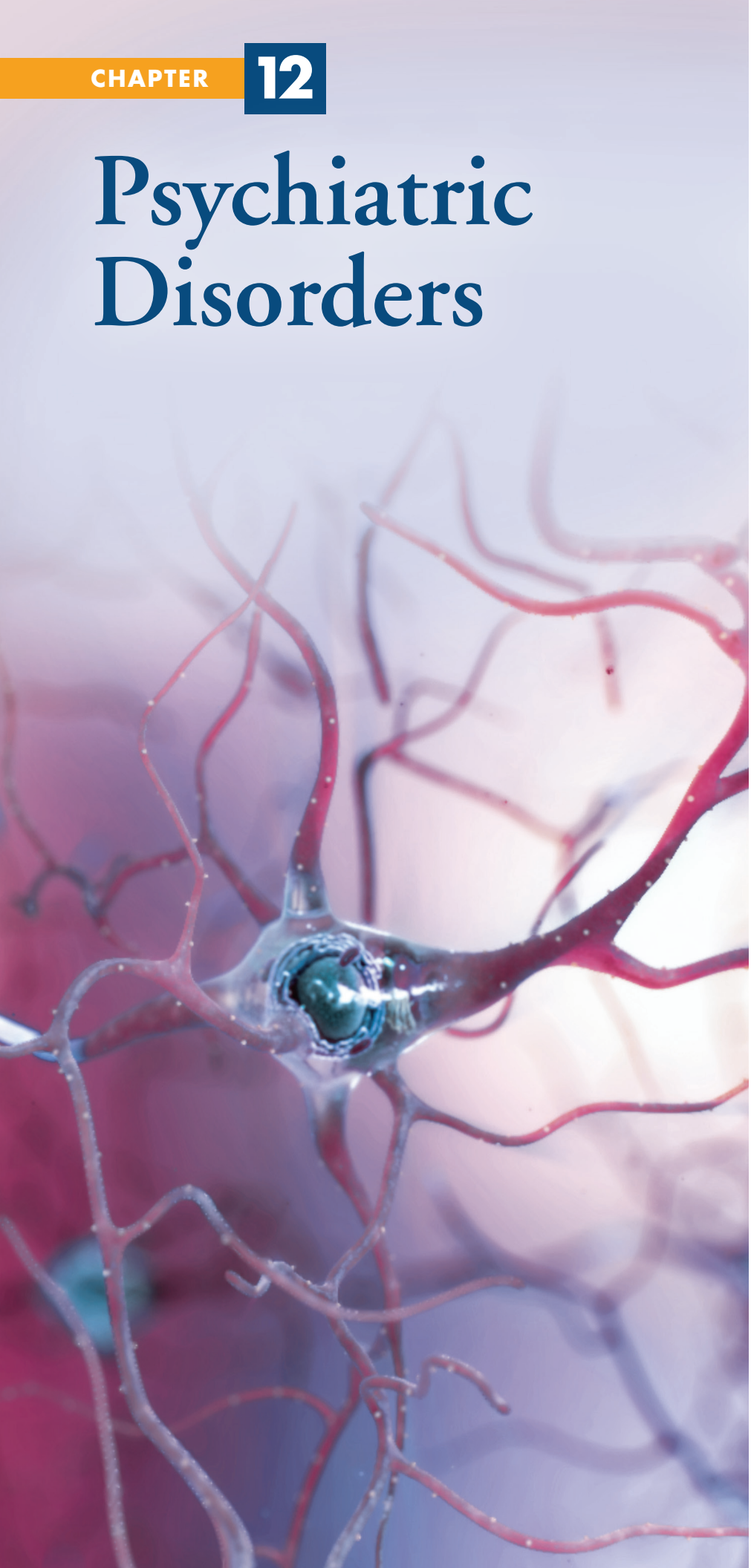
Seizures can also accompany or cause intellectual or psychiatric problems. For example, some seizures may suppress the growth of dendrites, leaving the person emotionally unsettled or less able to learn.

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

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

CHAPTER 12

Psychiatric Disorders



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

ANXIETY DISORDERS AND POST-TRAUMATIC STRESS DISORDER

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

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

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

Obsessive-Compulsive Disorder

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

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

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

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

Panic Disorder

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

Post-Traumatic Stress Disorder

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

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

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

Neuroimaging studies have begun to reveal the neurobiological signatures of PTSD, including changes in brain structure. Many people with PTSD have a smaller hippocampus (the brain region integral for learning and memory) and a smaller prefrontal cortex (the part of the brain that helps control thinking, emotions, and behavior). In contrast, the brain's emotional center, the amygdala, is apparently overactive in responding to stimuli in people with PTSD. Genes are involved in PTSD susceptibility, but research results are not yet conclusive regarding the importance of their role or which genes are involved. What is clear, however, is that genes affecting PTSD risk also affect the risk for major depression, generalized anxiety disorder, and panic disorder — suggesting common biological components of these psychiatric conditions. Neuroimaging studies that pinpoint brain regions disrupted in PTSD support the development of new drugs targeting neural function in those regions. Among these drugs are cannabinoids, glutamate, and oxytocin — the latter, sometimes called the "love" or "happiness" hormone, is released by both men and women during orgasm and is secreted by mothers during childbirth and breastfeeding.

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

MOOD DISORDERS

Mood is a vague term describing a person's general state of mind. You can easily recognize someone in a good mood and, likewise, in a not-so-good mood. Your moods change frequently with your emotional state, and such changes are normal when they suit your context and surroundings. Mood disorders, on the other hand, are mood changes that become longer lasting and independent of what is going on around you. The two main mood disorders are major depression and bipolar disorder. In recent years, neuroscientists have made major progress in linking genetic and other biological contributors to mood disorders and to disorders of cognition, like schizophrenia. Hopefully, their findings will lead to better treatments for people with more than one such condition.

Major Depression

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

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

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

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

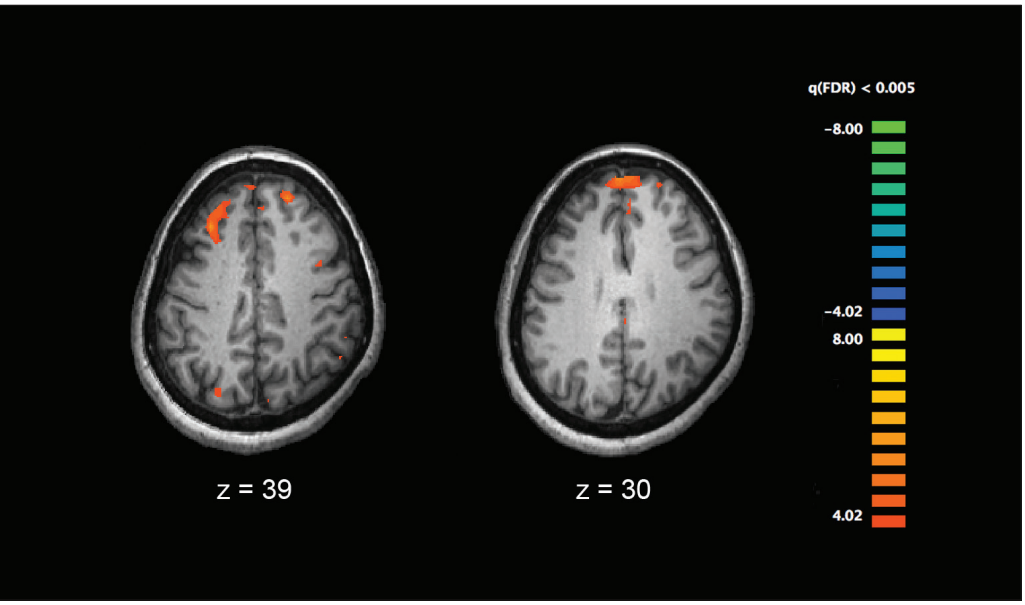
Identifying the underlying biological features of depression will help in the development of personalized therapy. Currently, approved antidepressant medications raise the levels of norepinephrine, serotonin, and dopamine in nerve cell synapses. Among the most widely used medications are SSRIs, which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

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

Bipolar Disorder

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

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



Kim, et al. PLoS One, 2010.

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

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

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

DISORDERS OF COGNITION

Schizophrenia

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

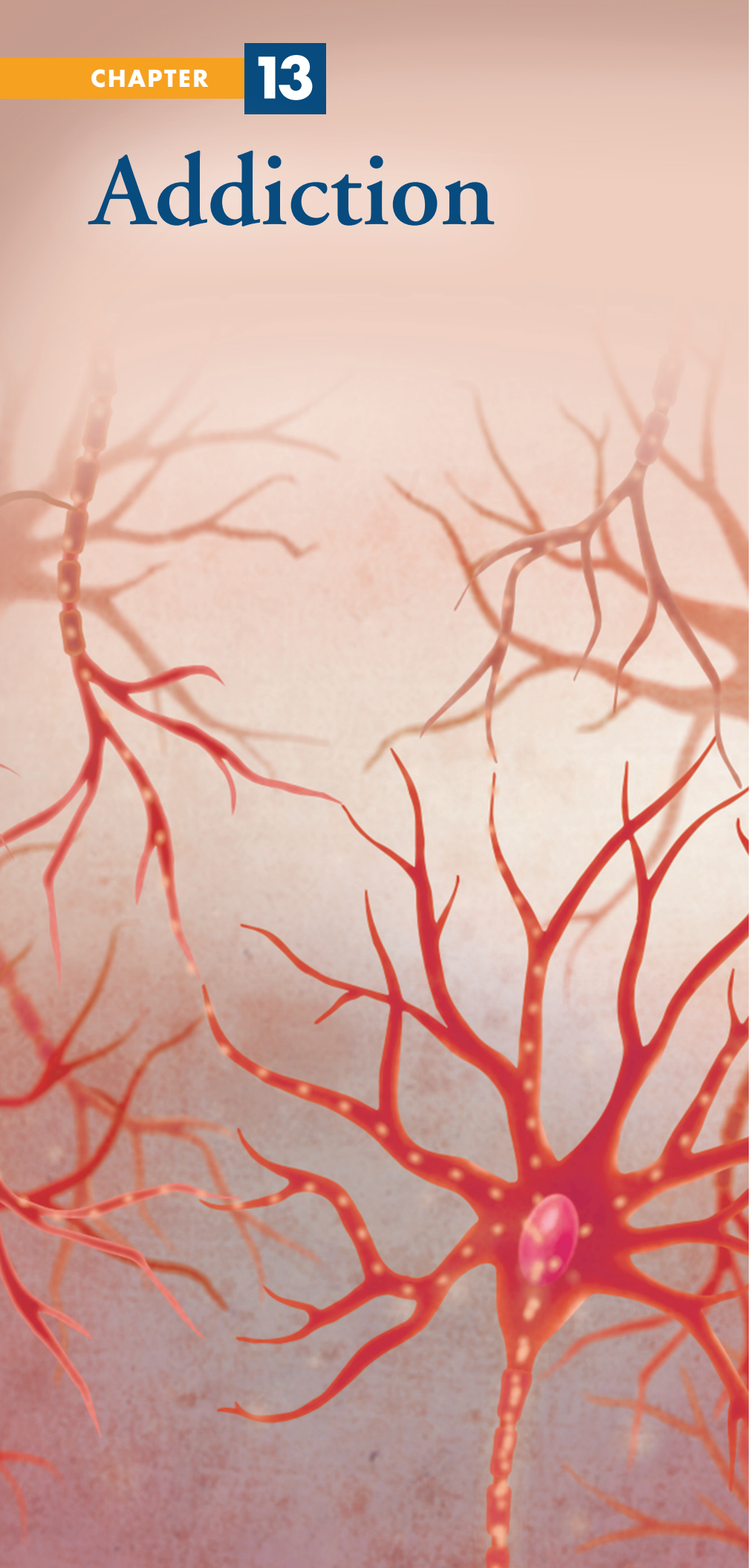
Although no cure exists for schizophrenia and many symptoms do not respond to treatment, some people can pursue personal and professional life goals with the help of medications, behavioral therapy, or a combination of these. Chlorpromazine, the first antipsychotic drug, was developed in the 1950s as an anesthetic for surgery but was soon employed to calm people with psychiatric disorders including schizophrenia. Since then, more than 20 similar antipsychotic drugs have been developed. Most of these drugs work by damping the dopamine response, which is thought to drive schizophrenia's "positive" symptoms. For that reason, these medications may cause tremors and other movement-related side effects resembling Parkinson's disease, which involves low dopamine activity. The most recently developed drugs also suppress some serotonergic activity, which seems to help with the negative symptoms of schizophrenia.

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

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

CHAPTER 13

Addiction



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

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

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

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

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

Mimics and Imposters

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

Who is susceptible to becoming addicted? A precise answer to this question is still elusive, but we now know a great deal about vulnerability. As with most health conditions, vulnerability to addiction involves internal risk factors, such as certain genes, and external risk factors, such as stress and a person's social environment. Often, a person's social environment both contributes to addictive behavior and is shaped by addictive behavior, creating a cycle that is difficult to break.

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

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

OPIOIDS

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

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

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

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

Treatment

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

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

NICOTINE

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

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

Treatment

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

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

ALCOHOL

Alcohol, although legal like tobacco, is also addictive. Together, alcohol abuse and alcohol addiction are a serious and costly national health issue. Aside from secondary behavioral impacts such as drunken driving, sexual assault, and domestic violence, a primary chronic health problem is associated with alcohol addiction: cirrhosis, a late-stage of scarring of the liver. The annual U.S. cost of alcohol abuse and addiction is estimated at $250 billion.

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

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

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

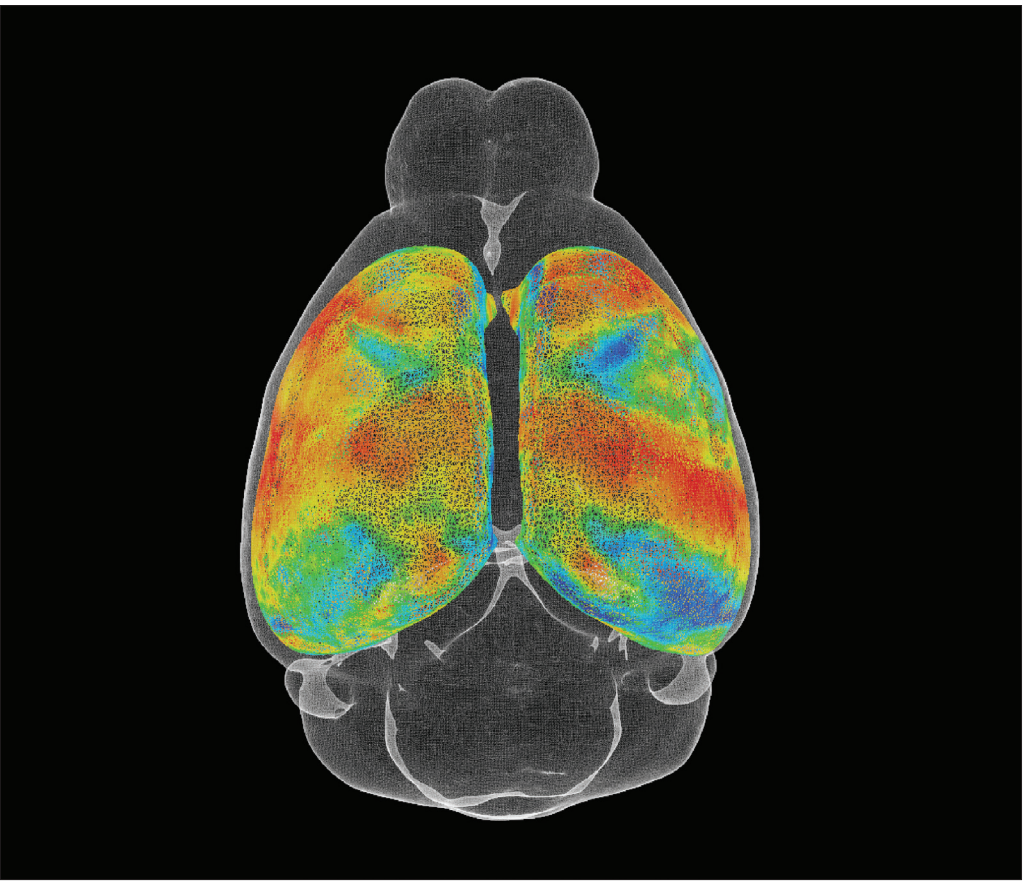
Binge drinking — excessive alcohol consumption in a short period of time — slows heart rate and causes breathing difficulties — usually the underlying cause of death in alcohol overdose.

Chronic, heavy ethanol use can also change brain structure. People with alcohol use disorder (formerly called alcoholism) can have an unsteady gait, tremors, and slurred speech; these symptoms result from damage to the cerebellum, a brain region important for movement and balance. They also suffer from memory loss due to the degeneration of neurons in the areas of the brain that govern learning and memory.

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

Treatments

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



Wheeler, et al. Journal of Neuroscience 2013.

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

MARIJUANA

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

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

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

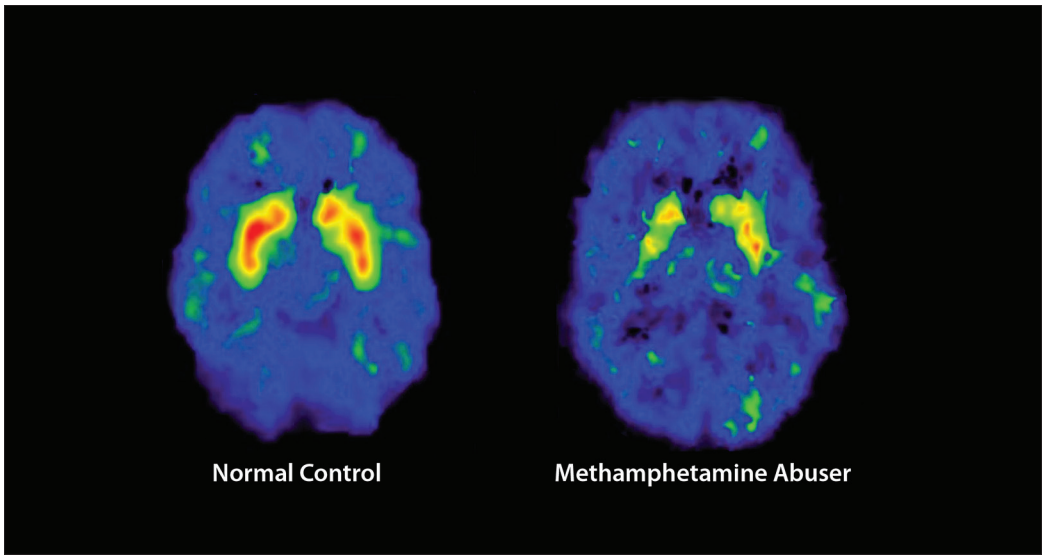
Many people with post-traumatic stress disorder (PTSD) self-medicate with marijuana to cope with anxiety, stress, and insomnia, and a few research studies appear to validate this strategy. These studies show that marijuana might reduce anxiety, improve sleep, and erase trauma-related memories in people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

PSYCHOSTIMULANTS

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

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

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



NIH.

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

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

Neuroscientists are working hard to figure out how to prevent and treat addiction to psychostimulants. In the course of their work, they have learned a great deal about the brain's normal function in motivated behavior. For example, in addition to increasing dopamine in the reward system, psychostimulants act in the prefrontal cortex to promote arousal and quicken our thinking. Studies show that low doses of psychostimulants (much less than taken in drug abuse) actually improve the brain's executive function (as in some ADHD treatments), helping with impulse and emotional control, planning and organizing, and productivity. Such low doses do not lead to tolerance and addiction, but high doses can impair brain function.

Treatments

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

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

DESIGNER DRUGS AND CLUB DRUGS

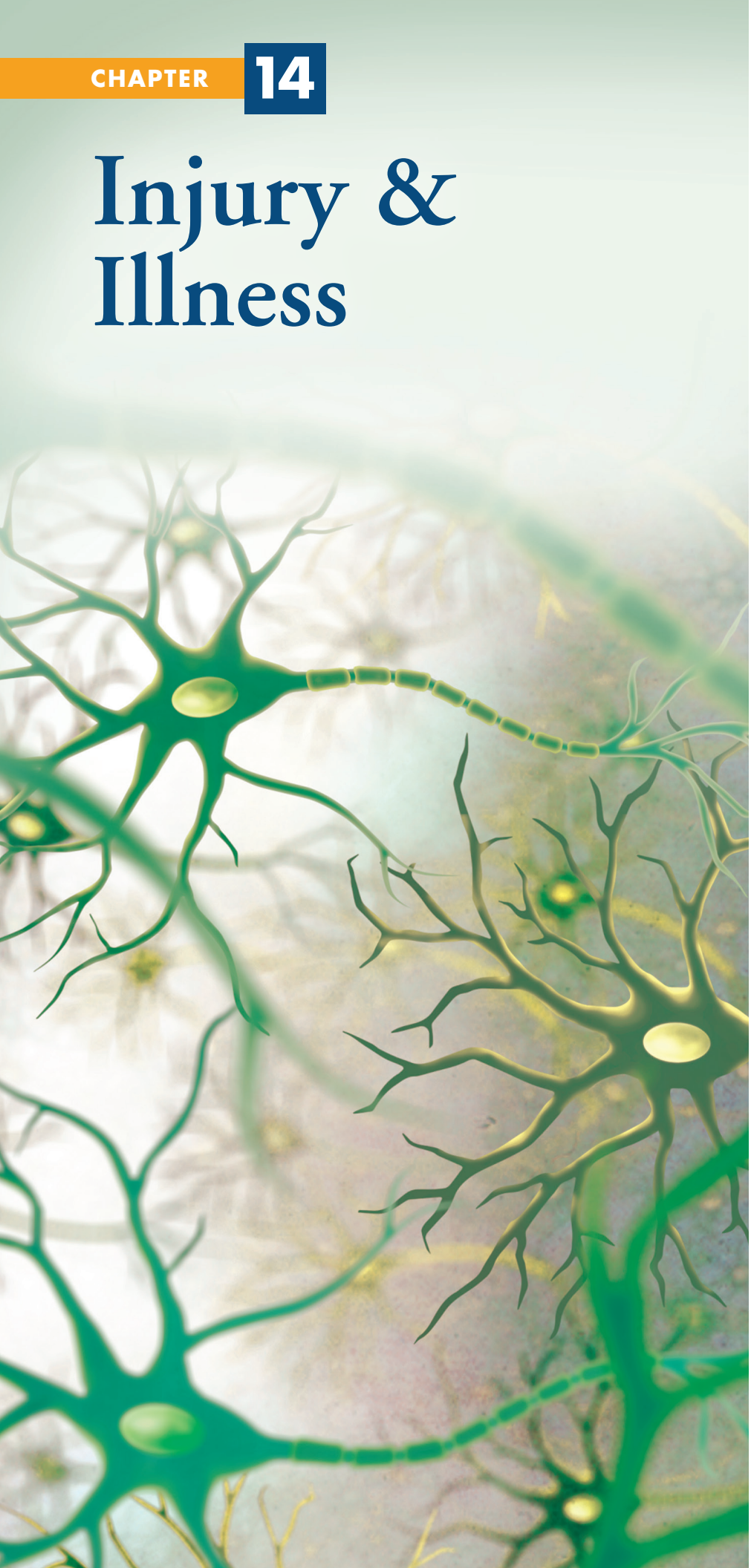
Designer drugs such as "bath salts" and "spice" (synthetic marijuana) are synthetic legal substances with psychoactive effects. They look like illicit drugs but can often be bought legally because the people who make them continually tweak their chemical structures to evade drug laws. We now know that these drugs can cause serious, permanent damage in many brain regions. Like designer drugs, club drugs are also synthetic psychoactive substances that look like legal drugs and are named for their use by youth at dance parties and all-night raves in crowded, high-energy surroundings. Examples of club drugs include 3,4-methylenedioxy-methamphetamine (also known as MDMA, Ecstasy, or Molly), rohypnol ("roofies"), GHB (gamma hydroxy-butyrate), and ketamine. Designer and club drugs can be stimulants — such as Ecstasy — or depressants like rohypnol, GHB, and ketamine.

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

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

CHAPTER 14

Injury & Illness



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

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

BRAIN TUMORS

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

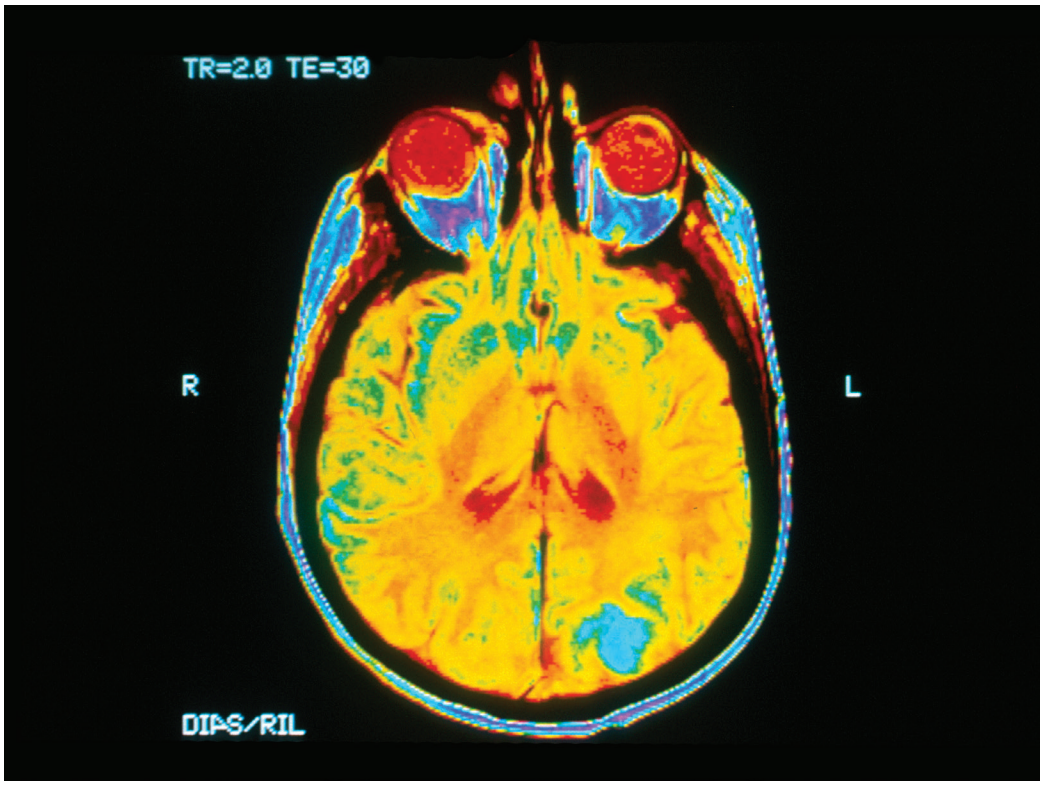
Regardless of its origin, a tumor, or any space-occupying lesion in the brain, can be lethal — thus surgical removal is required for survival.

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

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

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

If a tumor can be accessed without injuring nearby areas of the brain, surgery is usually the first step. Brain tumors can be removed with conventional techniques such as a craniotomy, in which the skull is opened and as much tumor as possible is removed. Another type of treatment for some tumors uses radiation. For this technique, called stereotactic radiosurgery, a high dose of radiation is aimed precisely at the tumor. A few radiation treatments can reduce or eliminate the tumor while sparing healthy tissue nearby. More recently, tumors are treated by multiple beams of ultrasound focused precisely to intersect exactly at the site of the tumor. These interventions can be carried out painlessly in awake patients inside imaging machines that visualize the tumor in the brain.



National Cancer Institute.

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

Following conventional surgery, doctors usually prescribe steroid medications to reduce swelling in the brain. Reduced swelling helps alleviate symptoms such as seizures, memory problems, or confusion that can occur after brain surgery. In patients with cancerous brain tumors, radiation may be administered to surrounding brain areas to help eliminate any cancer cells that remain in the brain after surgery. People with cancerous brain tumors can also be given chemotherapy to prevent growth or regrowth of their tumors. In the past decade, researchers have developed new ways to administer chemotherapy that allow medication to be delivered directly to the brain (tumor), rather than traveling through the body before reaching the brain. For example, after surgical removal of a brain tumor, small wafers containing anticancer drugs can be implanted in the space previously occupied by the tumor. Over time, the wafers slowly dissolve and release the chemotherapy drugs to nearby areas.

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

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

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

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

Other approaches also under development focus on targeted delivery of antibodies, toxins, and growth-inhibiting molecules that can attach specifically to tumor cells and interfere with their growth. Researchers are also exploring the role of stem cells in both the development and treatment of brain tumors. Stem cells are undifferentiated, or unspecialized, cells with the potential to develop into any of a number of specialized cells, such as neurons. Normally, regulatory processes prevent mature, specialized cells from dividing and spreading; *cancer* cells escape these regulations. Understanding the normal processes that allow stem cells to mature will allow researchers to understand what might be going awry in cancer cells.

NEUROLOGICAL TRAUMA

Traumatic brain and spinal cord injuries can lead to significant disabilities and death. In the United States, an estimated 1.7 million people sustain traumatic brain injuries (TBI) each year. Of those, 275,000 are hospitalized, and about 52,000 will die as a result of TBI. Falls are the leading cause of all traumatic brain injury, and motor vehicle/traffic injury is the leading cause of TBI-related death. The direct medical costs and indirect costs of TBI, such as lost productivity, are estimated to be more than $60 billion a year in the United States.

Each year, about 17,000 people suffer spinal cord injuries in the United States, and an estimated 282,000 people currently live with spinal cord injuries. Vehicle crashes are the leading cause of spinal cord injury, followed by falls, acts of violence (primarily gunshot wounds), and injuries due to participation in sports and recreational activities. Death rates among people with spinal cord injuries are significantly higher during the first year after the injury, especially people whose injuries cause severe neurological impairments.

Few effective remedies have been found to repair damage incurred by head and spinal cord injuries; however, new methods have come to light for preventing damage that develops after the initial injury. In addition, there are ongoing efforts to support better rehabilitation techniques as well as research into the regeneration and repair of injured tissue.

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Traumatic Brain Injury

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

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

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

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

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

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

Spinal Cord Injury

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

There is no cure for spinal cord injuries, but scientists are investigating new ways to repair damaged spinal cords. These include protecting surviving nerve cells from further damage, replacing damaged nerve cells, stimulating the regrowth of axons and targeting their connections, and retraining nerve circuits to restore bodily functions. In addition, scientists constantly search for new methods for rehabilitating patients with SCI and improving their quality of life. Rehabilitation focuses on physical therapy to strengthen muscles and improve mobility. Occupational therapy focuses on enhancing fine motor skills, such as the skills needed to write or type. Electrical stimulation is sometimes used to help restore function to muscles affected by the injury.

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

NEUROLOGICAL ACQUIRED IMMUNE DEFICIENCE SYNDROME

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

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

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

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

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

Mild forms of HAND have been reported in about one-third of people with HIV infection who have no other symptoms. In advanced disease, people can develop increasing problems with concentration and memory as well as an overall slowing of their mental processes. At the same time, they might experience leg weakness and loss of balance. MRI and CT scans show brain shrinkage in people with HAND. Examination of the brains of people who die with AIDS sometimes reveal loss of nerve cells, white matter abnormalities, and damage to cellular structures involved in cell-to-cell communication. Inflammation and vessel disease can also be present.

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

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

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

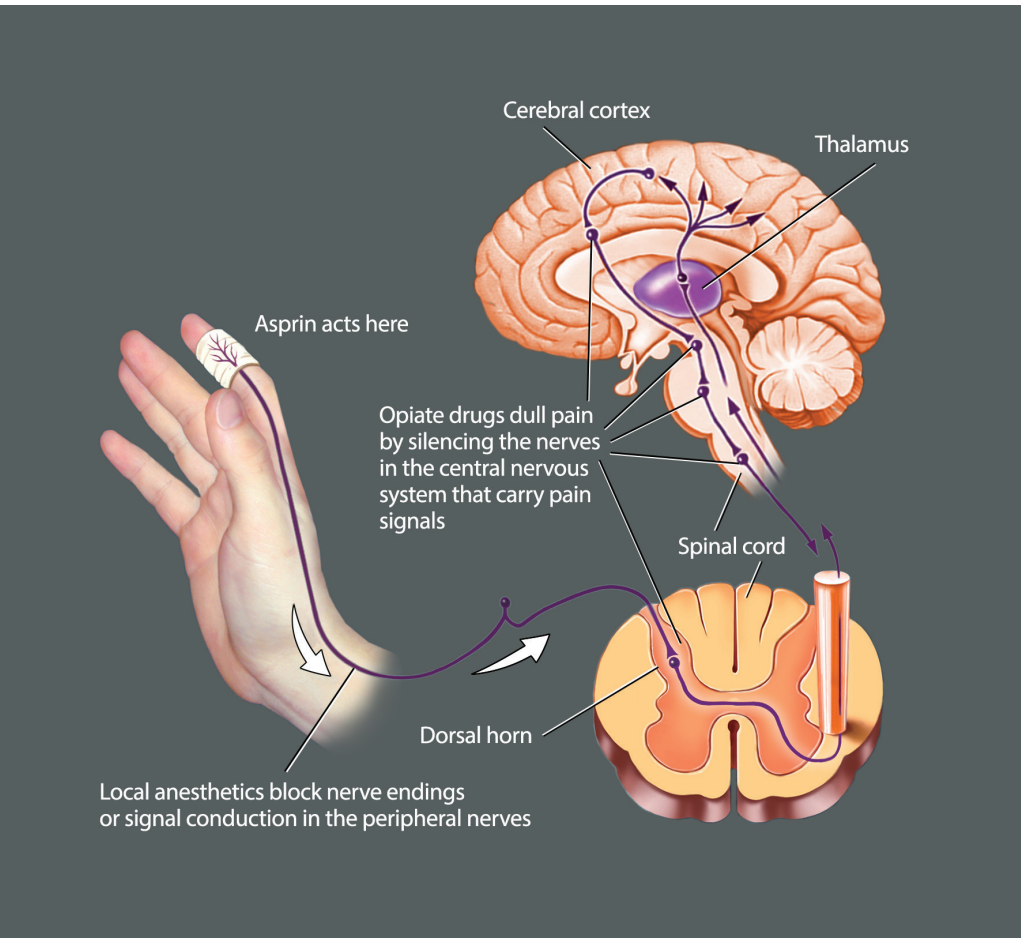
MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, usually diagnosed in people between 20 and 40 years of age. For unknown reasons, the immune system of a person with MS launches an attack against its own central nervous system, including the brain, spinal cord, and optic nerves. The target of this attack is the myelin sheath, a fatty substance that forms a protective coating around nerve fibers; the nerve fibers themselves can also be affected. As a result of the attack, the damaged myelin and the accompanying inflammatory cells form lesions, patches of scar tissue that look like sclerosis.

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

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

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



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

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

When a person is diagnosed with MS, treatment options depend on the type of disease that is present. Specialists classify MS as one of three categories: relapsing-remitting MS, characterized by flare-ups of new or worsening symptoms followed by complete or partial remission of symptoms; primary-progressive MS, defined by progressive worsening of symptoms after disease onset; and secondary-progressive MS, in which relapsing-remitting disease has transitioned into a progressive form of disease that worsens over time.

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

MS has no cure, but an increasing number of medications are becoming available or are under investigation. Since 2010, six new or revised disease-modifying therapies have been approved for use in people with MS. In addition, several medications can now help control the inflammation and immune system attacks in relapsing-remitting MS. Steroid drugs, specifically glucocorticoids, reduce the inflammation and might also help shorten acute attacks. Medications and therapies are also available to control symptoms such as muscle stiffness, pain, fatigue, mood swings, and bladder, bowel, or sexual dysfunction.

CHRONIC PAIN

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

Treating Pain

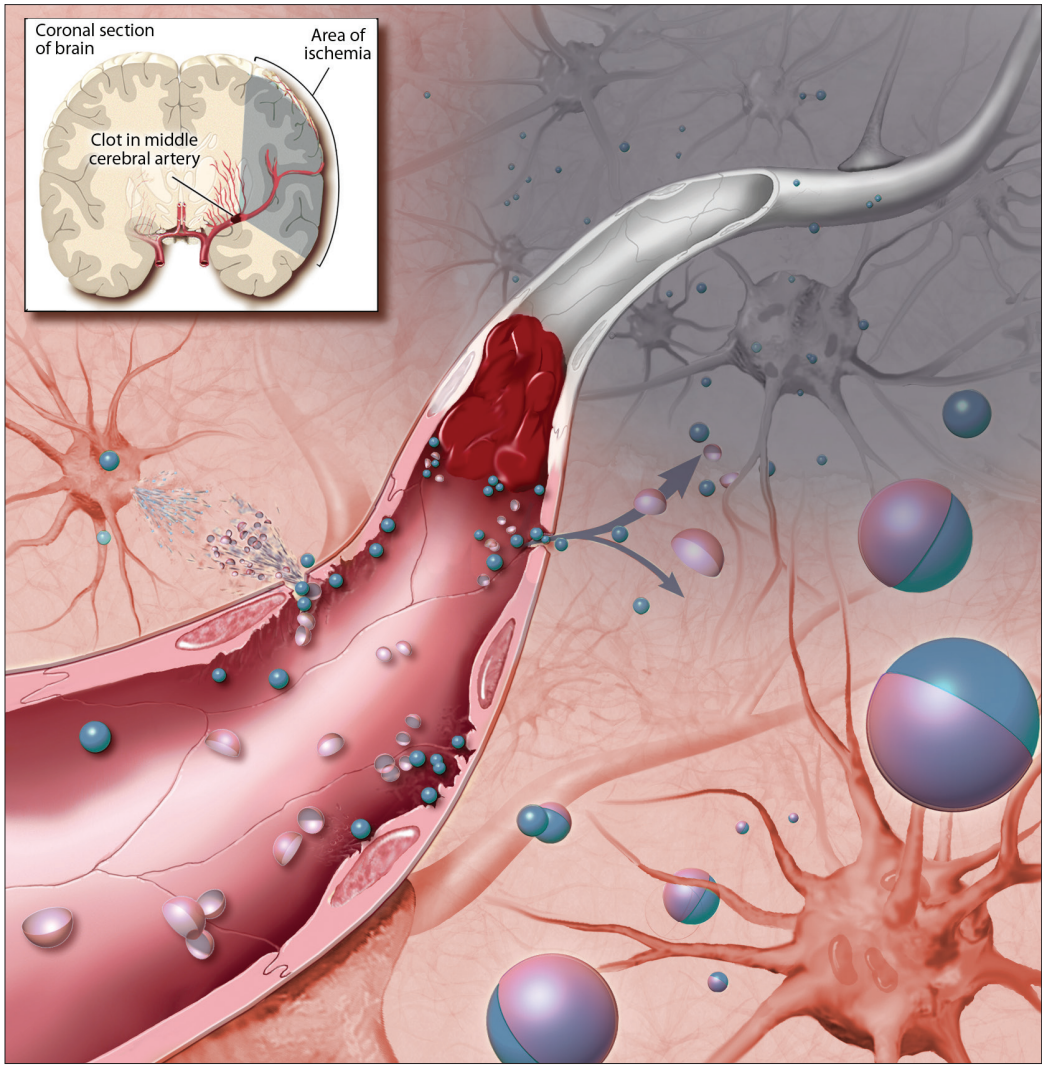
Anesthesia is used to prevent pain during a wide variety of medical procedures and surgery. Local anesthetics

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

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

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

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



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

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

Antiepileptic and antidepressant drugs are generally used to treat nerve pain that results from injury to the nervous system. Nerve damage and pain (neuropathy) can be due to chronic high blood sugar levels; viruses, such as shingles; phantom limb pain; or post-stroke pain.

The Body's Pain Control System

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

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

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

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

STROKE

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

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

Until recently, treatments for a stroke did not go far beyond physical or speech therapy. Today, however, clot-dissolving medications are a standard treatment. Tissue plasminogen activator (tPA), a clot-dissolving drug approved by the FDA in 1996, helps to break down blood clots and open blocked blood vessels. tPA can restore circulation before oxygen loss causes permanent brain damage; given within three hours of a stroke, its use often limits brain damage. In addition, surgery to clear clogged arteries and other treatments targeting heart disease can help prevent strokes. Anticoagulant drugs also help by reducing the likelihood of clots forming elsewhere in the body and traveling to the brain, causing a stroke.

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